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Exploration of the chemistry of alkynes and Selectfluor : search for cytotoxic agents from the Amazonian rainforest.

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EXPLORATION OF THE CHEMISTRY OF ALKYNES AND SELECTFLUOR. SEARCH FOR CYTOTOXIC AGENTS FROM THE AMAZONIAN RAINFOREST

By

Zhuang Jin

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A Dissertation Approved on

March 5, 2012

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Dr. Frederick A. Luzzio

Dr. Michael H. Nantz

DEDICATION

This dissertation is dedicated to three ladies:

My wonderful mother Xiulan Hai

My beautiful wife Lanlan Bao

My gorgeous daughter Solonga Julia Jin

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I am very grateful to my mentor, Dr. Gerald B. (GB) Hammond for giving me an opportunity to find beauty in discovery, for always keeping his trust in me, and for showing me that the real targets in life are not always chemical structures. I also greatly appreciate Dr. Bo Xu who has been my day-to-day mentor in all aspects of my research, providing me with guidance and ideas for my research, and helping me to find out 'why my reaction didn't work…'

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ABSTRACT

EXPLORATION OF THE CHEMISTRY OF ALKYNES AND SELECTFLUOR. SEARCH FOR CYTOTOXIC AGENTS FROM THE AMAZONIAN RAINFOREST

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Vicinal dithioethers and alkenyl thioethers were synthesized under environmentally friendly conditions using alkyne and thiol in water. Alkynes were also used to develop a multibond-forming reaction that formed cyclic ketones or ketoesters through a gold-catalyzed intramolecular oxygen transfer isomerization of 2-alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters.

The investigation of Selectfluor chemistry yielded a highly stereoselective synthesis of fluoroalky (*E*)-α,β-unsaturated ketones from allenyl esters, through a gold-catalyzed rearrangement that produced an intermediate dienyl ester. When Selectfluor was combined with copper, it produced two oxidative systems, F-TEDA-BF_4 and F-TEDA-PF_6, both of which efficiently converted amides into imides at room temperature in short time, but whereas the former employed stoichiometric amounts of copper(I), the latter only needed catalytic amounts.

The bioassay-directed fractionation of *Physalis angulata* L. afforded three new antiproliferative withanolides: physangulidines A, B and C. Each has shown significant

cytotoxic activity (GI_{50} is less than 4μg/mL) on DU145 and RWPE-1 *in vitro*. In addition, compared to positive drug 5-fluorouracil, physangulidine A had significant cytotoxic activity on different cells. The bioassay-guided fractionation of *Cremastosperma microcarpum* led to the isolation and identification of dehydrodiisoeugenol as its main cytotoxic agent. Lastly, selected fractions of *Hyptis lantanaefolia* have shown promising cytotoxic activities; with one of semipurified chromatographic fraction (LHL15) exhibiting very high bioactivity on various cell lines (IC_{50} is lower than 50 ng/mL).

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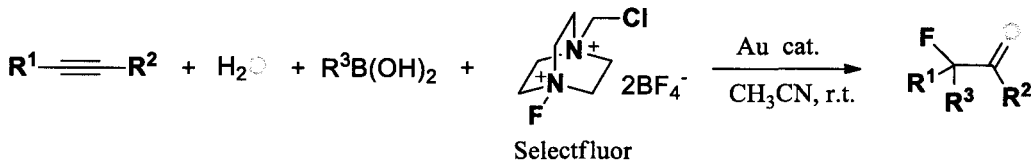
1. OVERVIEW OF THIS DISSERTATION

1.1. Alkyne and Fluorine Chemistry

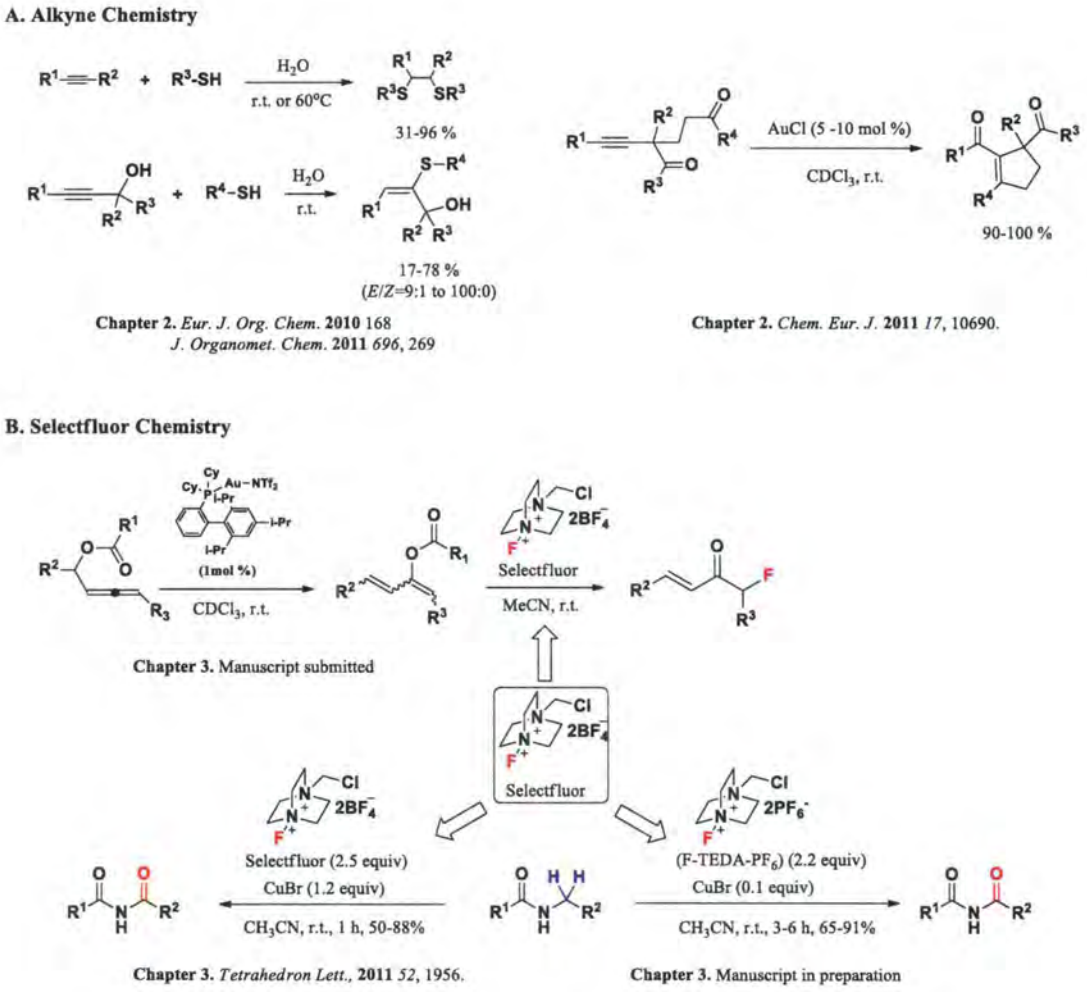
Alkyne is an important synthon in organic chemistry, as demonstrated by the many examples of elegant synthetic work centered on alkynes.[1] The Hammond group has dedicated much of their efforts to explore the chemistry of alkynes.[2] Of more relevance to the work presented herein, members of the Hammond group have recently reported a cationic gold-catalyzed functionalized hydration of alkynes (Scheme 1).[3]



Scheme 1. Gold Catalyzed Functionalized Hydration of Alkynes

Various types of alkynes were hydrated to give α-substituted α-fluorinated ketones using boronic acid, Selectfluor and trace amount of water in the presence of a cationic gold catalyst. The synthetic work contained in this dissertation is centered around alkynes and Selectfluor. This work (Scheme 2) includes the synthesis of vicinal dithioesters and alkenyl thioesters via a new environmentally friendly use of akynes and thiols in water; the gold-catalyzed intramolecular oxygen transfer reaction of 2-alkynyl-1,5-diketones or 2-alkynyl-5-diketoesters; and the stereoselective synthesis of fluoroalkyl *E*-α,β-

unsaturated ketones via gold-catalyzed rearrangement of allenyl carbinol ester followed by fluorination. Finally, two new oxidative systems containing Selectfluor have been investigated, namely the combination of CuBr (stoichiometric amounts) with excess Selectfluor (F-TEDA-BF_4), and the combination of catalytic CuBr with excess F-TEDA-PF_6--the anionic exchange product of Selectfluor. Both combinations can efficiently oxidize amides into imides at room temperature.



Scheme 2. Outline of Alkyne and Selectfluor Chemistry

1.2. Natural Products Research

Nature as source for drugs and inspiration for the development of front-line-drugs is indisputable if one considers that more than 75% of the world's population, especially in developing countries, rely on medicinal plants as primary source of medicinal care,[4] and that around 50% of the total new chemical entities launched onto the market in the last 25 years are natural products or natural products analogs.[5]

In order to demonstrate the medicinal value of natural products, a multidisciplinary and international group of scientists led by Professors Abraham J. Vaisberg (Universidad Peruana Cayetano Heredia), Walter H. Lewis (Washington University, St. Louis), and Gerardo Lamas (Universidad Nacional Mayor de San Marcos), under the auspices of the International Cooperative Biodiversity Group (ICBG) project--funded by a consortium of the following agencies, NIH, US AID, and NSF--embarked on an ethnobotanical study of Peruvian medicinal plants, guided by members of the Aguaruna community.[6] The Aguaruna are one of the four tribes that constitute the Jivaro linguistic family, living in the upper Amazon basin and adjacent foothills of the eastern Andes Mountains of northern Perú and nearby Ecuador. Northern Perú, particularly the eastern slopes of the Andes Mountains and adjacent upper Amazon basin, is exceedingly rich in diverse woody plants. Only a small percentage (~2%) of these Peruvian species have been investigated chemically and/or biologically, and it is estimated that over 2000 plants in the Amazon region are used in traditional medicine.[6] Since the early 1990's this group has collected 3591 plants, with, 1600 of them being rare or/and medicinal plants. Our group has isolated numerous bioactive agents from targeted plant through a bioassay-

guided fractionation,[6-7] then built library of drug candidates around them by synthesizing derivatives of the bioactive agents.[8]

This dissertation includes our results on 13 plant species collected in the Amazonian rain forest. Trans-dehydrodiisoeugenol was isolated as the main cytotoxic agent present in *Cremastosperma microcarpum* (Annonaceae) by bioassay-directed isolation. Similarly, three new antiproliferative withanolides with an unusual carbon framework, namely, physangulidines A, B and C were isolated and characterized from *Physalis angulata* (Solanaceae) (Figure 1). We have also found that selected fractions of *Hyptis lantanaefolia* (Lamiaceae) have promising cytotoxic activities; one of its semipurified chromatographic fraction (LHL15) has shown extremely high cytotoxic activity on different cell lines (IC_{50} is lower than 50 ng/mL). *Hyptis lantanaefolia*, together with *Bocconia intengrifolia* (Papaveraceae), are currently under investigation.

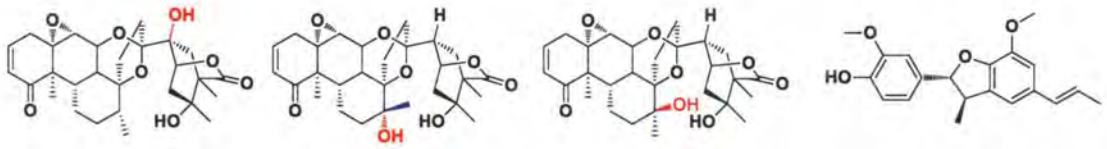


Figure 1. Outline of Natural Products Chemistry

2. EXPLORATION OF ALKYNE CHEMISTRY

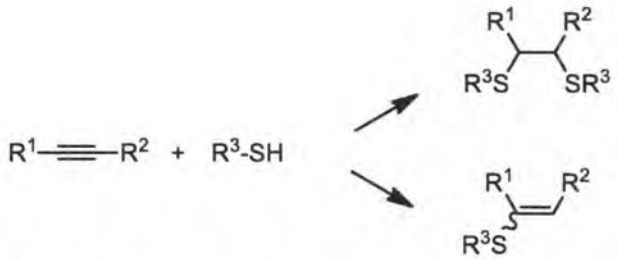
2.1. Environmentally Friendly Addition of Thiols to Alkynes

2.1.1 Background

Organosulfur compounds have become increasingly important as the role of sulfur is probed deeper in biological processes, new materials, and chemical synthesis.[9] As a result, the synthesis of organosulfur compounds has attracted much attention.[10] Specifically, vicinal dithioethers and alkenyl thioethers have been widely used as target or intermediates. For example, vicinal dithioethers have been used as ligands for zirconium or titanium complexes for alkene polymerization and hydroamination.[11]

Vicinal dithioethers can be made by nucleophilic substitutions,[11b, 11d] or nucleophilic ring-opening reaction of thiolate.[11a, 11c, 11e] Vicinal dithioethers can also be prepared from an alkene and a disulfide under acid or metals catalysis.[12] Hydroelementation is a versatile and atom-efficient method for installing heteroelements to unsaturated carbon-carbon bonds.[13] Therefore, one of the most straightforward methods to make vicinal dithioethers is the dihydrothiolation of an alkyne. Under controlled conditions, monohydrothiolation of alkynes could yield alkenyl thioethers (Scheme 3). There are reports on the preparation of vicinal dithioethers from alkynes and thiols in organic solvents[14] using various radical initiators, and/or heating or UV light. The use of water as solvent has also been reported

by Oshima and coworkers, who isolated the vicinal dithioether as a side product, during their investigation of thiol-yne radical reactions in water assisted by a water-soluble radical initiator.[15] In all these literature syntheses, there are detracting experimental limitations, including the use of metal catalysts, high temperatures or radical initiators, and organic solvent. The addition of thiols to alkenes has been used in the synthesis of dendrimers (so called 'thiol-ene click' chemistry).[16] The spectrum of application of these dendrimers, ranging from medicine to nanoengineering[17] should spur the development of novel and efficient synthesis of macromolecules. In this chapter we report an atom-economical and 'green' synthesis of vicinal dithioethers from the reaction of alkyne and thiol without the use of metal catalysts or radical initiators, and using water as the sole solvent. Furthermore, this method can also be used for regio- and stereo-selective monohydrothiolation of propargyl alcohols, which leads to an effective synthesis of alkenyl thioethers with exclusive *E*-selectivity.



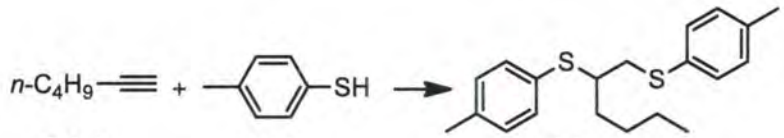
Scheme 3. Synthesis of Vicinal Dithioethers and Alkenyl Thioethers from Alkynes and Thiols

2.1.2 Scope of the Aqueous Dihydrothiolation of Alkynes

We used the reaction of 1-hexyne and 4-methylbenzenethiol as our model reaction (Table 1). While THF, MeOH, H_2O, individually or as a mixture, or non-solvent conditions gave

good results, traditional organic solvents, such as CH_3CN, CH_2Cl_2 and toluene, were not satisfactory.

Table 1. Effect of Solvents on Dihydrothiolation of Alkyne **2-1-1a**.[a]



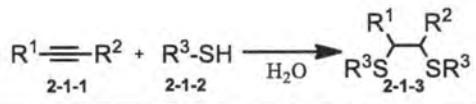
2-1-1a **2-1-2a** **2-1-3a**

Entry	Solvent	Yield[b] (%)
1	CH_3CN	31
2	CH_2Cl_2	24
3	Toluene	34
4	THF	72
5	MeOH	65
6	H_2O:MeOH (4:1)	76
7	H_2O	80
8	No solvent	72

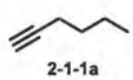
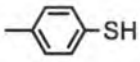
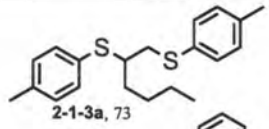
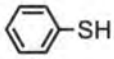
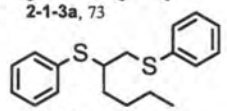
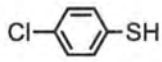
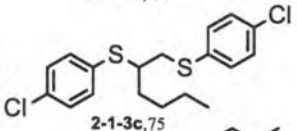
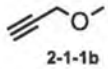
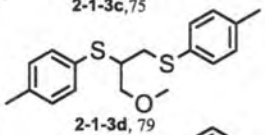
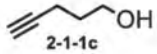
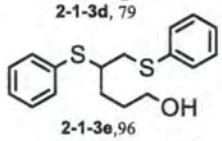
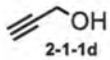
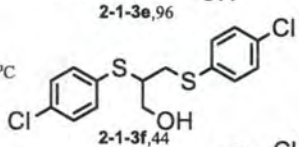
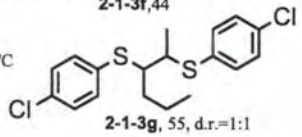
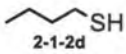
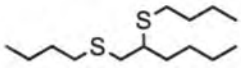
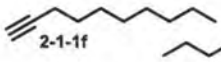
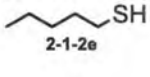
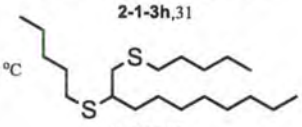
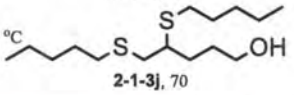
[a] **2-1-1a** (1 mmol), **2-1-2a** (2.4 mmol) and solvent (0.5 mL) reacted for 24 h at r.t.
[b] Determined by ^{1}HNMR, benzyl bromide (0.4 mmol) as internal standard.

Considering both, chemical yields and the increasing environmental consciousness of the scientific community, we chose water as the ideal reaction media. It is surprising that water was found to be the best solvent for the reaction considering that both starting material and product are virtually insoluble in water. According to Sharpless and co-workers,[18] reaction rates can be accelerated when insoluble reactants were stirred in aqueous suspension, denoted as "on water" conditions. Thus, this reaction could be considered as an 'on water' rea-ction. With optimized conditions in hand, we examined the scope of this dihydrothiolation reaction; the results are summarized in Table 2.

Table 2. Dihydrothiolation of Alkyne **2-1-1**.[a]



2-1-1 2-1-2 2-1-3

Entry	Alkyne 2-1-1	Thiol 2-1-2	Temp	Product 2-1-3 (%)[b]
1	 2-1-1a	 2-1-2a	r.t.	 **2-1-3a**, 73
2	2-1-1a	 2-1-2b	r.t.	 **2-1-3b**, 74
3	2-1-1a	 2-1-2c	r.t.	 **2-1-3c**,75
4	 2-1-1b	2-1-2a	r.t.	 **2-1-3d**, 79
5	 2-1-1c	2-1-2b	r.t.	 **2-1-3e**,96
6	 2-1-1d	2-1-2c	60°C	 **2-1-3f**,44
7	 2-1-1e	2-1-2c	60°C	 **2-1-3g**, 55, d.r.=1:1
8	2-1-1a	 2-1-2d	60 °C	 **2-1-3h**,31
9	 2-1-1f	 2-1-2e	60 °C	 **2-1-3i**,81
10	2-1-1c	2-1-2e	60 °C	 **2-1-3j**, 70

[a] Alkyne **2-1-1** (1 mmol), thiol **2-1-2** (2.4 mmol) and deionized water (0.5 mL), reacted at indicated temperature for 24 h. [b] Isolated yields.

1-Hexyne and aryl thiols reacted smoothly (entries 1, 2 and 3). The reaction of functionalized terminal alkynes, such as methyl propargyl ether and 4-pentyn-1-ol, with

an aryl thiol also gave good to excellent yields (entries 4 and 5). However, propargyl alcohol and 2-hexyne reacted with 4-chlorothiophenol to produce moderate yields of **2-1-3** (entries 6 and 7). The low yield in entry 8 is probably due to the volatility of the substrate, as higher molecular weight alkynes reacted effectively with aliphatic thiols under mild heating (entries 9 and 10).

Unfortunately, under our conditions, phenylacetylene and other internal alkynes reacted with thiols to give only the monohydrothiolation product.[12c, 19] Upon further investigation, we found that aryl thiols are more reactive than aliphatic thiols; electron withdrawing chlorine accelerates the dihydrothiolation, and weak electron donating groups slow the reaction. The observed reaction rates follow this order: 4-chlorothiophenol > thiophenol > 4-methylbenzenthiol. Strong electron withdrawing groups, such as nitro, methyl ester and carboxylic acid, on the *para* position of thiophenol hinder the reaction. This may be related to their ease of emulsification, as 4-nitrothiophenol, 4-mercaptobenzoic acid and 4-mercaptobenzoic acid methyl ester do not form an emulsion with alkynes, whereas the thiol in Table 2 readily formed an emulsion with alkyne in water upon stirring.

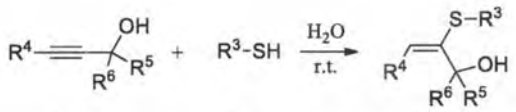
Our mechanistic studies hinted that the reaction probably proceeded through a radical mechanism, because no reaction occurred in the presence of galvinoxyl free radical (1.1 equiv to thiol).[20] The possibility of a nucleophilic addition could be ruled out since nucleophilic dihydrothiolation of alkynes normally gives thioacetals.[21] Furthermore, small amounts of disulfide (less than 5% yield based on thiol), formed from the homocoupling of thiolate radical, were observed in the course of this study, which is consistent with the proposed radical mechanism. Furthermore, no hydration product was

found in the reaction mixture. The radical initiator could be dioxygen in the air or light since reaction, done in dark area, gave low yield (entry 1 in Table 2, gave 30%). The specific role of the solvent is not clear at this time, it seems water has some ability to stabilize the radical intermediate and therefore facilitates the radical-mediated reaction. A literature report[22] speculated that a hydrogen bond between thiol and water could enable a nucleophilic addition to the alkene.

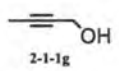
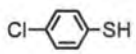
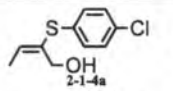
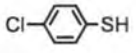
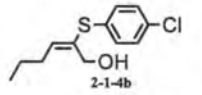
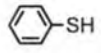
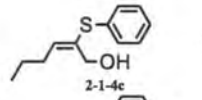
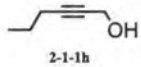
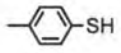
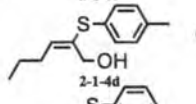
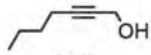
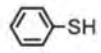
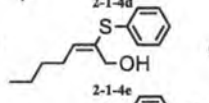
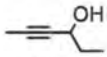
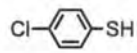
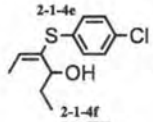
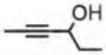
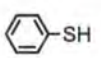
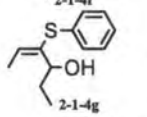
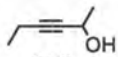
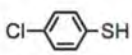
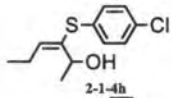
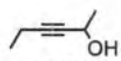
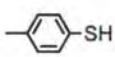
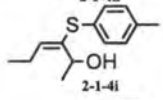
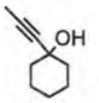
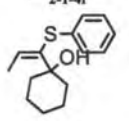
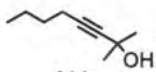
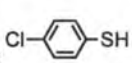
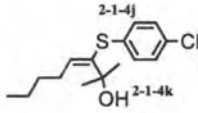
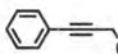
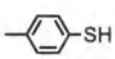
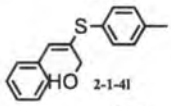
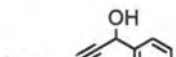
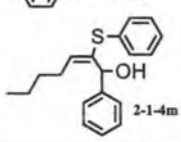
2.1.3 Regio- and Stereo-selective Monohydrothiolation of Non-Terminal Propargyl Alcohols

While investigating dihydrothiolation conditions for non-terminal propargyl alcohols (e.g. **2-1-1g**), we found, to our surprise, that only the monohydrothiolation product was obtained, and this reaction proceeded in a regio- and stereo-selective manner. The thiol only attacked the carbon next to the alcohol and only the *E*-isomer was isolated. The reaction scope is shown in Table 3. But-2-yn-1-ol and 4-chlorothiophenol gave a moderate yield of product with high stereoselectivity (entry 1). Similarly, **2-1-1h** reacted with three different thiophenols in moderate to high yields with high *E*-selectivity (entries 2-4). Entry 5 also showed satisfactory yield and stereoselectivity. Reaction of secondary alcohols (**2-1-1j** and **2-1-1k**) with thiophenols gave satisfactory yields and excellent stereoselectivity (entries 6-9), while tertiary propargyl alcohol **2-1-1l** gave very high stereoselectivity (100% *E*), albeit in low yield (entry 10). Reaction of **2-1-1m** and 4-chlorothiophenol **2-1-2c** was also highly stereoselective (entry 11).

Table 3. Regio and Stereoselective Monohydrothiolation of Propargyl Alcohols.[a]



2-1-1 2-1-2 2-1-4

Entry	Alkyne 2-1-1	Thiol 2-1-2	Product 2-1-4	Yield [b]
1	 2-1-1g	 2-1-2c	 2-1-4a	53 (*E*/*Z*=9:1)
2	 2-1-1h	 2-1-2c	 2-1-4b	76 (*E*/*Z*=9:1)
3	 2-1-1h	 2-1-2b	 2-1-4c	66 (*E*/*Z*=12.5:1)
4	 2-1-1h	 2-1-2a	 2-1-4d	58 (*E*/*Z*=12.5:1)
5	 2-1-1i	 2-1-2b	 2-1-4e	77 (*E*/*Z*=12.5:1)
6	 2-1-1j	 2-1-2c	 2-1-4f	64 (*E*/*Z*=17:1)
7	 2-1-1j	 2-1-2b	 2-1-4g	63 (*E*/*Z*=17:1)
8	 2-1-1k	 2-1-2c	 2-1-4h	78 (*E*/*Z*=17:1)
9	 2-1-1k	 2-1-2a	 2-1-4i	70 (*E*/*Z*=20:1)
10	 2-1-1l	 2-1-2b	 2-1-4j	17 (*E*/*Z*=100:0)
11	 2-1-1m	 2-1-2c	 2-1-4k	65 (*E*/*Z*=100:0)
12	 2-1-1n	 2-1-2a	 2-1-4l	42 (*E*/*Z*=100:0)
13	 2-1-1o	 2-1-2b	 2-1-4m	44 (*E*/*Z*=50:1)

[a] Alkyne **2-1-1** (1 mmol), thiol **2-1-2** (1.2 mmol) and deionized water (0.25 mL) reacted at r.t. for12 h.

[b] Isolated yield, *E* and *Z* were determined by NOESY study.

In entries 12 and 13, we investigated substrates having a phenyl group; both of them, without exception, reacted with aryl thiols to give products with very high stereoselectivity. Stereochemistry of alkenyl thiolethers (**2-1-4**) was determined by NOSEY study, and selected NOSEY speactra of **2-1-4c** is shown in Figure 2, which showing that Stereochemistry of **2-1-4c** is mainly *E*.

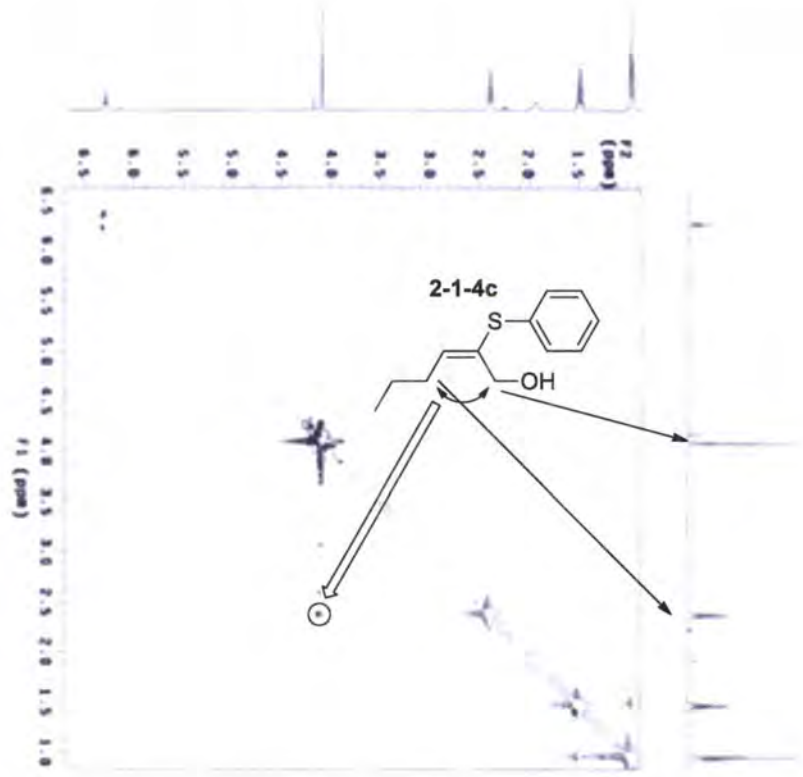
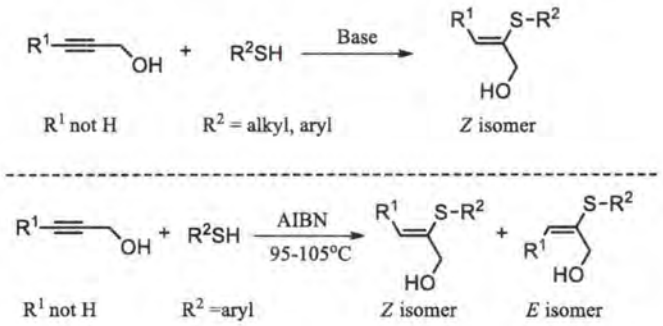


Figure 2. NOSEY Spectra of **2-1-4c**

During this study, we also found that alkyl thiols are not effective under these conditions, and terminal alkynes, such as propargyl alcohol, overreacted with thiophenol to give dihydrothiolation products (Table 2). Regio- and stereo-selective monohydrothiolation was observed only with non-terminal propargyl alcohols, even with excess thiol in water. While themonohydrothiolation of non-terminal propargyl alcohol with thiol has been

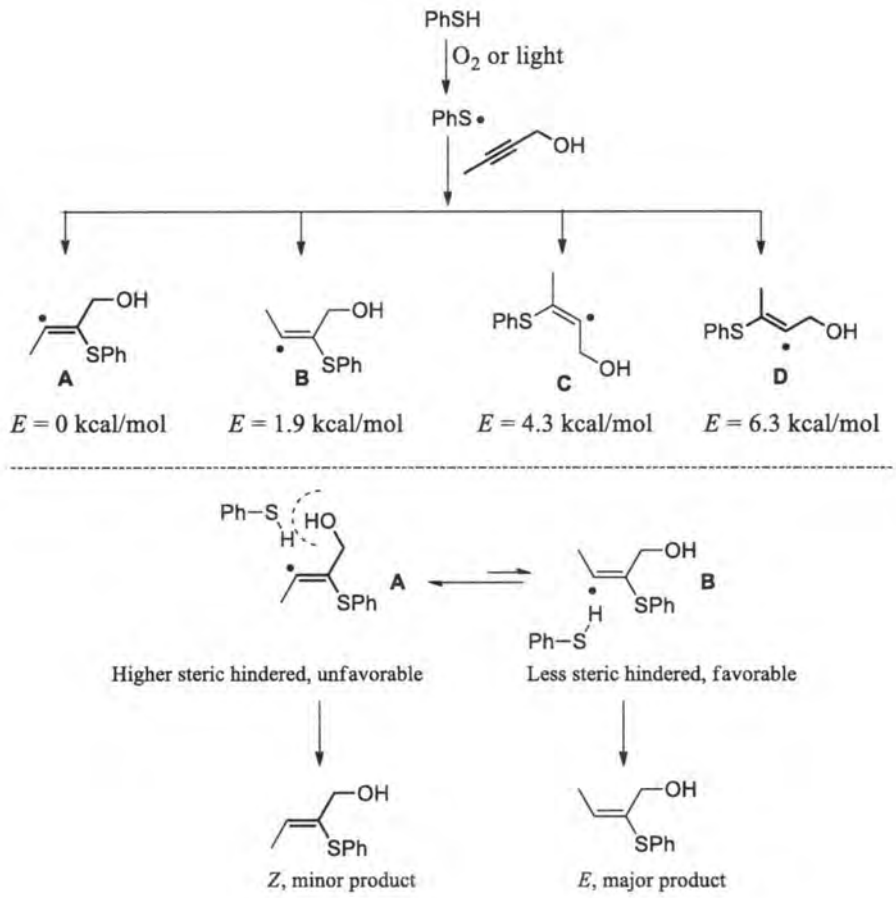
studied before,[23] our mild reaction conditions showed distinctive regio- and stereoselectivity for a wider range of substrates. A case in point is the base mediated nucleophilic addition of thiol to propargyl alcohol (Scheme 4, top) that yields the *trans* adduct product, *Z*-alkenyl thioether[23a-g] or a mixture of *Z* and *E*- alkenyl thioethers.[23h, i]



Scheme 4. Nucleophilic and Radical Additions of Thiol to Propargyl Alcohols

And, addition of a thiol, using a radical initiator, usually affords a mixture of *Z* (predominant) and *E*-alkenyl thioethers (Scheme 4, bottom).[23j, k]

The reason for the high regio and stereoselectivity of **2-1-4** can be explained by the relative stability of vinyl radical intermediates (Scheme 5, top). The vinyl radical intermediates **C** and **D** are higher in energy than **A** and **B** (Gaussian 03, UB3LYP/6-311+G(d)). This can explain why the thiol always attacks the carbon next to hydroxymethyl group. The stereoselectivity outcome of **2-1-4** may be explained by steric effects and the isomerization of vinyl radical **A** to **B**. It is widely accepted that a hydrogen donor can approach from the less hindered side of the vinyl radical.[24]

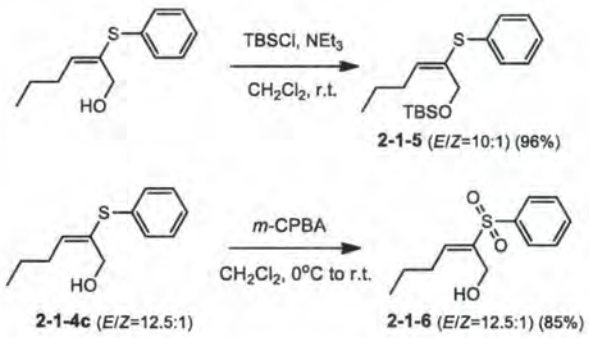


Scheme 5. Regioselectivity and Stereoselectivity Considerations

The bulkiness of hydroxymethyl group in radical **A** may hinder the approach of the hydrogen donor (thiol) to form a *Z*-isomer (Scheme 5, bottom) (Note: hydroxyl methyl group is bulkier than thiol ester group, because bond length between sp^2 and sp^3 carbons is 150 pm[25] and bond length between sp^2 carbon and sulfur is 175 pm[26]). However, the thiol can easily approach the less hindered side of the vinyl radical **B** to produce the *E*-isomer. As a result, radical **A** may slowly isomerize to radical **B**. This is consistent with the fact that the bulkier the hydroxyalkyl, the higher the stereoselectivity observed (Table 3). And, the mild conditions (room temperature/water as solvent) minimized the

isomerization of the final product. This is in contrast with literature reports in which isomerization may occur at high temperature (Scheme 5, bottom).[23j, k]

Alkenyl thioesters have already demonstrated their utility.[27] Compound **2-1-4** can be used in further transformations; for example, the free hydroxyl group in **2-1-4** can be protected to give **2-1-5**, and **2-1-4** can be easily oxidized to sulfone **2-1-6** with *m*-CPBA (Scheme 6). Both **2-1-5** and **2-1-6** have been used in nickel catalyzed cross-coupling reactions with Grignard reagents[28] or organozinc reagents[29] to give functionalized allylic alcohols, which are important intermediates in total synthesis[30] and methodology.[31]



Scheme 6. Synthetic Transformations of Alkenyl Thioethers

2.1.4 Summary

We have found that a wide range of alkynes react with excess thiols to give vicinal dithioethers under mild condition using only water as solvent, without radical initiator or UV light sources. Alternatively, non-terminal propargyl alcohols reacted with phenyl thiols in water to produce *E*-alkenyl thioethers in highly regio- and stereo-selective fashion. Considering the mild conditions of our reaction, it could have great potential in the preparation of highly branched dendrimers, and as linkers incorporating fluorescence tags in biological applications.

2.1.5 Experimental Section

General

Substrates **2-1-1m** and **2-1-1o** were prepared using a literature method.[32] Other substrates and reagents were commercially obtained from Alfa or Adrich, and were used without further purification. Structures were identified by NMR spectra, assisted by elemental analysis or/and IR spectra. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using $CDCl_3$ as solvent. The chemical shifts were reported in δ (ppm) value relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR), and multiplicities are indicated by s (for singlet), d (doublet), dd (double doublet), m (multiplet), and br (broad). Coupling constant, *J*, was reported in Hz. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. Melting points were measured using a DigiMelt PMA 160 melting point apparatus.

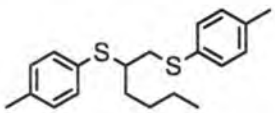
Typical procedure for preparation of 2-1-1m and 2-1-1o

To oven dried 10 mL reaction flask containing 1-Hexyne (340 μL, 3.0 mmoL), anhydrous THF (5.0 mL) and stir bar at -78 °C, n-Butyl lithium (3.0 mmoL) was added over 5 min by syringe, and slowly warm up to room temperature and stirred for another 2 h. Then benzaldehyde (306 μL, 3.0 mmoL) was added into the above reaction mixture by syringe, and stirred at room temperature for 2 h. The reaction mixture was quenched by saturated ammonium chloride (20 mL) and followed by diethyl ether extraction (25 mL×4). The ether layers were combined and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield amide **2-1-1o** (526.0 mg, 93 %).

General procedure for dihydrothiolation (of monohydrothiolation) of alkynes

To a reaction flask containing a stir bar, alkyne (1 mmol), thiol (2.4 mmol, or 1.2 mmol for monohydrothiolation), deionized water (0.5 mL, 0.25 mL for monohydrothiolation) was added, and the resulting mixture was sealed and stirred for 24 h (12 h for monohydrothiolation) at the indicated temperature. Then the mixture was subjected to silica gel column chromatography using gradient elution from hexane to a mixture of hexane: ethyl acetate (10:1) to get final pure product **2-1-3** (or **2-1-4**).

1,2-Bis(p-tolylsulfanyl)hexane (**2-1-3a**)



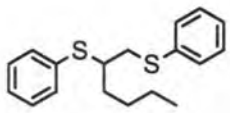
$C_{20}H_{26}S_2$ (330.2): Calcd. C 72.67, H 7.93; Found C 72.80, H 8.25.

FTIR (neat) / cm^{-1}: 2955, 2925, 1491 and 804;

^1H NMR (500 MHz; $CDCl_3$): δ 0.93 (t, *J*=7.0Hz, 3H), 1.29-1.39 (m, 2H), 1.43-1.46 (m, 1H), 1.53-1.59 (m, 2H), 1.95-1.98 (m, 1H), 2.34 (s, 3H), 2.36 (s, 3H), 2.86 (dd, *J*=13.25, 10Hz, 1H), 3.05-3.10 (m, 1H), 3.23 (dd, *J*=13.75, 4.0 Hz, 1H), 7.04 (d, *J*=8.0Hz, 2H), 7.09 (d, *J*=7.5Hz, 2H), 7.13 (d, *J*= 7.5Hz, 2H), 7.25 (d, *J*=8.0Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.29, 21.31, 21.41, 22.79, 29.22, 32.44, 40.11, 48.80, 129.92, 129.94, 130.52, 130.68, 132.45, 133.39, 136.51, 137.60.

1,2-Bis(phenylsulfanyl)hexane (**2-1-3b**)[12b]



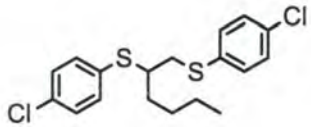
$C_{18}H_{22}S_2$ (302.1): Calcd. C 71.47, H 7.33; Found C 71.87, H 7.62.

FTIR (neat) / cm^{-1}: 2955, 2928, 1478, 1437, 738 and 690.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.83 (t, *J*=7.5Hz, 3H), 1.84-1.25 (m, 2H), 1.31-1.38 (m, 1H), 1.43-1.50 (m, 2H), 1.87-1.93 (m, 1H), 2.81 (dd, *J*=13.5, 9.5Hz, 1H), 3.02-3.15 (m, 1H), 3.17 (dd, *J*=13.5, 4.0Hz, 1H), 7.09-7.25 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.27, 22.77, 29.21, 32.51, 39.59, 48.54, 126.49, 127.47, 129.18, 129.23, 129.98, 132.78, 134.59, 136.10.

2-Bis(4-chlorophenylsulfanyl)hexane (**2-1-3c**)



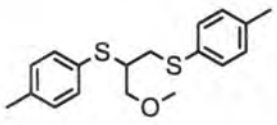
$C_{18}H_{20}Cl_2S_2$ (370.0): Calcd. C 58.21, H, 5.43; Found C 58.50, H 5.36.

FTIR (neat) / cm^{-1}: 2956, 2928, 1474, 1095, 1011, 817.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.92(t, *J*=7.0Hz, 3H), 1.27-1.35 (m, 2H), 1.39-1.42 (m, 1H), 1.53-1.55 (m, 2H), 1.96-2.00(m, 1H), 2.89 (dd, *J*=13.0, 9.0Hz, 1H), 3.01-3.05 (m, 1H), 3.15 (dd, *J*=13.0, 4.0Hz, 1H), 7.12 (d, *J*=8.5Hz, 2H), 7.20 (d, *J*=8.0Hz, 2H), 7.25-7.27 (m, 4H)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.90, 22.41, 28.90, 32.34, 39.79, 48.82, 129.05, 129.10, 131.27, 132.49, 132.74, 133.57, 133.96, 134.28.

1-Methoxy-2,3-bis(p-tolylsulfanyl)propane (**2-1-3d**)



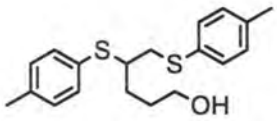
$C_{18}H_{22}OS_2$ (318.1): Calcd. C 67.88, H, 6.96; Found C 68.29, H 7.16.

FTIR (neat) / cm^{-1}: 2920, 2886, 1491, 1119 and 805.

^1H NMR ($CDCl_3$, 500 MHz): δ 2.33 (s, 3H), 2.36 (s, 3H), 3.12 (dd, *J*= 13.75, 5.0Hz, 1H), 3.19(dd, *J*= 13.5, 8.5Hz, 1H), 3.24-3.28(m, 1H), 3.34 (s, 3H), 3.62 (dd, *J*= 10.0, 4.5Hz, 1H), 3.70 (dd, *J*= 9.5, 5.0Hz, 1H), 7.05 (d, *J*=8.0Hz, 2H), 7.09 (d, *J*=8.0Hz, 2H), 7.16 (d, *J*=8.0Hz, 2H), 7.29 (d, *J*=8.0Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.96, 21.07, 35.85, 48.44, 58.96, 72.54, 129.65, 129.71, 129.94, 130.07, 132.01, 133.16, 136.25, 137.59.

4,5-Bis(phenylsulfanyl)pentan-1-ol (**2-1-3e**)



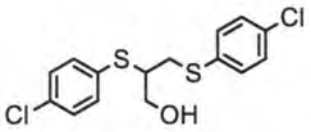
$C_{17}H_{20}OS_2$ (304.1): Calcd. C 67.06, H, 6.62; Found C 67.25, H 6.67.

FTIR (neat) / cm^{-1}: 3364, 2937, 1478, 1437, 1064, 1024, 739 and 691.

^1H NMR ($CDCl_3$, 500 MHz): δ 1.64-1.67 (m, 1H), 1.71-1.77 (m, 1H), 1.87-1.93 (m, 1H), 2.08-2.14 (m, 1H), 2.91 (dd, *J*= 13.75, 9.5 Hz, 1H), 3.14-3.19 (m, 1H), 3.30 (dd, *J*= 13.5, 4.0Hz, 1H), 3.67 (t, *J*=6.0Hz, 2H), 7.19-7.27 (m, 6H), 7.27-7.29 (m, 2H), 7.34-7.36 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.83, 29.87, 39.35, 48.07, 62.43, 126.29, 127.32, 128.91, 128.95, 129.72, 132.58, 133.92, 135.53.

2,3-Bis(4-chlorophenylsulfanyl)propan-1-ol (**2-1-3f**)



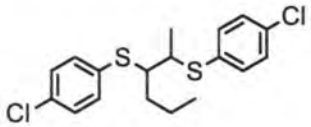
$C_{15}H_{14}Cl_2OS_2$ (343.9): Calcd. C 52.17, H 4.09; Found C 52.07, H 4.09.

FTIR (neat) / cm^{-1}: 3408, 2930, 2873, 1474, 1388, 1093 and 814.

^1H NMR ($CDCl_3$, 500 MHz): δ 3.08-3.14 (m, 2H), 3.16-3.23 (m, 1H), 3.76-3.84 (m, 1H), 3.84-3.86 (m, 1H), 7.19-7.32 (m, 8H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.70, 51.51, 62.44, 129.17, 129.30, 131.07, 131.16, 132.69, 133.67, 134.24, 134.33.

2,3-Bis(4-chlorophenylsulfanyl)hexane (**2-1-3g**) Diastereomers **1**



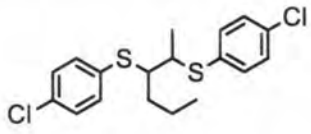
$C_{18}H_{20}Cl_2S_2$ (370.0) Calcd. C 58.21, H 5.43; Found C 58.46, H 5.47.

FTIR (neat) / cm^{-1}: 2958, 2929, 1474, 1094, 1012 and 819.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.94 (t, *J*=7.5Hz, 3H), 1.33 (d, *J*=7.0Hz, 3H), 1.36-1.45 (m, 2H), 1.68-1.72 (m, 1H), 1.95-1.98(m, 1H), 3.02 (d, *J*=10.5Hz, 1H), 3.31 (m, 1H), 7.08 (d, *J*=7.5Hz, 2H), 7.10(d, *J*=7.0Hz, 2H), 7.19 (d, *J*=8.5Hz, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.82, 14.11, 21.11, 29.74, 47.41, 53.05, 129.04, 133.09, 133.38, 133.51, 133.98.

2,3-Bis(4-chlorophenylsulfanyl)hexane (**2-1-3g**) Diastereomers **2**



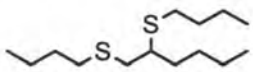
$C_{18}H_{20}Cl_2S_2$ (370.0) Calcd. C 58.21, H 5.43; Found C 58.74, H 5.54.

FTIR (neat) / cm^{-1}: 2958, 2929, 1474, 1094, 1011 and 819.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, *J*=7.5Hz, 3H), 1.36 (d, *J*=7.0Hz, 3H), 1.40-1.44 (m, 2H), 1.58-1.62 (m, 1H), 1.67-1.74 (m, 1H), 3.20 (dt, *J*=9.0, 4.5Hz, 1H), 3.45 (dt, *J*=11.0, 4.5Hz, 1H), 7.23-7.27(m, 6H), 7.32 (d, *J*=8.0Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.94, 18.03, 20.87, 35.79, 49.16, 56.12, 129.00, 129.04, 132.93, 133.10, 133.28, 133.87, 134.79.

1,2-Bis(butylsulfanyl)hexane (**2-1-3h**)



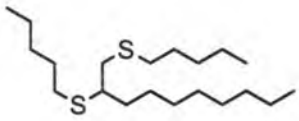
$C_{14}H_{30}S_2$ (262.1) Calcd. C 64.05, H 11.52; Found C 64.66, H 11.68.

FTIR (neat) / cm^{-1}: 2956, 2928, 2859 and 1457.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.90-0.93 (m, 9H), 1.26-1.49 (m, 9H), 1.54-1.59 (m, 4H), 1.78-1.82 (m, 1H), 2.52-2.55 (m, 4H), 2.65 (dd, *J*=12.25, 9.0Hz, 1H), 2.69-2.74 (m, 1H), 2.84 (dd, *J*=12.5, 4.5Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.67, 13.99, 21.97, 22.08, 22.58, 28.88, 30.51, 31.85, 31.92, 32.74, 33.19, 38.39, 45.71.

1,2-Bis(pentylsulfanyl)decane (**2-1-3i**)

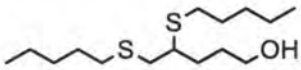


$C_{20}H_{42}S_2$ (346.2) Calcd. C 69.29, H 12.21; Found C 69.44, H 12.38.

FTIR (neat) / cm^{-1}: 2954, 2934, 2854 and 1457. ^1H NMR ($CDCl_3$, 500 MHz): δ 0.87-0.92 (m, 9H), 1.29-1.38 (m, 19H), 1.45-1.51 (m, 2H), 1.57-1.59 (m, 4H), 1.78-1.82 (m, 1H), 2.51-2.54 (m, 4H), 2.65 (dd, *J*=12.75, 8.5Hz, 1H), 2.70-2.73 (m, 1H), 2.84 (dd, *J*=12.5, 4.5Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.97, 14.10, 22.30, 22.65, 26.69, 29.27, 29.47, 29.53, 30.81, 31.05, 31.16, 31.85, 33.04, 33.46, 38.37, 45.71.

4,5-Bis(pentylsulfanyl)pentan-1-ol (**2-1-3j**)



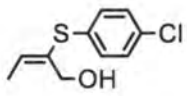
$C_{15}H_{32}OS_2$ (292.1) Calcd. C 61.58, H 11.03; Found C 61.61, H 11.13.

FTIR (neat)/ cm^{-1}: 3364, 2953, 2926, 2857, 1456 and 1058.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, *J*=7.0Hz, 6H), 1.29-1.40 (m, 8H), 1.53-1.62 (m, 5H), 1.66-1.74 (m, 1H), 1.76-1.82 (m, 1H), 1.84-1.96 (m, 1H), 2.52-2.55 (m, 4H), 2.65 (dd, *J*=12.75, 9.5Hz, 1H), 2.72-2.77 (m, 1H), 2.87(dd, *J*=12.75, 4.5Hz, 1H), 3.68 (brs, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.92, 22.26, 24.07, 29.42, 29.49, 29.64, 29.86, 30.87, 31.01, 31.11, 33.01, 38.43, 45.44, 62.61.

(*E*)-2-(4-Chlorophenylsulfanyl)but-2-en-1-ol (**2-1-4a**)



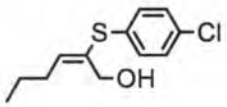
$C_{10}H_{11}ClOS$ (214.0): Calcd. C 56.00, H 5.12; Found C 55.94, H 5.16.

FTIR (neat) / cm^{-1}: 3355, 2912, 2854, 1474, 1388, 1079, 1011 and 816.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.94 (d, *J*=7.0Hz, 3H), 4.10 (s, 2H), 6.38 (q, *J*=6.5 Hz, 1H), 7.20-7.27 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.31, 65.99, 129.11, 130.04, 132.09, 132.96, 134.02, 135.91.

(*E*)-2-(4-Chloro-phenylsulfanyl)hex-2-en-1-ol (**2-1-4b**)

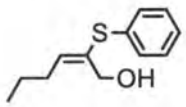


$C_{12}H_{15}ClOS$ (242.0) Calcd. C 59.37, H 6.23; Found C 59.50, H 6.25.

FTIR (neat) / cm^{-1}: 3354, 2958, 2929, 2869, 1474, 1092, 1011 and 815.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, *J*=7.5Hz, 3H), 1.44-1.49 (m, 2H), 2.36 (q, *J*=7.0Hz, 2H), 4.08 (d, *J*=5.0Hz, 2H), 6.29 (t, J=7.0Hz, 1H), 7.20-7.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.81, 22.26, 31.55, 65.78, 129.09, 130.12, 132.02, 133.29, 139.17, 141.55.

(*E*)-2-(Phenylsulfanyl)hex-2-en-1-ol (**2-1-4c**)



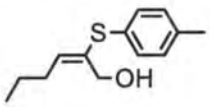
$C_{12}H_{16}OS$ (208.0) Calcd. C 69.19, H 7.74; Found C 69.22, H 7.80.

FTIR (neat) / cm^{-1}: 3351, 2957, 2929, 2869, 1582, 1476, 1438, 1086, 997 and 740.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.96 (t, *J*=7.5Hz, 3H), 1.46-1.52 (m, 2H), 2.39 (q, *J*=7.5Hz, 2H), 4.09 (d, *J*=5.5Hz, 2H), 6.29 (t, *J*=7.0Hz, 1H), 7.19-7.21 (m, 1H), 7.28-7.31 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.83, 22.32, 31.55, 65.85, 126.19, 128.99, 132.42, 134.56, 138.57, 140.97.

(*E*)-2-(p-tolylsulfanyl)hex-2-en-1-ol (**2-1-4d**)



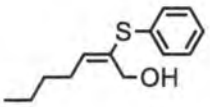
$C_{13}H_{18}OS$ (222.1) Calcd. C 70.22, H 8.16; Found C 70.18, H 8.10.

FTIR (neat) / cm^{-1}: 3380, 2957, 2927, 2869, 1491, 1455, 1086, 997 and 746.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.96 (t, *J*=7.5Hz, 3H), 1.46-1.50 (m, 2H), 2.33 (s, 3H), 2.39 (q, *J*=7.0Hz, 2H), 4.06 (s, 2H), 6.20 (t, *J*=7.0Hz, 1H), 7.10 (d, *J*=8.0Hz, 2H), 7.21 (d, *J*=8.5Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.83, 20.96, 22.36, 31.49, 65.73, 129.79, 129.84, 130.54, 133.10, 136.47, 137.38.

(*E*)-2-(phenylsulfanyl)hept-2-en-1-ol (**2-1-4e**)



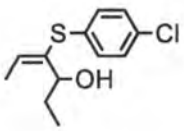
$C_{13}H_{18}OS$ (222.1) Found: C, 70.22, H, 8.16. Calcd. for: C, 70.06, H, 8.30.

FTIR (neat)/ cm^{-1}: 3348, 2955, 2926, 2857, 1476, 1438, 1087, 1008 and 739.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, *J*=7.5Hz, 3H), 1.34-1.45 (m, 4H), 2.40 (q, *J*=7.0Hz, 2H), 4.09 (d, *J*=5.0Hz, 2H), 6.28 (t, *J*=7.0Hz, 1H), 7.19-7.21 (m, 1H), 7.27-7.31 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.86, 22.31, 29.21, 31.18, 65.82, 126.17, 128.97, 129.02, 132.21, 134.58, 138.73.

(*E*)-4-(4-chlorophenylsulfanyl)hex-4-en-3-ol (**2-1-4f**)



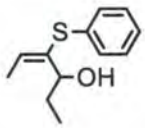
$C_{12}H_{15}ClOS$(242.0).

FTIR (neat) / cm^{-1}: 3388, 2963, 2931, 2874, 1473, 1388, 1091, 1011 and 816.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, *J*=7.5Hz, 3H), 1.58-1.69 (m, 2H), 1.86 (d, *J*=6.5Hz, 3H), 4.07(q, *J*=6.5Hz, 1H), 6.41 (q, *J*=7.0Hz, 1H), 7.18-7.23 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.01, 15.51, 29.09, 77.38, 128.78, 128.99, 131.34, 134.63, 134.83, 135.88.

(*E*)-4-(Phenylsulfanyl)hex-4-en-3-ol (**2-1-4g**)



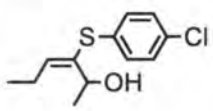
$C_{12}H_{16}OS$ (208.0) Calcd. C 69.19, H 7.74; Found C 69.36, H 8.02.

FTIR (neat) / cm^{-1}: 3405, 2963, 2932, 2874, 1477, 1438, 1024, and 739.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.91 (t, *J*=7.5Hz, 3H), 1.61-1.72 (m, 2H), 1.89(d, *J*=6.5Hz, 3H), 1.94 (d, *J*=6.5Hz, 1H), 4.08 (q, *J*=6.5Hz, 1H), 6.41 (q, *J*=6.5Hz, 1H), 7.31-7.17 (m, 1H), 7.24-7.29 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.03, 15.51, 29.07, 77.35, 125.51, 127.61, 128.91, 134.26, 135.92, 136.06.

(*E*)-3-(4-chlorophenylsulfanyl)hex-3-en-2-ol (**2-1-4h**)



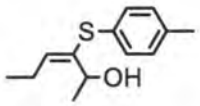
$C_{12}H_{15}ClOS$ (242.0) Calcd. C 59.37, H 6.23; Found C 60.05, H 6.66.

FTIR (neat) / cm^{-1}: 3365, 2967, 2929, 2872, 1474, 1092, 1011 and 815.

^1H NMR ($CDCl_3$, 500 MHz): δ 1.01 (t, *J*=8.0Hz, 3H), 1.35 (d, *J*=6.0Hz, 3H), 1.98 (s, 1H), 2.28-2.33 (m, 2H), 4.29-4.32 (m, 1H), 6.35 (t, *J*=7.5Hz, 1H), 7.18-7.24 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.39, 22.61, 23.17, 71.32, 128.91, 129.02, 131.47, 134.70, 135.53, 140.66.

(*E*)-3-(p-tolylsulfanyl)hex-3-en-2-ol (**2-1-4i**)



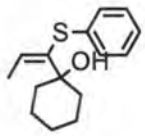
$C_{13}H_{18}OS$ (222.1) Calcd. C 70.22, H 8.16; Found C 70.35, H, 8.30.

FTIR (neat) / cm^{-1}: 3378, 2966, 2928, 2871, 1491, 1118, 1074 and 805.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.02 (t, *J*=7.5Hz, 3H), 1.34 (d, *J*=6.5Hz, 3H), 2.03 (d, *J*=5.5Hz, 1H) 2.31 (s, 3H), 2.33-2.37 (m, 2H), 4.28-4.30 (m, 1H), 6.28 (t, *J*=7.5Hz, 1H), 7.08 (d, *J*=8.0Hz, 2H), 7.18 (d, *J*=8.0Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.51, 20.91, 22.48, 23.11, 70.98, 128.38, 129.73, 132.08, 135.72, 136.35, 139.09.

(*E*)-1-(1-phenylsulfanylpropenyl)cyclohexanol (**2-1-4j**)



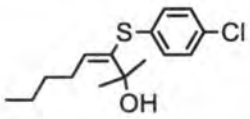
$C_{15}H_{20}OS$ (248.1) Calcd. C 72.53, H 8.12; Found C 72.77, H, 8.33.

FTIR (neat) / cm^{-1}: 3402, 2931, 2853, 1477, 1438 and 737.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.56-1.75 (m, 10H), 1.81 (d, *J*=6.5Hz, 3H), 2.00 (s, 1H), 6.56 (q, *J*=7.0Hz, 1H), 7.09-7.11 (m, 1H), 7.20-7.25 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.21, 21.97, 25.51, 36.32, 74.92, 124.84, 126.19, 128.81, 132.90, 136.90, 140.91.

(*E*)-3-(4-chlorophenylsulfanyl)2-methyl-oct-3-en-2-ol (**2-1-4k**)



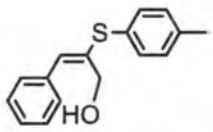
White crystal, mp 44-46 °C (from hexane and ethyl acetate). $C_{15}H_{21}ClOS$ (284.1) Calcd. C 63.25, H 7.43; Found C 63.38, H, 7.56.

FTIR (neat) / cm^{-1}: 3419, 2958, 2927, 2858, 1474, 1091 and 814.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.86 (t, *J*=7.5Hz, 3H), 1.26-1.29 (m, 2H), 1.32-1.36 (m, 2H), 1.43 (s, 6H), 2.20-2.23 (m, 3H), 6.46 (t, *J*=7.0Hz, 1H), 7.14 (d, *J*=9.0Hz, 2H), 7.20 (d, *J*=9.0Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.85, 22.34, 29.21, 30.13, 30.84, 74.31, 127.59, 128.87, 130.75, 135.78, 138.83, 138.87.

(*E*)-3-(phenyl-2-p-tolylsulfanyl)prop-2-en-1-ol (**2-1-4l**)



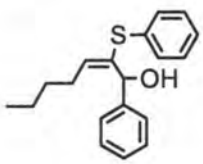
$C_{16}H_{16}OS$ (256.0) Calcd. C 74.96, H 6.29; Found C 74.96, H, 6.39.

FTIR (neat) / cm^{-1}: 3399, 2921, 2869, 1491, 1016, 808 and 759.

^1H NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 4.34(d, *J*=5.5Hz, 1H), 6.84 (s, 1H), 7.18 (d, *J*=7.5Hz, 2H), 7.29 (t, *J*=7.0Hz, 1H), 7.35-7.41 (m, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.11, 60.25, 127.53, 128.43, 128.61, 129.33, 130.13, 132.32, 133.71, 136.02, 137.61, 138.01.

(*E*)-1-(phenyl-2-phenylsulfanyl)hept-2-en-1-ol (**2-1-4m**)



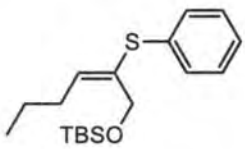
$C_{19}H_{22}OS$ (298.1) Calcd. C 76.46, H 7.43; Found C 76.70, H 7.64.

FTIR (neat) / cm^{-1}: 3365, 2956, 2931, 2870, 1454, 1002 and 759.

^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, *J*=7.5 Hz, 3H), 1.30-1.36 (m, 2H), 1.37-1.42 (m, 2H), 2.33-2.39 (m, 2H), 2.43 (d, *J*=5.0Hz, 1H), 5.22 (d, *J*=5.5 Hz, 1H), 6.39 (t, *J*=7.5Hz, 1H), 7.15-7.18 (m,1H), 7.25-7.35 (m, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.89, 22.39, 29.48, 31.06, 76.75, 125.85, 126.68, 127.75, 128.29, 128.32, 128.94, 134.99, 135.57, 139.99, 141.67.

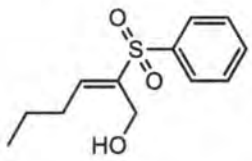
(*E*)-tert-butyl-dimethyl-(2-phenylsulfanyl-hex-2-enyloxy)silane (**2-1-5**)



^1H NMR ($CDCl_3$, 500 MHz): δ 0.02 (s, 6H), 0.90 (s, 9H), 0.94 (t, *J*=7.5Hz, 3H), 1.44-1.49 (m, 2H), 2.38 (q, *J*=7.5Hz, 2H), 4.13 (d, *J*=1.0Hz, 2H), 6.39 (t, *J*=7.5Hz, 1H), 7.15 (t, *J*=4.5Hz, 1H), 7.25 (d, *J*=4.0Hz, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ -5.39, 13.86, 18.37, 22.50, 25.87, 31.31, 65.87, 125.58, 128.14, 128.83, 130.81, 135.77, 136.98.

(*E*)-2-benzenesulfonyl-hex-2-en-1-ol (**2-1-6**)



^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, *J*=7.0Hz, 3H), 1.34-1.38 (m, 2H), 2.50 (q, *J*=7.5Hz, 2H), 4.33 (s, 2H), 6.34 (t, *J*=7.5Hz, 1H), 7.54 (t, *J*=7.0Hz, 2H), 7.62 (t, *J*=7.5Hz, 1H), 7.94 (d, *J*=7.5Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.56, 21.81, 30.29, 63.89, 127.20, 129.13, 133.39, 140.27, 141.34, 146.84.

2.2. Gold-Catalyzed Intramolecular Oxygen Transfer Reaction of 2-Alkynyl-1,5-diketones and 2-Alkynyl-5-Ketoesters

2.2.1 Background and Introduction

The Hammond group has been particularly interested in the interactions of allene and gold.[2d, 33] This led to the finding that 2-alkynyl-1,5-kiketones or 2-alkynyl-5-ketoesters can easily isomerized into 1,5-diketo cyclopentene in the presence of catalytic amounts of gold (I) chloride. This methodology makes available substituted cyclopentenones, which are core structures or precursors of important natural products (Figure 3).[34]

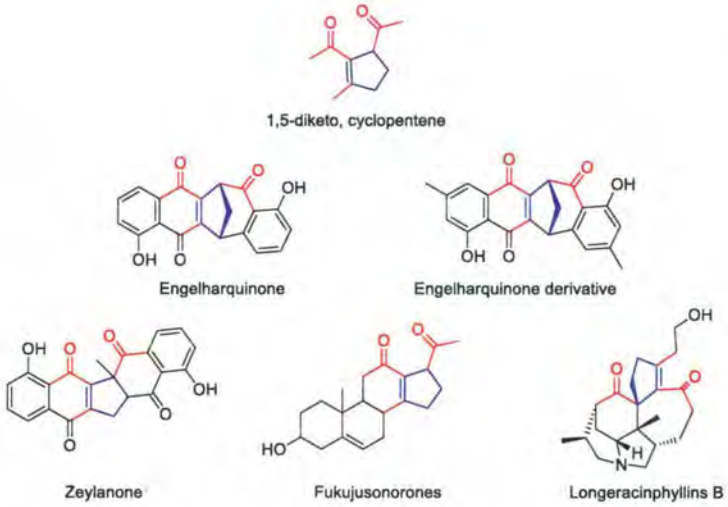


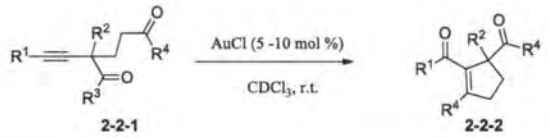
Figure 3. Natural Product Containing the Cyclopentenone Core Structure

Isotopic experiments and theoretical calculations performed by members of the Hammond group supported the novel proposed intramolecular [4+2] cycloaddition of a gold-containing furanium intermediate to a carbonyl group, instead of the previous well-accepted [2+2] pathway.

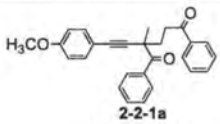
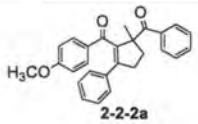
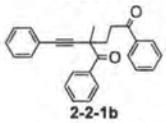
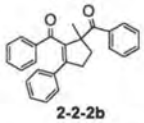
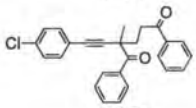
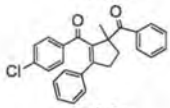
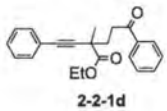
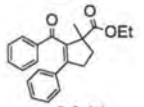
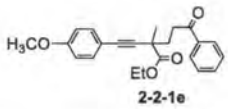
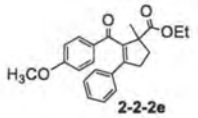
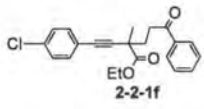
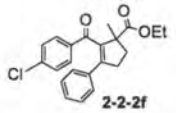
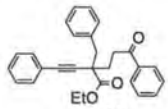
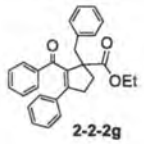
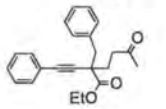
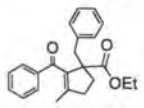
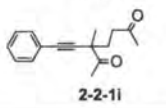
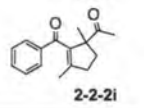
2.2.2 Result and Discussion

From entry 1 to 3, aromatic rings at R^1 were examined, giving excellent yield of 2-2-**2a**, 2-2-**2b**, 2-2-**2c** at room temperature (Table 4).

Table 4. Isomerization of 2-Alkynyl-1,5-Diketones and 2-Alkynyl-5-Ketoesters



2-2-1 2-2-2

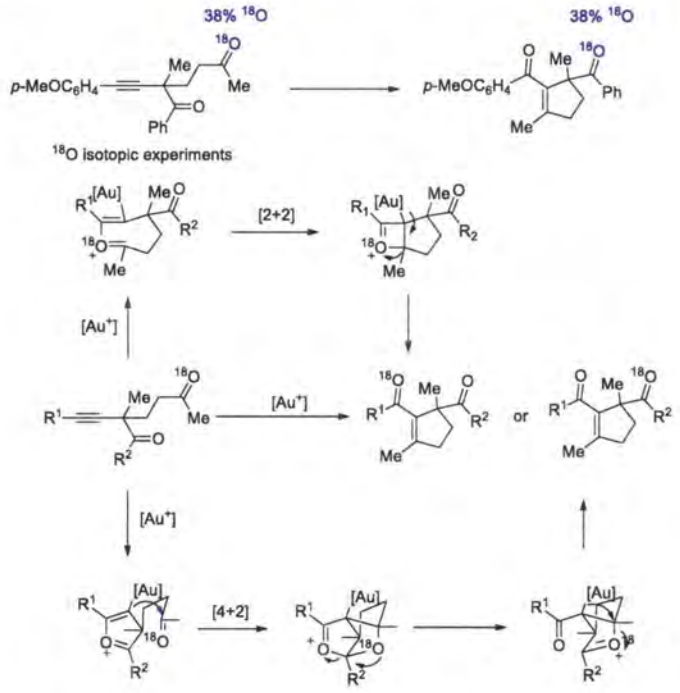
Entry	Substrate	Product	(Yield %)
1	 2-2-1a	 2-2-2a	91%
2	 2-2-1b	 2-2-2b	93%
3	 2-2-1c	 2-2-2c	100%
4	 2-2-1d	 2-2-2d	91%
5	 2-2-1e	 2-2-2e	92 %
6	 2-2-1f	 2-2-2f	92 %
7	 2-2-1g	 2-2-2g	90 %
8[a]	 2-2-1h	 2-2-2h	50 %
9	 2-2-1i	 2-2-2i	92 %

[a] Yield on conversion.

[Note: My participation in this collective work from the Hammond's group was restricted to the isomerization of 2-alkynyl-1,5-diketones and 2-alkynyl-5-ketoesters].

Similarly, the same aromatic rings at R^1 worked equally well with the 2-alkynyl-5-ketoester system (entries 4 to 6). In entries 7 and 8, the benzyl group at R^2 was tested on a 2-alkynyl-5-ketoester system. While substrate **2-2-7a** gave excellent yield, **2-2-8a** was not suitable, affording moderate yields of the desired product, together with an unidentified side product. In the last entry, substrate **2-2-9a**, having two methyl groups at R^3 and R^4, still isomerized well using this methodology.

We proposed a very unique and unprecedented intramolecular [4+2] cycloaddition (Scheme 7) for this transformation, rather than the well-accepted [2+2] cycloaddition.



Scheme 7. ^{18}O Isotopic Labeling Experiment for Mechanistic Studies

Mechanistic investigations on the cycloisomerization were carried out by means of both ^{18}O isotopic experiments and quantum chemical calculations. The results from both, the designed isotopic experiments and theoretical calculations (omitted in this thesis because they were done by Dr. Leping Liu and Professor Kenneth Houk at UCLA), satisfactorily supported the novel proposed intramolecular [4+2] cycloaddition of a gold-containing furanium intermediate to a carbonyl group, instead of the previously accepted [2+2] pathway.[35]

2.2.3 Experimental Section

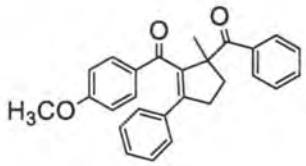
2-Alkynyl-1,5-diketones or 2-alkynyl-5-ketoesters were prepared according to our previously published paper.[2d] Gold(I) chloride was purchased from Aldrich. 2-Alkynyl-1,5-diketone (or 2-alkynyl-5-ketoester) (0.02-0.15 mmol), gold(I) chloride (5-10 mol %) were dissolved in $CDCl_3$ (0.6 mL) in NMR tube and monitored constantly until the reaction was completed. The reaction mixture was then subjected to a short chromatography separation, eluted by a hexane: ethyl acetate system, to give the cyclized product. The products were characterized by ^1H, ^{13}C NMR, HRMS and IR spectra.

Typical procedure for preparation of 2-((4-methoxyphenyl)ethynyl)-2-methyl-1,5-diphenylpentane-1,5-dione (2-2-1a)

4-(4-methoxyphenyl)-2-methyl-1-phenylbuta-2,3-dien-1-one (528.0 mg, 2.0 mmoL), 1-phenylprop-2-en-1-one (396 mg, 3.0 mmoL) and TBAF (0.2 mmoL) were dissolved in THF (3 mL) and stirred at room temperature for 5 h. The reaction mixture was quenched by saturated ammonium chloride (15 mL) and followed by diethyl ether extraction (25 mL×3). The ether layers were combined and dried over anhydrous Na_2SO_4, filtered and

evaporated under reduced pressure, the resulting residue was subjected to silica gel chromatography eluted by hexanes and ethyl acetate system to yield 2-((4-methoxyphenyl)ethynyl)-2-methyl-1,5-diphenylpentane-1,5-dione (**2-2-1a**) (475.0 mg, 60 %).

(5-Benzoyl-5-methyl-2-phenyl-cyclopent-1-enyl)-(4-methoxy-phenyl)-methanone (**2-2-2a**)



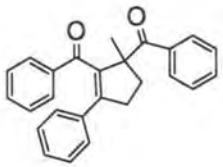
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.90 (d, J = 8.0Hz, 2H), 7.67 (d, J = 8.0Hz, 2H), 7.42 (t, J = 6.8Hz, 1H), 7.35 (t, J = 6.8Hz, 2H), 7.15 (brs, 2H), 7.09 (brs, 3H), 6.62 (d, J = 8.4 Hz, 2H), 3.70 (s, 3H), 3.02-3.29 (m, 1H), 2.95-3.01 (m, 1H), 2.61-2.69 (m, 1H), 2.17-2.23 (m, 1H), 1.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 203.4, 195.1, 162.9, 146.7, 141.1, 137.7, 135.7, 131.8, 131.3, 130.1, 128.6, 128.3, 128.2, 128.1, 113.1, 65.9, 55.2, 36.1, 35.7, 24.2.

HRMS *m/z* (ES^+) calcd for $C_{27}H_{25}O_3$ ($[M+H]^+$) 397.1798, found 397.1790, *m/z* (ES^+) calcd for $C_{27}H_{24}O_3Na$ ($[M+Na]^+$) 419.1618, found 419.1608.

FTIR (neat)/cm^{-1}: 1675, 1637, 1596, 1508, 1334, 1255, 1162, 763, 698.

(5-Benzoyl-5-methyl-2-phenyl-cyclopent-1-enyl)-phenylmethanone (**2-2-2b**)



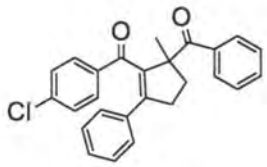
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.90 (d, J = 7.2Hz, 2H), 7.65 (d, J = 7.6Hz, 2H), 7.44 (t, J = 7.2Hz, 1H), 7.37 (t, J = 7.6Hz, 2H), 7.24 (t, J = 7.6Hz, 1H), 7.05-7.13 (m, 7H), 3.22-3.29 (m, 1H), 3.00-3.09 (m, 1H), 2.64-2.72 (m, 1H), 2.22-2.28 (m, 1H), 1.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 203.3, 196.5, 148.6, 141.2, 137.4, 137.3, 135.6, 132.1, 131.5, 129.5, 128.6, 128.4, 128.3, 128.1, 127.9, 127.7, 66.2, 36.4, 35.8, 24.3.

HRMS m/z (ES^+) calcd for $C_{26}H_{23}O_2$ ($[M+H]^+$) 367.1693, found 367.1687, m/z (ES^+) calcd for $C_{26}H_{22}O_2Na$ ($[M+Na]^+$) 389.1512, found 389.1505.

FTIR (neat)/cm^{-1}: 1674, 1637, 1447, 1277, 1251, 968, 725, 693.

(5-Benzoyl-5-methyl-2-phenyl-cyclopent-1-enyl)-(4-chloro-phenyl)-methanone (**2-2-2c**)



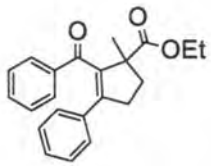
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.88 (d, J = 8.0Hz, 2H), 7.60 (d, J = 8.0Hz, 2H), 7.46 (t, J = 7.2Hz, 1H), 7.38 (t, J = 7.6Hz, 2H), 7.10 (brs, 7H), 3.17-3.25 (m, 1H), 3.04-3.12 (m, 1H), 2.64-2.72 (m, 1H), 2.26-2.72 (m, 1H), 1.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 203.4, 195.4, 148.5, 140.8, 138.3, 136.8, 135.8, 135.4, 131.7, 130.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 66.8, 36.3, 36.0, 24.6.

HRMS *m/z* (ES^+) calcd for $C_{26}H_{22}O_2Cl$ ($[M+H]^+$) 401.1303, found 401.1297, *m/z* (ES^+) calcd for $C_{26}H_{21}O_2NaCl$ ($[M+Na]^+$) 423.1122, found 423.1113.

FTIR (neat)/cm^{-1}: 1674, 1637, 1576, 1275, 1251, 1089, 968, 747, 697.

2-Benzoyl-1-methyl-3-phenyl-cyclopent-2-enecarboxylic acid ethyl ester (**2-2-2d**)



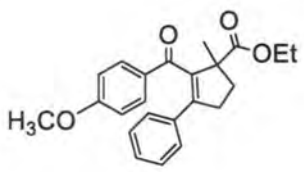
^1H NMR ($CDCl_3$, 400MHz) δ 7.65 (d, *J* = 8.0Hz, 2H), 7.26 (t, *J* = 7.6Hz, 1H), 7.09-7.13 (m, 4H), 7.03-7.06 (m, 3H), 3.93-4.05 (m, 2H), 3.10-3.18 (m, 1H), 2.92-2.98 (m, 1H), 2.54-2.59 (m, 1H), 2.00-2.06 (m, 1H), 1.62 (s, 3H), 1.00 (t, *J* = 7.2Hz, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 197.0, 175.7, 148.7, 139.4, 137.3, 135.6, 132.3, 129.4, 128.2, 128.2, 127.9, 127.8, 60.8, 59.9, 36.4, 35.7, 23.1, 13.8.

HRMS *m/z* (ES^+) calcd for $C_{22}H_{23}O_3$ ($[M+H]^+$) 335.1642, found 335.1637, *m/z* (ES^+) calcd for $C_{22}H_{22}O_3Na$ ($[M+Na]^+$) 357.1461, found 357.1456, *m/z* (ES^+) calcd for $C_{19}H_{17}O$ ($[M-COOEt]^+$) 261.1279, found 261.1272.

FTIR (neat)/cm^{-1}: 1731, 1646, 1447, 1279, 1254, 1173, 1093, 696.

2-(4-Methoxy-benzoyl)-1-methyl-3-phenyl-cyclopent-2-enecarboxylic acid ethyl ester (**2-2-2e**)



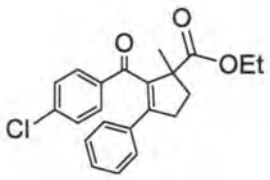
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.67 (d, J = 8.8Hz, 2H), 7.14 (brs, 2H), 7.07 (brs, 3H), 6.64 (d, J = 8.4Hz, 2H), 3.91-4.05 (m, 2H), 3.72 (s, 3H), 3.10-3.18 (m, 1H), 2.87-2.94 (m, 1H), 2.54-2.61 (m, 1H), 1.97-2.04 (m, 1H), 1.58 (s, 3H), 1.00 (t, J = 7.2Hz, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 195.7, 175.7, 163.0, 146.8, 139.2, 135.7, 131.8, 130.3, 128.2, 128.1, 127.9, 113.1, 60.8, 60.0, 55.3, 36.3, 35.4, 23.2, 13.8.

HRMS *m/z* (ES^+) calcd for $C_{23}H_{25}O_4$ ($[M+H]^+$) 365.1747, found 365.1741, *m/z* (ES^+) calcd for $C_{23}H_{24}O_4Na$ ($[M+Na]^+$) 387.1567, found 387.1560, *m/z* (ES^+) calcd for $C_{20}H_{19}O_2$ ($[M-COOEt]^+$) 291.1385, found 291.1377.

FTIR (neat)/cm^{-1}: 1729, 1637, 1597, 1507, 1256, 1162, 1093, 1027, 760, 697.

2-(4-Chloro-benzoyl)-1-methyl-3-phenyl-cyclopent-2-enecarboxylic acid ethyl ester (**2-2-2f**)



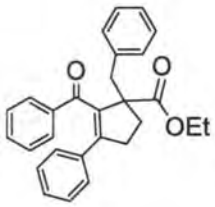
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.59 (d, J = 7.6Hz, 2H), 7.08 (brs, 7H), 3.95-4.07 (m, 2H), 3.10-3.17 (m, 1H), 2.88-3.10 (m, 1H), 2.51-2.58 (m, 1H), 2.00-2.06 (m, 1H), 1.62 (s, 3H), 1.02 (t, J = 6.8Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.7, 175.6, 149.2, 139.1, 138.5, 135.8, 135.4, 130.8, 128.6, 128.2, 128.1, 128.1, 60.8, 60.1, 36.5, 35.7, 23.2, 13.9.

HRMS *m/z* (ES^+) calcd for $C_{22}H_{22}O_3Cl$ ($[M+H]^+$) 369.1252, found 369.1248, *m/z* (ES^+) calcd for $C_{22}H_{21}O_3ClNa$ ($[M+Na]^+$) 391.1071, found 391.1064, *m/z* (ES^+) calcd for $C_{19}H_{16}OCl$ ($[M-COOEt]^+$) 295.0890, found 295.0881.

FTIR (neat)/cm^{-1}: 1732, 1646, 1278, 1253, 1166, 1091, 860, 755, 697.

Ethyl 2-benzoyl-1-benzyl-3-phenylcyclopent-2-enecarboxylate (**2-2-2g**)



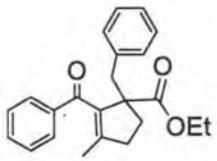
^1H NMR ($CDCl_3$, 400MHz) δ 7.68 (d, *J* = 7.2Hz, 2H), 7.38 (d, *J* = 6.8Hz, 2H), 7.28 (t, *J* = 7.6Hz, 1H), 7.13-7.25 (m, 6H), 7.01 (brs, 4H), 3.88-4.03 (m, 2H), 3.70 (d, *J* =13.6Hz, 1H), 3.33 (d, *J* = 13.6Hz, 1H), 2.75-2.83 (m, 1H), 2.46-2.54 (m, 1H), 2.27-2.32 (m, 1H), 1.77-1.86 (m, 1H), 0.94 (t, *J* = 6.8Hz, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 197.8, 175.1, 151.1, 137.5, 136.2, 135.6, 132.2, 130.6, 129.5, 128.2, 128.0, 127.8, 127.8, 127.7, 126.5, 65.3, 61.0, 42.3, 35.7, 32.7, 13.7.

HRMS *m/z* (ES^+) calcd for $C_{28}H_{27}O_3$ ($[M+H]^+$) 411.1955, found 411.1949, *m/z* (ES^+) calcd for $C_{28}H_{26}O_3Na$ ($[M+Na]^+$) 433.1774, found 433.1762, (ES^+) calcd for $C_{25}H_{21}O$ ($[M-COOEt]^+$) 337.1592, found 337.1583.

FTIR (neat)/cm^{-1}: 1727, 1642, 1447, 1278, 1247, 1175, 697.

2-Benzoyl-1-benzyl-3-methyl-cyclopent-2-enecarboxylic acid ethyl ester (**2-2-2h**)



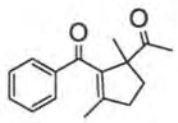
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, J = 7.5Hz, 2H), 7.55 (t, J = 8.0Hz, 1H), 7.45 (t, J = 8.0Hz, 2H), 7.25 (brs, 2H), 7.20 (brs, 3H), 4.00-4.08 (m, 2H), 3.64 (d, J =13.0Hz, 1H), 3.24 (d, J = 13.0Hz, 1H), 2.18-2.27 (m, 1H), 2.11-2.16 (m, 2H), 1.36-1.40 (m, 4H), 1.04 (t, J =7.0Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.3, 175.7, 151.5, 139.3, 137.8, 135.7, 132.5, 130.6, 129.3, 128.3, 127.6, 126.2, 64.2, 60.8, 41.5, 37.7, 32.6, 16.8, 13.8.

HRMS *m/z* (ES^+) calcd for $C_{23}H_{25}O_3$ ($[M+H]^+$) 349.1798, found 349.1799, *m/z* (ES^+) calcd for $C_{23}H_{24}O_3Na$ ($[M+Na]^+$) 371.1618, found 371.1614, *m/z* (ES^+) calcd for $C_{20}H_{19}O$ ($[M-COOEt]^+$) 275.1436, found 275.1431.

FTIR (neat)/cm^{-1}: 1728, 1643, 1447, 1280, 1238, 1172, 1074, 703.

1-(2-Benzoyl-1,3-dimethyl-cyclopent-2-enyl)-ethanone (**2-2-2i**)



^{1}H NMR ($CDCl_3$, 400MHz) δ 7.75 (d, J = 7.6Hz, 2H), 7.52 (t, J = 7.2Hz, 1H), 7.42 (t, J = 7.6Hz, 2H), 2.61-2.66 (m, 2H), 2.09-2.17 (m, 4H), 1.78-1.83 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 210.7, 196.1, 150.1, 140.4, 139.2, 132.6, 129.0, 128.5, 64.8, 38.7, 34.9, 25.7, 22.0, 17.3.

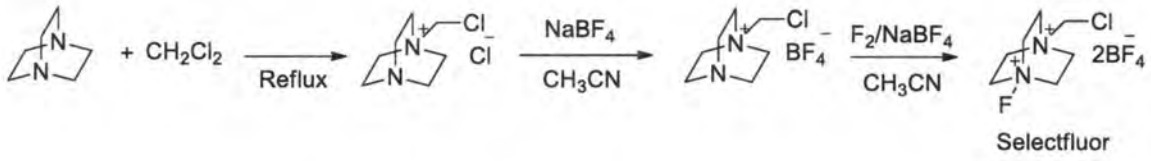
HRMS *m/z* (ES^+) calcd for $C_{16}H_{19}O_2$ ($[M+H]^+$) 243.1380, found 243.1381, *m/z* (ES^+) calcd for $C_{16}H_{18}O_2Na$ ($[M+Na]^+$) 265.1199, found 265.1199.

FTIR (neat)/cm^{-1}: 1706, 1640, 1447, 1346, 1281, 739, 696.

3. EXPLORATION OF THE CHEMISTRY OF SELECTFLUOR

3.1 Selectfluor™

Recently, a number of N-F fluorinating agents have been emerged as electrophilic fluorinating agents, which are easy to handle, safe and stable. They are either quaternary ammonium salt $R_3N^+F\ A^-$ or R_2NF,[36] in which Selectfluor™ (F-TEDA-BF_4) (Scheme 8) is one of cheapest and most reactive ones.[37] Selectfluor is commercially prepared by Air Products by following process shown in Scheme 8.[38]



Scheme 8. Commercially Synthetic pathway for Selectfluor

There are many nice examples of fluorination by Selectfluor in literature.[39] Selectfluor can fluorinate electron rich aromatic systems[40], aliphatic hydrocarbon,[41] aliphatic amines[42], alkenes and their derivatives[43] and asymmetric fluorination.[44] In addition to fluorination, Selectlfuor can be oxidant for functional groups transformation,[45] halogens (iodine),[46] C-H functionalization,[47] gold catalyzed oxidative C-C and C-heteroatom bond formation,[48] palladium catalyzed C-C and C-heteroatom bond formation.[49]

In this section, Selectfluor will be explored as fluorinating agent to prepare fluoroalkyl (*E*) α,β-unsaturated ketones, which are very important intermediates for synthesis of bioactive agents. Then, combination of copper and selectfluor was found as a powerful oxidant, which readily oxidizes amide into imide at room temperature.

3.2. Stereoselective Synthesis of Fluoroalkyl α,β-Unsaturated Ketones

3.2.1 Background

Monofluoroalkyl α, β-unsaturated ketones **3-2-1**, such as **A**,[50] **B**[51] and **C**,[52] are important molecular synthons, as showcased by their use in the synthesis of numerous bioactive agents (Figure 4).[50-53] Fluoroketone **3-2-1** is most commonly synthesized either by using a fluorine-containing building block or through the fluorination of an unsaturated ketone. But the above literature methodologies have limitations.

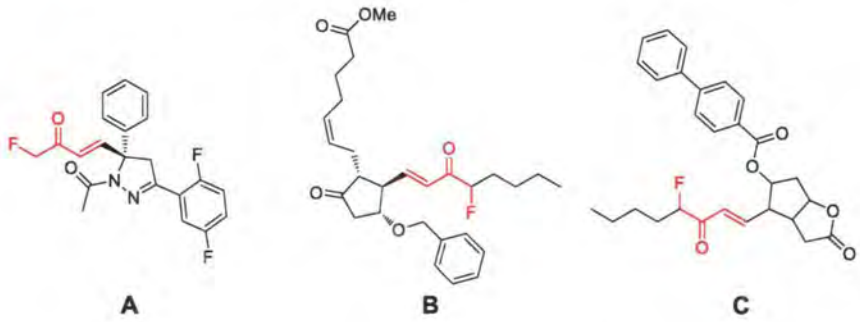
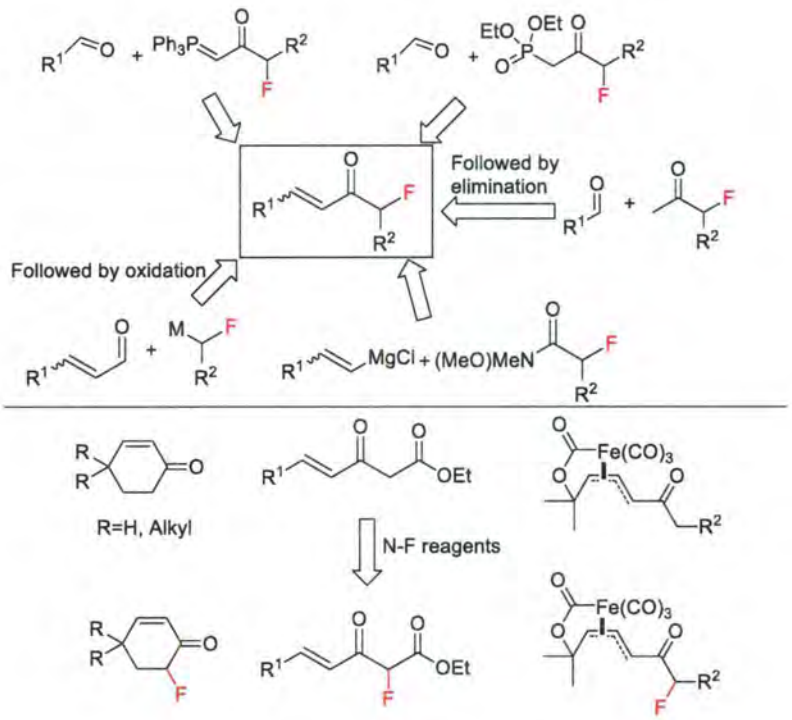
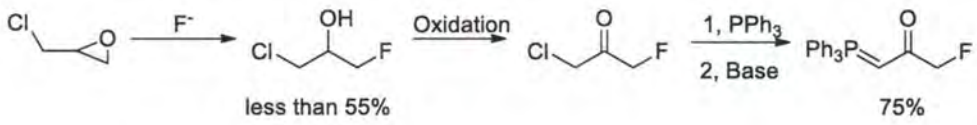


Figure 4. Monofluoroalkyl (*E*)-α,β-Unsaturated Ketones **A**, **B** and **C** are Important Building Blocks for Bioactive Agents

The building block approach relies on a shallow pool of fluorine containing moiety (Scheme 9, top), [50-54] whose preparation is not always trivial; for example, the synthesis of fluorine-containing Wittig reagents is lengthy and inefficient (Scheme 10).[54a, 54d, 55]



Scheme 9. Literature Construction of Monofluoroalkyl α,β-Unsaturated Ketones by Fluorine Containing Building Blocks (Top) and Fluorination of Specific Ketones (Bottom)

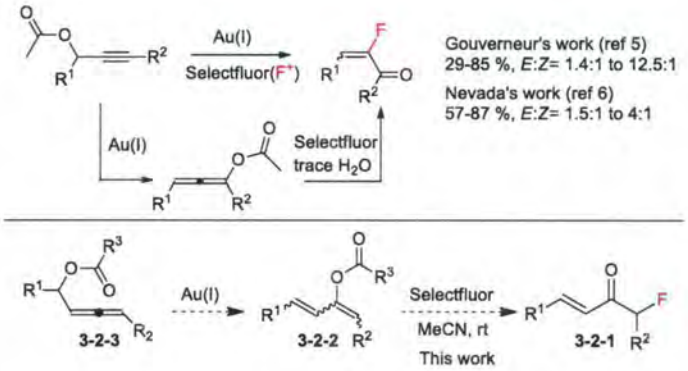


Scheme 10. Lengthy Preparation Pathway for a Fluorine-Containing Wittig Reagent

On the other hand, the fluorination approach[56] is hampered by the fact that regioselective fluorination of the starting unsaturated ketone is case specific (Scheme 9, Bottom). Owing to these limitations, medicinal chemists find it difficult to build libraries of fluoroalkyl α,β-unsaturated ketone. An efficient preparation of the said ketones is highly desirable.

3.2.2 Our Efficient Strategy to Prepare Ketone 3-2-1

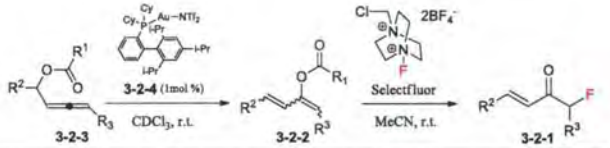
Inspired by the works of Gouverneur [57] and Nevado[58] (Scheme 11, top), we envisioned an environmentally friendly and efficient fluorination process to overcome aforementioned drawbacks (Scheme 11, bottom). We posited that an electron rich 1,3-butadien-2-ol ester **3-2-2** could be a suitable substrate for electrophilic fluorination. The diene **3-2-2** is readily made by the gold-catalyzed isomerization of allenyl carbinol ester **3-2-3** using Gagosz's methodology.[59] Gagosz and co-workers had reported that terminal allenyl carbinol ester **3-2-3** isomerize to 1,3-butadien-2-ol ester **3-2-2** with moderate to good stereoselectivity in presence of gold catalyst **3-2-4**.

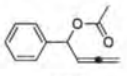
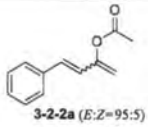
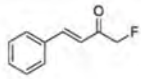
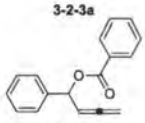
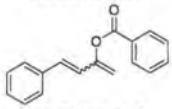
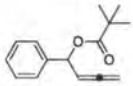
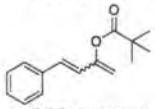
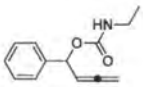
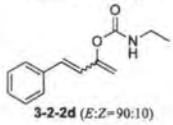
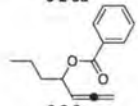
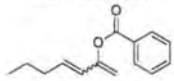
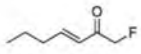
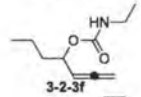
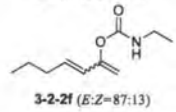
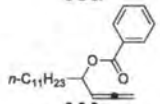
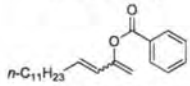
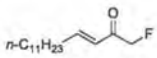
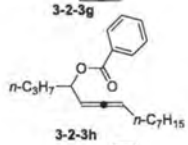
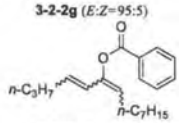
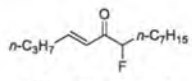
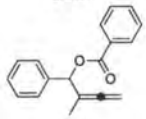
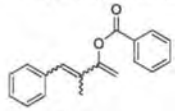
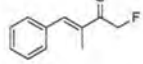
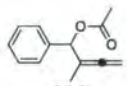
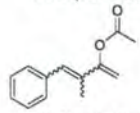


Scheme 11. Gold-catalyzed Isomerization of Alkyne and Allene and Following Fluorination Strategy

In this chapter we report that a stereomixture of **3-2-2** can be fluorinated at room temperature by Selectfluor to give fluoroalkyl α,β-unsaturated ketone **3-2-1** in high yields and with exclusive *E* stereoselectivity. All results are shown in Table 5.

Table 5. Preparation of α,β-Unsaturated Ketones **3-2-1** from *in Situ* Generated Dienes **3-2-2**.[a]



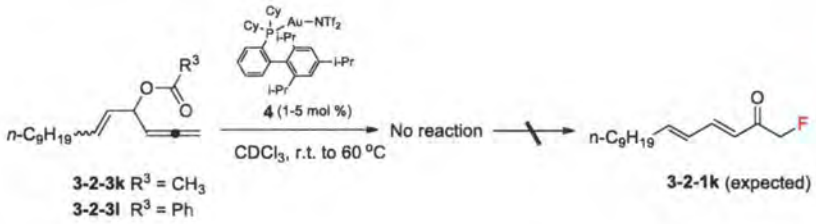
Entry	Substrate (1)	Dienes (2)	Ketone (3), Yield [b]
1	 **3-2-3a**	 **3-2-2a** (*E*:*Z*=95:5)	 **3-2-1a**, 90%(*E*:*Z*=99:1)
2	 **3-2-3b**	 **3-2-2b** (*E*:*Z*=95:5)	**3-2-1a**, 95%(*E*:*Z*=99:1)
3	 **3-2-3c**	 **3-2-2c** (*E*:*Z*=95:5)	**3-2-1a**, 96%(*E*:*Z*=99:1)
4	 **3-2-3d**	 **3-2-2d** (*E*:*Z*=90:10)	**3-2-1a**, 95%(*E*:*Z*=99:1)
5	 **3-2-3e**	 **3-2-2e** (*E*:*Z*=95:5)	 **3-2-1e**, 95%(*E*:*Z*=99:1)[c]
6	 **3-2-3f**	 **3-2-2f** (*E*:*Z*=87:13)	**3-2-1e**, 80%(*E*:*Z*=99:1)[c]
7	 **3-2-3g**	 **3-2-2g** (*E*:*Z*=95:5)	 **3-2-1g**, 83%(*E*:*Z*=99:1)[d]
8	 **3-2-3h**	 **3-2-2h** (1:0.41:0.68:0.87)	 **3-2-1h**, 72%(*E*:*Z*=99:1)[d]
9	 **3-2-3i**	 **3-2-2i** (*E*:*Z*=87:13)	 **3-2-1i**, 79%(*E*:*Z*=99:1)[d]
10	 **3-2-3j**	 **3-2-2j** (*E*:*Z*=87:13)	**3-2-1i**, 70%(*E*:*Z*=97:3)[d]

[a] Reaction condition: allenyl carbinol ester (**3-2-3**) (0.25 M) and the gold catalyst **3-2-4** (1 mol %) in $CDCl_3$ and monitored by ^{1}HNMR until no progress. Then $CDCl_3$ was dried in vacuum, Selectfluor (1.2 equiv.) and acetonitrile (1.5 mL) were added and stirred for 3 h. [b] Yield was calculated on starting allenyl carbinol ester (**3-2-3**). [c] ^{19}F NMR yield due to their volatility, 𝔅,𝔅,𝔅 -trifluorotoluene as internal standard. [d] Yield of allylic alcohol owing to their instability on long silica gel column. Allylic alcohols of **3-2-1g** and **3-2-1h** contain less than 3 % of corresponding saturated alcohol. d.r. of the allylic alcohol (from **3-2-1h**) is 4:1.

Carbinol ester **3-2-3a** (entry 1) isomerizes to diene **3-2-2a** in $CDCl_3$ in the presence of gold catalyst **3-2-4**,[60] and diene **3-2-2a** reacts readily with Selectfluor in MeCN to yield the corresponding fluorinated ketone **3-2-1a** in excellent yield and with exclusive *E* stereoselectivity.[61] It is noteworthy that dienes **3-2-2a** (*E*:*Z* = 95:5), during fluorination, yielded exclusively the *E* isomer. There are two possibilities to produce exclusively fluoroalkyl (*E*)-α,β-unsaturated ketone **3-2-1a**. First, the (*Z*)-diene **3-2-2a** may be isomerized, upon fluorination, into *E* stereomer and give *E* ketone **3-2-1a** after subsequent hydrolysis. Secondly, (*E*)-diene **3-2-2a** is probably more reactive, than (*Z*)-diene **3-2-2a**, with Selectfluor and no fluorine cation-enabled isomerization happened. The isomerization is proposed as main pathway to give exclusively *E* ketone, since unreacted (*E*)-diene **3-2-2a** and corresponding side products were failed to be isolated. Similarly, aromatic substrates **3-2-3b**, **3-2-3c** and **3-2-3d** isomerized to the corresponding dienes **3-2-2** as a mixture of *E*/*Z* isomers, but upon fluorinations, these isomers afforded **3-2-1a** in high stereoselectivity and excellent chemical yields, regardless of the type of carboxylic acid derivatives used. Aliphatic allenyl esters **3-2-5e** (entry 5) and **3-2-6f** (entry 6) were also examined. Both of them efficiently isomerized and were fluorinated to give **3-2-3e** (*E*:*Z* = 99:1) in good yield.[62] The high molecular weight aliphatic allenyl ester **3-2-3g** (entry 7) was tested in order to isolate the desired pure product (not volatile). Because all substrates used in Gagosz's work were terminal allenyl esters, we were intrigued as to how would an internal allenyl ester such **3-2-3h** behave under our reaction conditions (entry 8). We were pleasantly surprised to discover that even though **3-2-3h** isomerized readily to give a complex mixture of stereoisomers **3-2-2h** (1:0.41:0.68:0.87), this mixture produced the desired **3-2-1h** in good yield as a single *E*-isomer. Benzoate

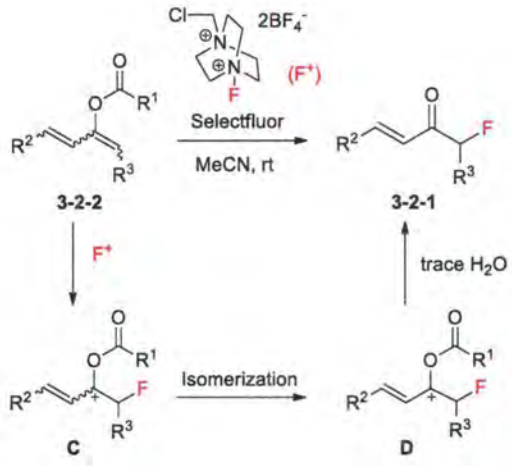
and acetate derivatives of 1,1-disubstituted allenyl esters **3-2-3i** and **3-2-3j** were also tested (entries 9 and 10). Their isomerizations furnished dienes **3-2-2i** and **3-2-2j**, respectively, but after fluorination, only **3-2-1i** was obtained in very good yield and with exclusive *E* selectivity.

We also investigated the possibility of preparing fluoroalkyl *E*,*E*-α,β,γ,δ-unsaturated ketone **3-2-1k** using our protocol, but, unfortunately, this attempt failed because no isomerization of the two substrates tested, **3-2-3k** and **3-2-3l**, took place in the presence of gold catalyst **3-2-4** (Scheme 12).



Scheme 12. Limitations of Our Protocol

A plausible mechanism for the isomerization of a diene mixture is proposed in Scheme 13. The electron-rich double bond of diene **3-2-2** attacks the electrophilic fluorine in Selectfluor to form cationic intermediate **C**, which instantly isomerizes to form the more stable intermediate **D**, and after hydrolysis with trace amounts of water present in the reaction media, yields fluoroalkyl *E*-α,β-unsaturated ketone **3-2-1**.



Scheme 13. Proposed Mechanism for Fluorinated Cation Enabled Isomerization

The reported electrophilic fluorination-nucleophilic addition reactions of glycals[63] and other substrates[57] using Selectfluor lend support to our proposal. It is likely that in our case an electrophilic fluorinated cation-enabled isomerization occurred to form the most stable stereoisomer before nucleophilic attack of trace water from the reaction mixture happened.

3.2.3 Summary

Our protocol can efficiently fluorinate a mixture of dienes **3-2-2** under mild conditions to give fluoroalkyl *E*-α,β-unsaturated ketone **3-2-1** in good to excellent yield. Because all starting allenyl alcohols can be readily prepared using literature methodologies[64] our methodology can be used to prepare a large variety of fluoroalkyl *E*-α,β-unsaturated ketones. These ketones could be further functionalized; a case in point is the conversion to a fluorosugar precursor[65] through dihydroxylation of a double bond.[54a]

3.2.4 Experimental Section

General

The gold complex (**3-2-4**) and Selectfluor were purchased from Aldrich. All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a Combiflash system or Chromatotron apparatus or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 500 (or 400), 126 (or 100) and 470 (or 376) MHz respectively, using $CDCl_3$ (or CD_3CN) as a solvent. The chemical shifts are reported in δ (ppm) values relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) and $CFCl_3$ (0 ppm for ^{19}F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. RTIR spectra were recorded in ATR (attenuated total reflection) solid mode using a Perkin Elmer Spectrum 100.

Experimental procedure

1. Preparation of allenyl alcohol

Allenyl alcohol precursors of **3-2-3a**, **3-2-3e** and **3-2-3g** were prepared by Crabbe reaction.[64a]

1-Phenylprop-2-yn-1-ol (396.0 mg, 3.0 mmoL), paraformaldehyde (180.0 mg, 6.0 mmoL), diisopropylamine (834.0 μL, 6.0 mmoL), CuBr (257.4 mg, 1.8 mmoL) and 1,4-dioxane (20 mL) were added into 50 mL round bottom reaction flask containing stir bar, and the flask was equipped with reflux condenser. The reaction mixture was refuxed in oil bath for 2 h, cooled to room temperature and filtered through silica gel (about 15 g) and washed by mixture of hexanes and ethyl acetate (100 mL, ration is 4:1). The solvent was removed in vacuum and the resulting residue was purified on silica gel column, which was eluted by hexanes and ethyl acetate to give 1-phenylbuta-2,3-dien-1-ol (292.0 mg, 67 %).

Allenyl alcohol precursor of **3-2-3h** was prepared by Ma's methodology.[64b]

Hex-1-yn-3-ol (556.2 μL, 5.0 mmoL), octanal (779.5 μL, 5.0 mmoL), morpholine (691.2 μL, 8.0 mmoL), ZnI_2 (1276 mg, 4.0 mmoL) and toluene (20 mL) were added into 50 mL round bottom reaction flask containing stir bar, and the flask was equipped with refluxing condenser. The reaction mixture was refluxed for 8 h in oil bath, cooled to room temperature and filtered through silica gel (about 20 g) and washed by mixture of hexanes and ethyl acetate (120 mL, ration is 4:1). The solvent was removed in vacuum and the resulting residue was purified on silica gel column, which was eluted by hexanes and ethyl acetate to give tetradeca-5,6-dien-4-ol (262.5 mg, 25 %).

Allenyl alcohol precursor of **3-2-3i** was prepared by Harada's methodology.[64c]

Stannous chloride (568.8 mg, 3.0 mmoL), 1-bromo-2-butyne (262.55 μL, 3.0 mmoL), sodium iodide (450.0 mg, 3.0 mmoL) and DMF (5 mL) were added into 10 mL reaction

flask containing stir bar, and the reaction mixture was stirred for 1.5 h at room temperature. Then the reaction mixture was cooled at 0 °C, and benzaldehyde (305.7 55 μL, 3.0 mmoL) in DMF (1 mL) was added dropwise and stirred for overnight. The reaction mixture was quenched by saturated ammonium chloride (20 mL) and followed by diethyl ether extraction (25 mL×4). The ether layers were combined and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, the resulting residue was subjected to silica gel chromatography eluted by hexanes and ethyl acetate system to yield 2-methyl-1-phenylbuta-2,3-dien-1-ol (384.0 mg, 80 %).

2. Esterification of allenyl alcohol

Allenyl carbinol esters (**3-2-3**) were prepared from allenyl alcohols under standard conditions.[59a]

1-Phenylbuta-2,3-dien-1-ol (292.1 mg, 2.0 mmoL), and triethylamine (417 μL, 3 mmol) were dissolved in dry dichloromethane (5.0 mL) at 0°C, in which the acetyl chloride (213 μL, 3 mmol) was added slowly over a 5 min period, and stirred for 10 min at 0 °C. The resulting solution was stirred for 5 h at room temperature, and then saturated ammonium chloride solution (20 mL) was added to the reaction mixture, followed by diethyl ether extraction (25 mL×3). The ether layers were combined and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield **3-2-3a** (357.2 mg, 95%).

3. Isomerization of allenyl carbinol esters (3-2-3) by gold complex 3-2-4.[59a]

Allenyl carbinol esters (**3-2-3**) (0.25 mmol) and gold complex (**3-2-4**) (1 mol %) were dissolved in $CDCl_3$ (1 mL), and stirred at room temperature and monitored by ^{1}H-NMR until the reaction was completed. All allenyl carbinol esters **3-2-3** efficiently isomerized into dienes **3-2-2**, and NMR yields were at least 95 %.

4. Fluorination of dienes (3-2-2) with Selectfluor

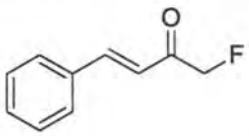
The solvent ($CDCl_3$) in the above reaction was carefully removed in vaccum, and Selectfluor (106 mg, 1.2 equiv.) and acetonitrile (1.5 mL) were added and stirred at room temperature for 3 h.

For **3-2-1a**, the reaction mixture was subjected to short silica gel chromatography separation, which was eluted by gradient elution of hexanes and ethyl acetate.

For **3-2-1e**, α,α,α-trifluorotoluene (12.5 μL, 0.1 mmol) and CD_3CN (0.5 mL) were added into reaction mixture to measure ^{19}F NMR yield.

For **3-2-1g**, **3-2-1h** and **3-2-1i**, the reaction mixture was filtered through approximately 10 g of silica gel, and washed by mixture of hexanes and ethyl acetate (4:1, 70 mL). Then, the solvent was evaporated, and the residue was dissolved in methanol (2-3 mL). $CeCl_3 \cdot 7 H_2O$ (186 mg, 0.4 mmol) was added into the methanol solution and the solution was placed at 0 °C (ice bath), and $NaBH_4$ (15 mg, 0.4 mmol) was added over 15 min, and the reaction was stirred for another 20 min at room temperature. Then the mixture was directly subjected to silica gel chromatography, eluted by a hexane-ethyl acetate system to give the corresponding allylic alcohols.

(*E*)-1-fluoro-4-phenylbut-3-en-2-one (**3-2-1a**)



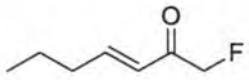
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 16.5 Hz, 1H), 7.61 (m, 2H), 7.44 (m, 3H), 7.03 (dt, J = 16.0, 2.0 Hz, 1H), 5.05 (dd, J = 47.5, 1.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.84 (d, J = 18.3 Hz), 145.09 (d, J = 3.1 Hz), 134.06, 131.20, 129.06, 128.73, 119.77, 84.78 (J = 184.1 Hz)

^{19}F NMR (470 MHz): δ -228.68 (dt, J = 47.5, 2.4 Hz).

FTIR (ATR, Attenuated Total Relextance)/ cm^{-1}: 3029, 2927, 1709, 1689, 1607, 1576, 1495, 1450, 1333, 1202, 1167, 1036, 998, 977, 748, 688.

(*E*)-1-fluorohept-3-en-2-one (**3-2-1e**)

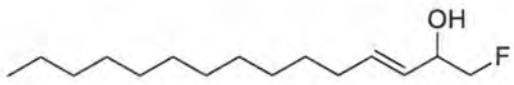


NMR spectra was performed on mixture of **1e** and ethyl acetate.

^{1}H NMR (500 MHz, $CDCl_3$): (significant peaks) δ 7.05 (dt, J = 16.0, 6.6 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 47.5Hz, 2H), 2.26 (m, 2H).

^{19}F NMR (470 MHz): δ -229.53 (t, J = 47.9 Hz).

(*E*)-1-fluoropentadec-3-en-2-ol, derived from (**3-2-1g**)



Contain less than 3 % saturated alcohol.

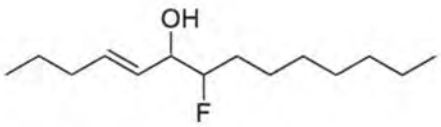
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (dt, J = 15.2, 8.0 Hz, 1H), 5.41 (dd, J = 15.6, 6.4 Hz, 1H), 4.45 (m, 0.5H), 4.34 (m, 2H), 4.20 (m, 0.5H), 2.04 (q, J = 6.8 Hz,1H), 1.25-1.39 (m, 18H), 0.87 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.54 (d, J = 1.5 Hz), 125.89 (d, J = 8.5 Hz), 86.36 (d, J = 171.2 Hz), 71.48 (d, J = 19.4 Hz), 32.31, 31.89, 29.64, 29.61, 29.56, 29.44, 29.32, 29.12, 28.91, 22.66, 14.09.

^{19}F NMR (376 MHz): δ -225.54 (dt, J = 48.1, 17.7 Hz).

FTIR (ATR)/ cm^{-1}: 3420, 2924, 2854, 1466, 1012.

(*E*)-7-fluorotetradec-4-en-6-ol (dr = 4:1), derived from (**3-2-1h**)



Contain less than 3 % saturated alcohol.

Major diastereomers:

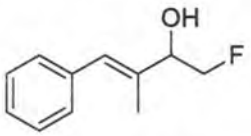
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (dt, J = 15.2, 7.2 Hz, 1H), 5.42 (dd, J = 15.6, 7.6 Hz, 1H), 4.37 (m, 0.5H), 4.23 (m, 0.5H), 4.05 (m, 1H), 2.04 (m, 2H), 1.26-1.62 (m, 14H), 0.87 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.47, 127.34 (d, J = 7.0 Hz), 96.61 (d, J = 171.1 Hz), 74.72 (d, J = 20.9 Hz), 34.38, 31.72, 30.94, 29.34, 29.09, 24.93, 22.59, 22.08, 14.04, 13.61.

^{19}F NMR (376 MHz): δ -192.30 (m).

FTIR (ATR)/ cm^{-1}: 3427, 2926, 2857, 1464, 970.

(*E*)-1-fluoro-3-methyl-4-phenylbut-3-en-2-ol, derived from (**3-2-1i**)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 2H), 7.27 (m, 3H), 6.67 (s, 1H), 4.61 (dd, J = 9.0, 2.5 Hz, 0.5H), 4.51 (m, 2H), 4.39 (t, J = 7.5 Hz, 0.5H), 1.92 (d, J = 1.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.95, 134.67 (d, J = 7.0 Hz), 128.97, 128.16,127.73 (d, J = 1.6 Hz), 126.79, 85.73 (d, J = 172.2 Hz), 75.80 (d, J = 19.4 Hz), 14.58.

^{19}F NMR (470 MHz): δ -225.33 (dt, J = 47.5, 17.4 Hz).

Stereochemistry was determined by ROSEY spectra.

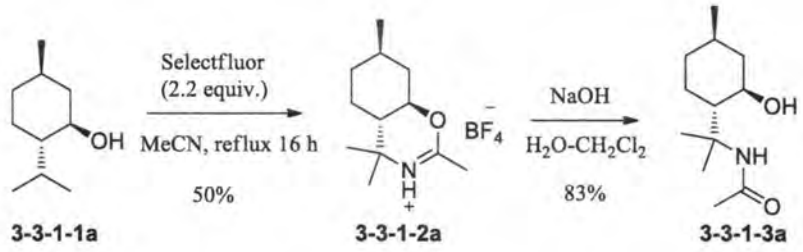
FTIR (ATR)/ cm^{-1}: 3397, 2977, 1723, 1448, 1055, 903, 751, 698.

3.3. Combination of Copper and Selectfluor: a Strong yet Selective Oxidant System

3.3.1 Hydroxyl Group Directed C-H Amination

3.3.1.1 Background

Selectfluor is not only a good fluorinating agent, but also a good oxidant. Selectfluor can be an oxidant in functional group transformations,[45] halogens (iodine),[46] C-H functionalization,[47] gold-catalyzed oxidative C-C and C-heteroatom bond formation,[48] and palladium catalyzed C-C or C-heteroatom bond formation.[49] Banks and co-workers have reported a hydroxyl group directed C-H amination using Selectfluor in refluxing acetonitrile (Scheme 14).[66] (-)-Menthol **3-3-1-1a** and Selectfuor (2.2 equiv.) were refluxed in acetonitrile for 16 h, and oxazoline derivative **3-3-1-2a** was isolated in moderate yield; **3-3-1-2a** gave amination product **3-3-1-3a** after basic hydrolysis.



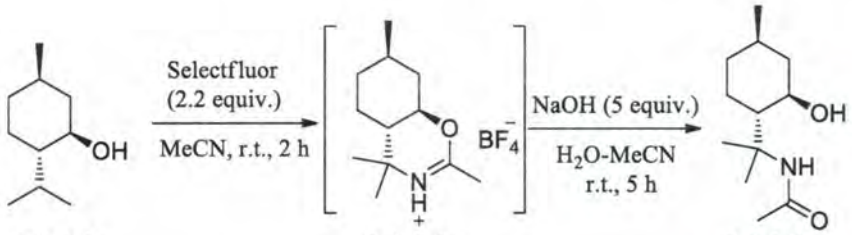
Scheme 14. Hydroxyl Group Directed C-H amination by Selectfluor in Acetonitrile

Although Bank's amination protocol is novel and potentially very useful, its harsh reaction conditions make it unattractive for synthetic purposes.

3.3.1.2 Copper Catalyzed C-H Amination by Selectfluor

To make Bank's amination milder, we screened various transition metal catalysts and found that copper salts could be suitable catalysts, but CuBr was the best (Table 6).

Table 6. Screening for a Suitable Transition Metal Catalyst



3-3-1-1a **3-3-1-2a** **3-3-1-3a**

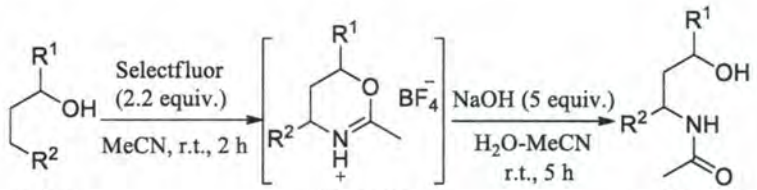
Entry	Cat. (10 %)	Yield [a] of **3-3-1-3a**
1	—	No Reaction
2	$Sc(OTf)_3$	No Reaction
3	$Eu(OTf)_3$	No Reaction
4	$In(OTf)_3$	No Reaction
5	AgOTf	No Reaction
6	AuCl	No Reaction
7	$FeCl_2\ 4H_2O$	No Reaction
8	$FeBr_2$	No Reaction
9	CuCl	43%
10	CuBr	50%
11	CuI	45%
12	$CuCl_2$	43%
13	$Cu(OAc)_2$	36%

[a] Isolated yield, calculated on the menthol.

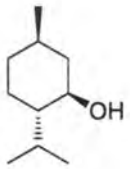
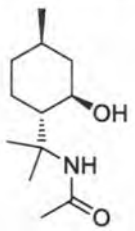
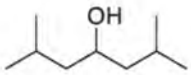
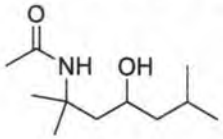
(-)-Menthol (1 equiv.), Selectfluor (2.2 equiv.) and CuBr (10 mol %) were mixed in acetonitrile at room temperature for 2 h, and following basic hydrolysis the reaction gave moderate yields of the amination product **3-3-1-3a** (entry 10, Table 6). We confirmed through HRMS that the reaction goes through an oxazoline intermediate. Our conditions were definitely milder than Banks' but when we examined the substrate scope using our optimized conditions, we were disappointed to find that only two alcohol substrates worked well (Table 7); most of the other alcohols tried were oxidized by the combination

of CuBr and Selectfluor. The two alcohols in Table 7 that were successfully aminated using our conditions share a similar feature, that is, they are sterically very hindered.

Table 7. Substrate Scope of Hydroxyl Group Directed C-H Amination



3-3-1-1 **3-3-1-2** **3-3-1-3**

Entry	Alcohol (**1**)	Yield [a] of **3**
1		
	3-3-1-1a	**3-3-1-3a**, 50%
2		
	3-3-1-1b	**3-3-1-3b**, 43%

[a] Isolated yield, calculated on **3-3-1-1**.

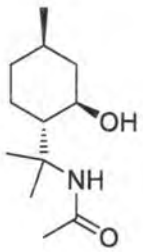
We were not the only ones that realized the importance of Bank's approach; very recently, Baran and co-workers reported a C-H amination protocol,[67] which is very similar to ours, but with wider scope. The key to their success was the use of a zinc salt in combination with copper(II) bromide. In the following sections, we explore the oxidative ability of copper and Selectfluor.

3.3.1.3 Experimental

The alcohol **3-3-1-1** (0.25 mmol, 1 equiv.), Selectfluor (0.55 mmol, 2.2 equiv.) and CuBr (0.025 mmol, 0.1 equiv.) were dissolved in acetonitrile (5 mL) and stirred at room

temperature for 2 h. NaOH (1.25 mmol, 5 equiv.) and water (5 mL) were added into the reaction mixture and stirred at room temperature for 5 h. Then, saturated ammonium chloride solution (30 mL) was added into the reaction mixture and extracted with diethyl ether (25 mL×4). The ether layers were combined and dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product. Silica gel flash chromatography of the crude product [hexanes-ethyl acetate (4:1) to hexanes-ethyl acetate (2:1)] yielded the amination product **3-3-1-3**, which was **3-3-1-3** characterized by its ^1H and ^{13}C NMR spectra.

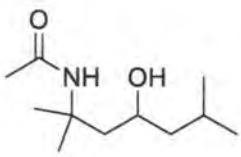
N-(2-((1S,2R,4R)-2-hydroxy-4-methylcyclohexyl)propan-2-yl)acetamide (**3-3-1-3a**)



^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (d, *J*=6.5Hz, 3H), 0.93 (m, 2H), 1.06 (m, 1H), 1.30 (s, 3H), 1.46 (s, 3H), 1.50 (m, 2H), 1.66 (m, 1H), 1.78 (m, 1H), 1.86 (s, 3H), 1.91 (m, 1H), 3.67 (dt, , *J*=4.0, 10Hz, 1H), 5.52 (bs, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.379, 21.836, 24.965, 25.392, 25.499, 31.374, 34.387, 45.756, 51.539, 56.819, 72.186, 169.710.

N-(4-hydroxy-2,6-dimethylheptan-2-yl)acetamide (**3-3-1-3b**)



^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (d, *J*=6.5Hz, 3H), 0.91 (d, *J*=6.5Hz, 3H), 1.20 (m, 1H), 1.38 (s, 3H), 1.42 (s, 3H), 1.44 (m, 2H), 1.70 (m, 2H), 1.87 (s, 3H), 2.96 (d, *J*=4.5Hz, 1H), 3.95 (m, 1H), 7.09 (bs, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.203, 23.072, 24.308, 24.537, 25.216, 28.398, 48.220, 48.976, 53.309, 67.096, 169.985.

3.3.2 Copper-Mediated Oxidation of Amides into Imides by Selectfluor (F-TEDA-BF_4)

3.3.2.1 Background

Imides are core structures in many therapeutic and agrochemical agents (Figure 5).[68] Imides can be prepared through condensation of carboxylic acid derivatives and ammonia or primary amine,[69] or other protocols,[70] such as cross coupling,[70d, e] oxidation of oxazoles,[70b] N-formylation,[70c] and reaction of aziridines.[70a]

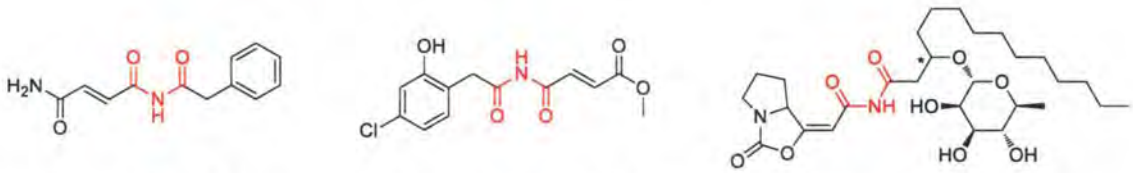


Figure 5. Therapeutic and Agrochemical Agents Containing the Imide Moiety

We were interested in a direct synthetic pathway to prepare an unsymmetrical imide by direct oxidation of the α-methylene group of an amide. Several methods to accomplish this transformation have been reported.[71] However, efficient methodologies for α-methylene oxidation are relatively rare;[71e, 71i] most of the reported oxidative methods suffer from low yields and/or limited substrate scope.[71a-d, 71f-h, 71j] For example, although RuO_4 is widely recognized as a strong oxidant for amide oxidation,[71a, 71f, 71j] it can oxidize even unactivated tertiary C-H bonds.[72] Of the efficient oxidative methods reported thus far, one employs a heavy metal (chromium VI) reagent,[71i] and although Nicolau and coworkers demonstrated that such toxic heavy metal oxidant could be supplanted by the more environmentally benign Dess–Martin periodinane (DMP), their method required heating the hypervalent iodine reagent to relatively high temperatures (80-85°C).[71e] In this

section we report a room temperature synthesis of imides from amides using a combination of copper (I) bromide and Selectfluor (F-TEDA-BF_4).

3.3.2.2 Screening for Suitable Oxidative Conditions

Selectfluor is an easy-handling and bench-stable electrophilic fluorinating agent.[37] In the course of our work on Selectfluor/gold-mediated oxidative coupling[3] and copper catalyzed amination,[73] we found that a combination of copper (I) bromide and Selectfluor is a strong oxidation system that can efficiently oxidize amides into imides. We chose amide **3-3-2-1a** as a substrate to screen for optimum oxidation conditions (Table 8). Amide **3-3-2-1a**, Selectfluor (2.2 equiv.) and copper bromide (10%) were mixed in acetonitrile at room temperature for 1 h to afford 10% yield of imide **3-3-2-2a**--the same yield as the load of the copper salt--together with unreacted starting material (entry 1). When the copper load was increased to 1 equivalent, we obtained a moderate yield of imide (entry 2); however, use of 1 equivalent of Selectfluor gave a low yield (entry 3). Entries 4 and 5 showed that both copper bromide and Selectfluor are indispensable for the oxidation to proceed. $CuCl_2$ alone, or together with Selectfluor (entries 6 and 7), has no effect on the transformation. Similarly, the use of different copper salts, such as CuOTf, $CuBF_4$, CuCl, CuI and $Cu(OTf)_2$ gave small amounts of imide (entries 8 to 12). Since the main difference among these copper salts is the counterion, which showed remarkably dissimilar results, and because it has been reported that bromide can be oxidized to bromine cation[74] we examined the role of bromide, and found that bromide itself (KBr) was not the active species (entry 13). Inspired by White's work,[75] CuBr was added in five portions over 32 min, improving our results (entry 14). Using a similar portion-wise addition, the highest yield of imide was attained increasing the amount of

both Selectfluor and CuBr (entry 15); hence, it was chosen as the optimized condition for this oxidation.

Table 8. Screening for Optimal Oxidation Conditions[a]

3-3-2-1a 3-3-2-2a

Entry	Selectfluor (equiv.)	Metal (or other) (equiv.)	% Yield[b] (SM)[c]
1	2.2	CuBr (0.1)	10(90)
2	2.2	CuBr (1.0)	66(33)
3	1.0	CuBr (1.0)	12(88)
4	2.2	——	0(100)
5	——	CuBr (1.0)	0(100)
6	——	$CuCl_2$ (1.0)	0(100)
7	2.2	$CuCl_2$ (1.0)	0(100)
8	2.2	CuOTf (1.0)	25(75)
9[d]	2.2	$CuBF_4$ (1.0)	0(100)
10	2.2	CuCl (1.0)	7(93)
11	2.2	CuI (1.0)	6(94)
12	2.2	$Cu(OTf)_2$ (1.0)	19(81)
13	2.2	KBr (1.0)	0(100)
14[e]	2.2	CuBr (1.0)	83(17)
15[f]	2.5	CuBr (1.0)	92(8)
16[f,g]	2.5	CuBr (1.0)	37(63)

[a] All reactions were conducted in acetonitrile at room temperature for 1 h. [b] NMR yield. Benzyl bromide as internal standard. [c] Starting material. [d] $CuBF_4$ was generated in situ. [e] Copper bromide was added 5 portions over 32 min. [f] Copper bromide was added 6 portions over 40 min. [g] Acetonitrile: water=100:3 (v/v).

Although water may be a possible oxygen source in this oxidation, small amounts of water (entry 16) had a deleterious effect in this reaction.

3.3.2.3 Examination of Amide Scope

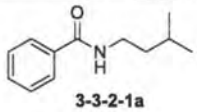
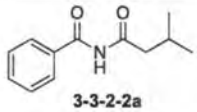
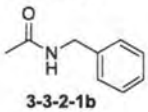
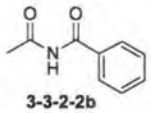
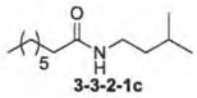
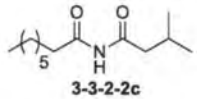
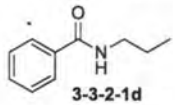
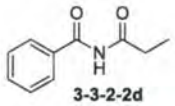
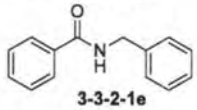
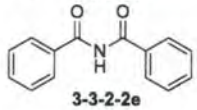
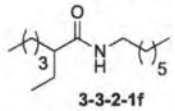
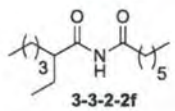
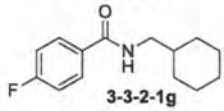
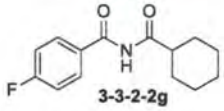
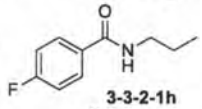
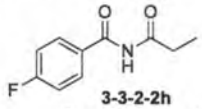
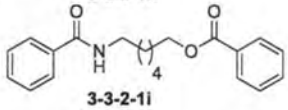
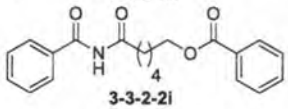
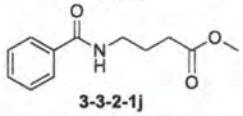
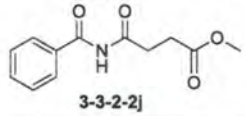
Next, we examined the substrate scope. Amide **3-3-2-1a** (Table 9, entry 1, Condition **A**) was readily oxidized by the combination of copper bromide and Selectfluor to give imide **3-3-2-2a** in excellent yield after 1 h, together with small amounts of unreacted starting material. Similarly, amides **3-3-2-1b**, **3-3-2-1c**, **3-3-2-1d** and **3-3-2-1e** afforded the corresponding imides in high yields (entries 2-5). Branched amide **3-3-2-1f** gave moderate yields (entry 6); this may be due to the steric hindrance, but the unreacted amide could be recycled. Amide **3-3-2-1g** also gave moderate yield of **3-3-2-2g** together with small amount of unreacted **3-3-2-1g** (entry 7), but the reason for this lower yield is unknown. The oxidation of **3-3-2-1h** gave **3-3-2-2h** in high yield (entry 8); and the reaction with amidoesters **3-3-2-1i**, **3-3-2-1j** was chemoselective (entries 9 and 10). Unfortunately, the presence of hydroxyl groups, double or triple bonds is not tolerated in this reaction due to a possible over oxidation.

3.3.2.4 Investigation of the Oxygen Source

There are two possible sources of oxygen for the newly incorporated oxygen in imide **3-3-2-2**, namely dioxygen in air and trace amounts of water in the reaction media. We conducted the reaction under nitrogen, and found that 50% of the imide was formed.[76] Since commercial Selectfluor always contains trace amounts of water,[77] we could not conduct the reaction under strictly anhydrous conditions. On the other hand, when substrate **3-3-2-1b** was oxidized in acetonitrile (dried shortly before use) containing 0.1 % $H_2{}^{18}O$, we observed ^{18}O (45%) incorporation in imide **3-3-2-2b** (confirmed by HRMS and ^{13}C NMR of **3-3-2-2b**) (Figure 6 and 7 in experimental section), which

Table 9. Comparison of the Effectiveness of Selectfluor (F-TEDA- BF_4) (Condition **A**) and F-TEDA- PF_6 (Condition **B**) in Amide Oxidation

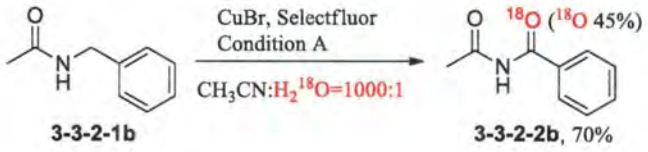
3-3-2-1 **3-3-2-2**

Entry	Amides	Imides	% Yield [a] (SM)[b]	
			A[c]	**B**[d]
1	 **3-3-2-1a**	 **3-3-2-2a**	88 (7)	90 (2)
2	 **3-3-2-1b**	 **3-3-2-2b**	83	79
3	 **3-3-2-1c**	 **3-3-2-2c**	79 (13)	83 (5)
4	 **3-3-2-1d**	 **3-3-2-2d**	77 (10)	90 (3)
5	 **3-3-2-1e**	 **3-3-2-2e**	84 (11)	85 (6)
6	 **3-3-2-1f**	 **3-3-2-2f**	66 (30)	71 (12)
7	 **3-3-2-1g**	 **3-3-2-2g**	50 (10)	65 (15)
8	 **3-3-2-1h**	 **3-3-2-2h**	80 (5)	91
9	 **3-3-2-1i**	 **3-3-2-2i**	84 (6)	70 (10)
10	 **3-3-2-1j**	 **3-3-2-2j**	82 (6)	78 (8)

[a] Yield was based on starting amide. [b] Starting material recovery. [c] Condition **A**: Amide **3-3-2-1** (0.25 mmol), Selectfluor (F-TEDA- BF_4) (0.625 mmol, 2.5 equiv.) and CuBr (0.3 mmol, 1.2 equiv., added in six portions over 40 min) reacted in acetonitrile (5 mL) at room temperature for 1 h. [d] Condition **B**: Amide **3-3-2-1** (0.25 mmol), F-TEDA- PF_6 (0.55 mmol, 2.2 equiv.) and CuBr (0.025 mmol, 0.1 equiv.) reacted in acetonitrile (5 mL) at room temperature for 3-6 h.

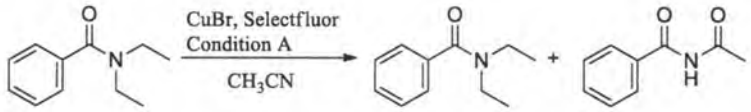
clearly demonstrated that trace water in the reaction acts as the oxygen source (Scheme 15).

Since all amides in Table 9 are secondary amides, a tertiary amide **3-3-2-1k** was employed to examine whether the N-H moiety is important (Scheme 16). Most of the unreacted amide **3-3-2-1k** was recycled and only small amounts of oxidation product **3-3-2-2b** (20%) were isolated, together with an unknown by-product, the yield being lower than that obtained with a similar substrate in entry 2 of Table 9, hinting to the possibility that N-H played a role in the oxidation.



3-3-2-1b **3-3-2-2b**, 70%

Scheme 15. Evidence of Trace H_2O as Ultimate Oxygen Source



3-3-2-1k **3-3-2-1k**, 60% **3-3-2-2b**, 20%

Scheme 16. Tertiary Amide not Suitable for This Oxidation

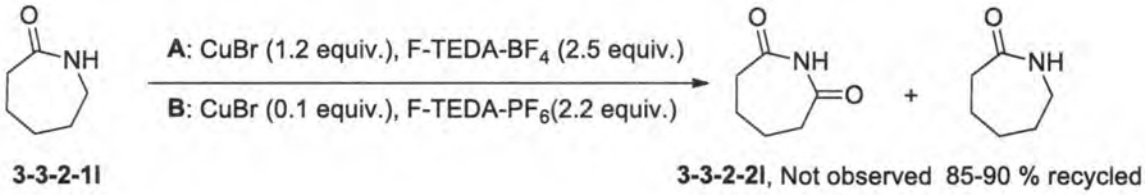
3.3.3 Copper Catalyzed Oxidation of Amide into Imide by F-TEDA-PF_6

3.3.3.1 Examination of Amide Substrate Scope

We reported above that a combination of stoichiometric amounts of CuBr and excess Selectfluor (F-TEDA-BF_4) can oxidize amides into imides at room temperature.[78] Although this method is efficient, the use of a stoichiometric amount of copper makes the methodology unattractive for process chemists, so we investigated alternative conditions that would permit use of a catalytic amount of a cuprous salt. Here we are pleased to disclose an exciting finding: a simple counterion exchange on Selectfluor (F-TEDA-PF_6 instead of F-TEDA-BF_4) permits the amount of copper catalyst to be reduced significantly (to 10 mol %). The oxidizing power of F-TEDA-PF_6, which can be prepared easily from Selectfluor, is at least as potent as Selectfluor itself; amides are oxidized to imides as rapidly and efficiently as we reported previously despite the significant reduction in CuBr loading.

The results of amide oxidation experiments are summarized in Table 9, Condition **B**. First, amide **3-3-2-1a**, CuBr (10 mol %) and F-TEDA-PF_6 (2.2 equiv.) reacted in acetonitrile for 5 h, giving a similar yield of imide (**3-3-2-2a**) (entry 1) (condition **B**) to our previous result using condition **A**, albeit utilizing longer reaction times. Similarly, amides **3-3-2-1b** (entry 2) and **3-3-2-1c** (entry 3) were also efficiently oxidized to the corresponding imides in good yield under the new condition **B**. Entry 4 (amide **3-3-2-1d**) demonstrated that condition **B** was superior to condition **A**. In entries 5, 6 and 7, amides worked well with the new protocol, without exceptions. The highest yield was observed with fluorinated amide **3-3-2-1h** (entry 8), and esters groups tolerated both, the new and the former oxidative systems (entries 9 and 10). Unfortunately, both oxidative systems,

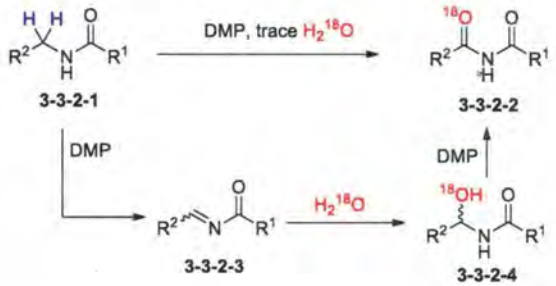
the combination of CuBr (1.2 equiv.) and F-TEDA-BF_4 or the combination of CuBr (0.1 equiv.) and F-TEDA-PF_6, failed to oxidize lactam **3-3-2-1l** (Scheme 17), indicating that only acyclic amides are suitable substrate for these two oxidative systems.



Scheme 17. Limitation of The Copper Catalyzed/Mediated oxidations

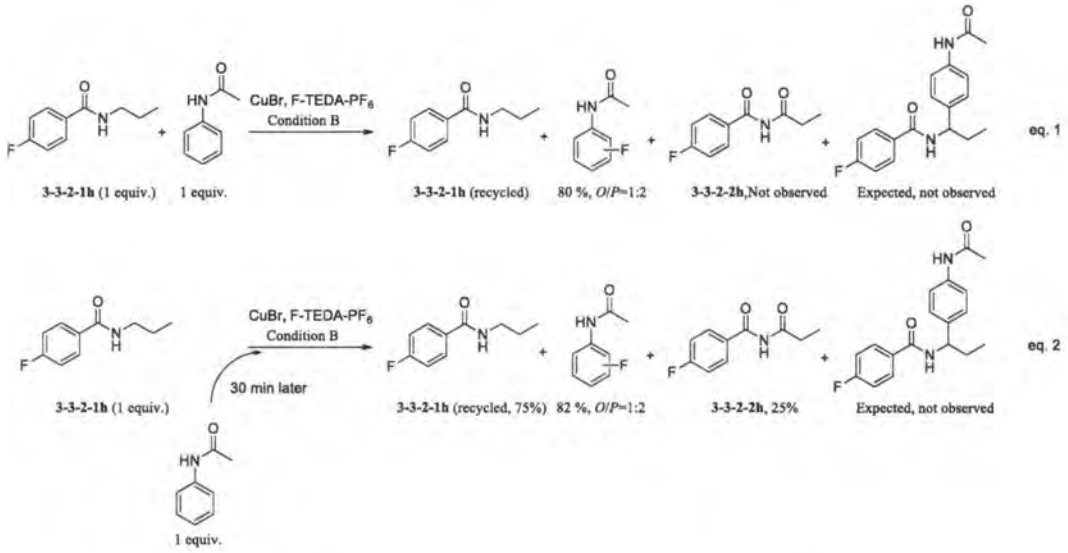
3.3.3.2 Mechanistic Investigations

Nicolaou has proposed a mechanism[71e] for amide oxidation by DMP, in which the amide was dehydrogenated to form imine intermediate **3-3-2-3**. Compound **3-3-2-3** reacts with water to generate hemiaminal **3-3-2-4**, which can be further oxidized by DMP to give the final product **3-3-2-2** (Scheme 18). Initially, we thought that our oxidation probably proceeded through a similar reaction mechanism since the ultimate source of the newly formed oxygen comes from trace water in the reaction mixture.



Scheme 18. Nicolaou's Proposal of Amide Oxidation by DMP

In order to confirm the above assumption, we added an aromatic compound with moderate electron density, N-arylacetamide, to the reaction mixture to capture intermediate **3-3-2-3**; two attempts are outlined in Scheme 19.

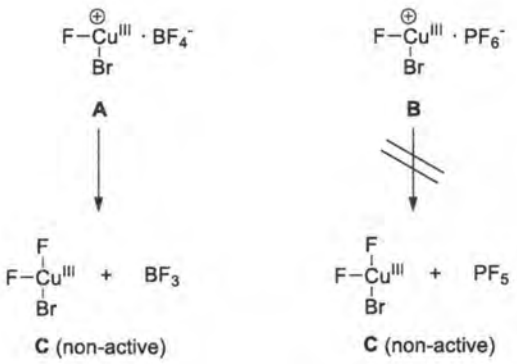


Scheme 19. Attempt to Capture Possible Imine Intermediate

Amide **3-3-2-1h** and N-arylacetamide were mixed using condition **B** in Table 9 (eq. 1, Scheme 17). Surprisingly, amide **3-3-2-1h** was not oxidized into **3-3-2-2h**; instead N-arylacetamide was fluorinated and no imine-captured product was observed. Then we added N-arylacetamide to the reaction mixture 30 min later (eq. 2). Imide (25%) and fluorinated N-arylacetamide were observed, but no imine-captured product was detected. The above two observations indicate that the oxidation pathway probably does not involve any imine intermediate. Lactam **3-3-2-1l** can not be oxidized in both systems (Scheme 17), which may be owed to that imine intermediate of lactam **3-3-2-1l** is much harder to be formed compared to acyclic amide. Therefore, possible formation of imine intermediate **3-3-2-3** can not be excluded.

It is not clear to us yet what is the role of copper salt in this oxidation. We observed that ^{1}H NMR of the reaction was complicated by line broadening effects when Selectfluor (or F-TEDA-PF_6) was added; however, we failed to detect the presence of paramagnetic Cu(II) by EPR ar room temperature. Therefore, high valent Cu(III), possibly formed from oxidation of Cu(I) by Selectfluor, is proposed to be a possible oxidant for this reaction. Considering that a Cu(III) species may not be very stable (isolable only using specific ligands), a multi-portion addition of CuBr (in the case of Selectfluor) could reduce the decomposition of Cu(III) complex and thus improve the yield of **3-3-2-2** (see entries 2 and 14 in Table 8). A premixed solution of CuBr and Selectfluor is still active, although it gave lower yields.[79]

While Selectfluor (F-TEDA-BF_4) uses stoichiometric amount of CuBr to oxidize amide, F-TEDA-PF_6 needs only catalytic amount of CuBr (10%). Browsing through literature reports of fluorination reactions, the difference between PF_6^- and BF_4^- is not significant.[80] Our rationale to explain the above difference in reactivity is the following: we assume that the different copper loading is due to the stability of the active Cu(III) species (**A**) and (**B**) (Schemes 20). Although both complexes **A** and **B** may have oxidative activity, high valence copper in **A** easily removes a fluoride ion from BF_4^- to form complex **C**, which is probably less reactive than **A**. Therefore, large amounts of CuBr are needed for oxidation in the case of F-TEDA-BF_4. Another possibility is that the smaller water content in F-TEDA-PF_6 compared with commercial Selectfluor could account for the improved imide yields.



Scheme 20. Proposed Rationale for Different Effect of BF_4^- and PF_6^-

However, for the high valence copper in **B** it is difficult to take up the fluoride ion from PF_6^- to form complex **C** due to the stronger P-F bond in the PF_6^-, therefore, **B** remains active in the reaction system. Computational studies reported by Christe and co-workers,[81] support our rationale: PF_5 has a much stronger affinity (94.9 kcal/mol) towards fluoride ion than BF_3 (83.1 kcal/mol).

3.3.3.3 Summary

We have developed a mild and efficient methodology of copper-mediated oxidation of amide into imide by Selectfluor. Simply changing the counterion on Selectfluor (F-TEDA-PF_6 instead of F-TEDA-BF_4) can significantly reduce the amount of copper (CuBr, 10 mol %) needed. The oxidative ability of copper bromide (10 mol %) and F-TEDA-PF_6 is as efficient as that of stoichiometric amount of copper bromide and Selectfluor. Both methodologies could be useful to synthesize the imide group, but more detailed mechanistic studies are needed to clarify the effects of the anion BF_4 viz-a-viz PF_6.

3.3.3.4 Experimental Section

General

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on a Varian MR400 NMR spectrometer. Chemical shifts (δ) were reported as part per million (ppm). δ 7.26, δ 77.00 of $CHCl_3$, 0.00 of $CFCl_3$ were used as internal standards for ^{1}H NMR, ^{13}C-NMR and ^{19}F-NMR spectra, respectively. High-resolution mass spectra (HRMS) were performed at mass spectrometry facility of Center for Regulatory and Environmental Analytical Metabolomics, University of Louisville. Melting points were measured using a DigiMelt MPA160 melting point apparatus. RTIR spectra were recorded in ATR (attenuated total reflection) solid mode using a Perkin Elmer Spectrum 100.

General procedure for the preparation of amides 3-3-2-1

The corresponding amine (3 mmol, 1.0 equiv.) and triethylamine (3 mmol, 1.0 equiv.) were dissolved in dry dichloromethane (6 mL) at 0°C, in which the corresponding acid chloride (3 mmol, 1 equiv.) was added slowly over a 10 min period, and stirred for 10 min at 0 °C. The resulting solution was stirred for 30 min at room temperature, and then saturated ammonium chloride solution (15 mL) was added to the reaction mixture, followed by diethyl ether extraction (25 mL×4). The ether layers were combined and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield amide **3-3-2-1**.

General procedure for copper-mediated oxidation of amide 3-3-2-1 to imide 3-3-2-2 by Selectfluor (F-TEDA-BF_4) (Condition A)

Amide **3-3-2-1** (0.25 mmol, 1 equiv.) and Selectfluor (0.625 mmol, 2.5 equiv.) were dissolved in acetonitrile (5 mL) at room temperature, and CuBr (0.3 mmol, 1.2 equiv.)

was added over a 40 min period in 6 portions. After all the CuBr was added, the resulting mixture was stirred for extra 20 min, and then acetonitrile was evaporated under reduced pressure. Saturated ammonium chloride solution (20 mL) was added into reaction mixture and extracted with diethyl ether (25 mL×4); the ether layers were combined and dried over Na_2SO_4, filtered, evaporated under reduced pressure to give the crude product. Silica gel flash chromatography of the crude product [hexanes-ethyl acetate (10:1) to hexanes-ethyl acetate (4:1)] yielded pure imide **3-3-2-2**.

Preparation of F-TEDA-PF_6 from Selectfluor (F-TEDA-BF_4)

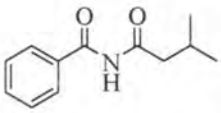
The procedure followed a literature report.[80] Since a large amount of BF_4^- has a deleterious effect on CuBr loading, it is strongly recommended that F-TEDA-PF_6 contain small amounts of BF_4, and that the ratio of PF_6 and BF_4 is at least 5.5:1.

Selectfluor (1062 mg, 3.00 mmoL) and ammonium hexafluorophosphate (2934 mg, 18.0 mmoL) were dissolved in H_2O (10 mL) at room temperature and stirred for 1.5 h. The mixture was filtered and washed with H_2O (10 × 5 mL) and Et_2O (30 mL) to afford F-TEDA-PF_6 (1400 mg, 97 %).

General procedure for copper-catalyzed oxidation of amide 3-3-2-1 to imide 3-3-2-2 by F-TEDA-PF_6 (Condition B)

Amide **3-3-2-1** (0.25 mmol, 1 equiv.), F-TEDA-PF_6 (0.625 mmol, 2.5 equiv.) and CuBr (0.025 mmol, 0.1 equiv.) were dissolved in acetonitrile (5 mL) and stirred at room temperature for 3-6 h, monitored by TLC until the reaction showed no further progress. The work-up was the same as in Condition **A**.

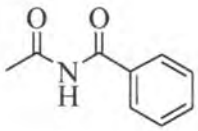
N-(3-Methyl-butyryl)-benzamide, (**3-3-2-2a**)[70b]



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (bs, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 6.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 2.82 (d, J = 6.8 Hz, 2H), 2.18 (m, 1H), 0.96 (d, J = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 165.6, 133.1, 132.9, 128.9, 127.7, 46.2, 24.8, 22.52.

N-Acetyl-benzamide, (**3-3-2**-2b)[70b]

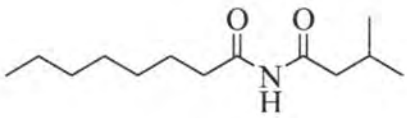


^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (bs, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 2.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): d 173.9, 165.9, 133.2, 132.6, 128.9, 127.8, 25.6.

HRMS *m/z* (ES^+) calcd for $C_9H_9NO_2Na$ ($[M+Na]^+$) 186.0525, found 186.0525.

3-Methyl-*N*-octanoyl-butyramide (**3-3-2-2c**)



White crystal, mp: 52-54°C.

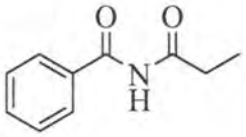
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (bs, 1H), 2.57 (t, J = 6.0 Hz, 2H), 2.43 (d, J = 5.6 Hz, 2H), 2.12 (m, 1H), 1.60 (m, 2H), 1.25-1.29 (m, 8H), 0.95-0.97 (m, 6H), 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 173.6, 46.3, 37.4, 31.6, 29.0, 28.9, 25.2, 24.3, 22.6, 22.4, 14.0.

FTIR (neat)/cm^{-1}: 3269, 3175, 2957, 2927, 1732, 1505, 1161.

HRMS *m/z* (ES^+) calcd for $C_{13}H_{25}NO_2Na$ ($[M+Na]^+$) 250.1777, found 250.1777.

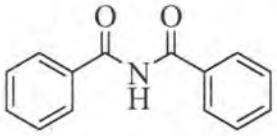
N-Propionyl-benzamide (**3-3-2-2d**)[70b]



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (bs, 1H), 7.90 (d, J=8.4Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 3.00 (q, J = 7.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 165.8, 133.1, 132.8, 128.8, 127.8, 31.2, 8.2.

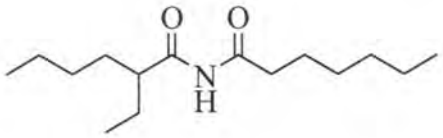
N-Benzoyl-benzamide (**3-3-2-2e**)[70b]



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (bs, 1H), 7.81 (d, J = 8.0 Hz, 4H), 7.53 (t, J = 7.2 Hz, 2H), 7.42 (t, J = 7.6 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 133.3, 132.9, 128.8, 127.9.

Heptanoic acid (2-ethyl-hexanoyl)-amide (**3-3-2-2f**)



White crystal, mp: 45-47°C.

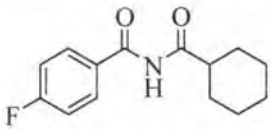
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (bs, 1H), 2.74 (t, J = 7.6 Hz, 2H), 2.42 (m, 1H), 1.57-1.66 (m, 4H), 1.36-1.47 (m, 2H), 1.22-1.26 (m, 10H), 0.84-0.90 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 176.0, 49.4, 37.5, 31.7, 31.5, 29.5, 28.8, 25.4, 24.2, 22.7, 22.5, 13.9, 13.8, 11.7.

FTIR (neat)/cm^{-1}: 2959, 2931, 2860, 1738, 1686, 1510, 1166.

HRMS *m/z* (ES$^+$) calcd for $C_{15}H_{29}NO_2H$ ($[M+H]^+$) 256.2271, found 256.2271. Calcd for $C_{15}H_{29}NO_2Na$ ($[M+Na]^+$) 278.2090, found 278.2090.

Cyclohexanecarboxylic acid 4-fluoro-benzoylamide (**3-3-2-2g**)



White crystal, mp: 136-138°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (bs, 1H), 7.89-7.93 (m, 2H), 7.12-7.17 (m, 2H), 3.32-3.38 (m, 1H), 1.22-1.98 (m, 11H).

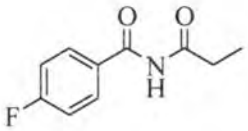
^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 165.6 (J = 253.8 Hz), 164.4, 130.4 (J = 8.9 Hz), 129.2 (J = 3.7 Hz), 116.0 (J= 22.3 Hz), 44.5, 28.9, 25.8, 25.5.

^{19}F NMR (376 MHz): δ -105.1 (m).

FTIR (neat)/cm^{-1}: 3426, 2932, 2855, 1680, 1602, 1492, 1237, 1157.

HRMS *m/z* (ES$^+$) calcd for $C_{14}H_{16}FNO_2H$ ([M+H]$^+$) 250.1237, found 250.1237. Calcd for $C_{14}H_{16}FNO_2Na$ ([M+Na]$^+$) 272.1057. found 272.1056.

4-Fluoro-*N*-propionyl-benzamide (**3-3-2-2h**)



White crystal, mp: 118-120°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (bs, 1H), 7.95-7.98 (m, 2H), 7.12-7.16 (m, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

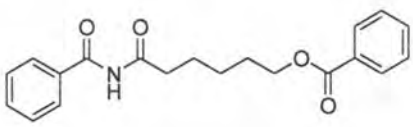
^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 165.6 (*J* = 253.8 Hz), 164.8, 130.6 (*J* = 9.7 Hz), 128.9 (*J* = 3.8 Hz), 115.9 (*J* = 22.3 Hz), 31.2, 8.1.

^{19}F NMR (376 MHz): δ -105.1 (m).

FTIR (neat)/cm^{-1}: 1690, 1604, 1469, 1370, 1239.

HRMS *m/z* (ES$^+$) calcd for $C_{10}H_{10}FNO_2H$ ([M+H]$^+$) 196.0768, found 196.0768. Calcd for $C_{10}H_{10}FNO_2Na$ ([M+Na]$^+$) 218.0587, found 218.0587.

Benzoic acid 6-benzoylamino-6-oxo-hexyl ester (**3-3-2-2i**)



White crystal, mp: 86-88°C.

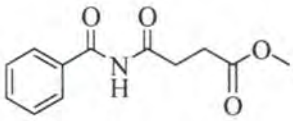
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (bs, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.37-7.57 (m, 6H), 4.30 (t, J = 6.8 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 1.73-1.83 (m, 4H), 1.52-1.57 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 166.6, 165.9, 133.1, 132.8, 132.7, 130.4, 129.5, 128.8, 128.3, 127.9, 64.8, 37.5, 28.6, 25.6, 23.7.

FTIR (neat)/cm^{-1}: 3426, 1716, 1683, 1457, 1275, 1244.

HRMS *m/z* (ES$^+$) calcd for $C_{20}H_{21}NO_4H$ ($[M+H]^+$) 340.1543, found 340.1544. Calcd for $C_{20}H_{21}NO_4Na$ ($[M+Na]^+$) 362.1363, found 362.1363.

4-Benzoylamino-4-oxo-butyric acid methyl ester (**3-3-2-2j**)[82]



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (bs, 1H), 7.90 (d, J = 6.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 3.63 (s, 3H), 3.31 (t, J = 6.0 Hz, 1H), 2.67 (t, J = 6.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 172.9, 165.9, 133.1, 132.5, 128.8, 127.9, 51.8, 32.9, 28.1.

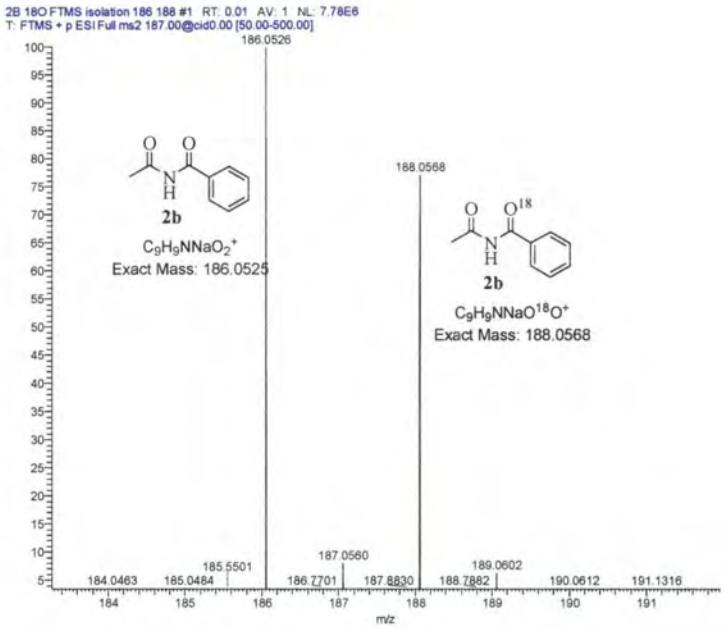


Figure 6. HRMS of Imide **3-3-2-2b** and O^{18} labeled **3-3-2-2b**

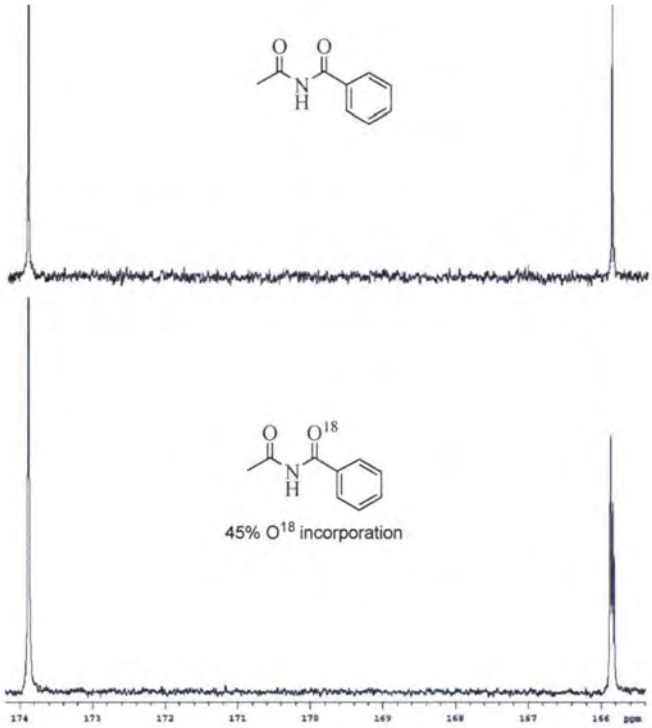


Figure 7. ^{13}C NMR of Carbonyl Groups in Imide **3-3-2-2b** and O^{18} labeled **3-3-2-2b**

4. SEARCH FOR CYTOTOXIC AGENTS FROM THE AMAZONIAN RAINFOREST

4.1. Background

Nature has been a major source of inspiration for the development of front-line-drugs for cancer, Alzheimer's and other diseases. Some well-known drugs or drug candidates isolated from natural source are shown in Figure 8.

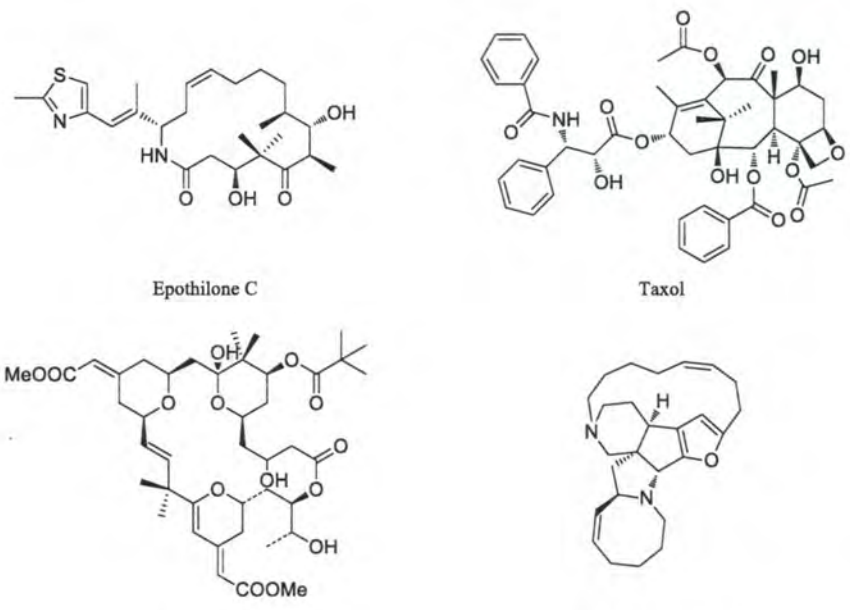


Figure 8. Drugs and Drug Candidates Isolated from Natural Source

All of them have interesting biological activities and complex architecturally skeletons, but they pose a synthetic challenge.[83] A multidisciplinary and international program that included the Hammond group--formed in the early 1990's--isolated many bioactive compounds from different plant sources in the Amazonian rainforest. In some cases bioactive analogs were synthesized in the Hammond group and our collaborators tested their biological activities. This chapter reports our results with 13 targeted plants from the Amazonian rainforest (Table 10).

Table 10. List of Targeted Plants

Plant	Extract No.	Voucher No.	3T3	H460	ME180	DU145	MCF-7	M-14	HT-29	PC3	K562
Cremastosperma microcarpum (Annonaceae)	2967	19759	5	7	5	6	7	5	7	5	7
Physalis angulata (Solanaceae)	1159	18597	9	7	9	7	7	7	9	7	7
Humiria balsamifera (Humiriaceae)	2278	19478	5		1		1	5		3	5
Rollinia andicola (Annonaceae)	2900	19877	7	9	5	3	7	5	5	5	5
Bocconia intengrifolia (Papaveraceae)	2367	19644	9	9	9	9	9	9	9	9	9
Hyptis Lantanaefolia (Lamiaceae)	2352	19547	9	9	9	9	9	9	9	9	9
Hippeastrum puniceum (Amaryllidaceae)	435	17506	9	9	9	9	7	9	9	9	9
Aniba riparia (Lauraceae)	2239	19366	7	7	7	7	7	7	7	7	1
Terminalia Amazonia (Combretaceae)	3531	20515	5	5	5	3	5	5	5	5	3
Piper concinnatoris (missing)	1962	19065	9	9	9	7	9	7	9	9	9
Paullinia (missing) (Sapindaceae)	2940	19705	9	7	7	7	7	7	6	7	7
Plukenetia volubillis (Euphorbiaceae)	3498	20465	7	7	7	7	9	7	7	9	7
Scutia (missing) (Phammaceae)	3579	19883	9	9		9	9		9	9	9

	GI50
1	> 0.5 mg/mL
2	= 0.5 mg/mL
3	between 0.125 and 0.5 mg/mL
4	= 0.125 mg/mL
5	between 0.031 and 0.125 mg/mL
6	=0.031mg/mL
7	between 0.008 and 0.031 mg/mL
8	=0.008mg/mL
9	< 0.008mg/mL

3T3, BALB/3T3 clone A31 embryonic mouse fibroblast cells;
H460, human large cell lung cancer;
ME180, human cervical carcinoma;
DU145, human prostate carcinoma ;
MCF-7, human breast adenocarcinoma;
M-14, human melanoma;
HT-29, human colon adenocarcinoma;
PC3, human prostate adenocarcinoma;
K562, human chronic myelogenous leukemia cells.

4.2. *Physalis angulata* L. (Solanaceae)

The genus *Physalis* (Solanaceae) is represented by almost 90 species distributed throughout the tropical and subtropical regions of the world where it has been widely used in folk medicine by developing countries.[84] As a result of its medicinal value, there has been significant interest to evaluate the phytochemical and pharmaceutical properties of *Physalis angulate* L. Previously, physanolide,[85] and other withanolides,[86] including withangulatin,[86b, c, 86f] physangulin,[86a, 86d, 86k, l] and physalin,[86c, 86g-i, 87] in addition to other constituents[86e] isolated from *P. angulata,* were found to show significant biological activity.[88]

Here we disclose the discovery of three new anti-proliferative withanolides with an unusual carbon framework, namely, physangulidines A (**1**), B (**2**) and C (**3**), isolated from *P. angulata* L. using a bioassay-directed isolation technique. The ethanol extract of the dried plant was partitioned between water and dichloromethane, the active organic layer subjected to silica gel column chromatography and the most active fractions further purified via HPLC to afford the three active components.

Physangulidine A (**1**), mp is 213.0-215.0°C (MeOH), was isolated as white crystalline needles, whose molecular formula was determined to be $C_{28}H_{36}O_8$ by HRMS (*m/z* 501.2493 $[M+H]^+$, 523.2311 $[M+Na]^+$). Simple analysis of ^1H, ^{13}C and HSQC spectra revealed four methyls, seven methylenes, eight methines and nine quaternary carbons, and suggested 2 two hydroxyl groups, consistent with this formula. Subsequent 2D analysis (gCOSY, ROESY and HMBC) lead to the structure **1** shown in Figure 9 (For numbering see Figure 10) and the complete NMR assignment is summarized in Table 11.

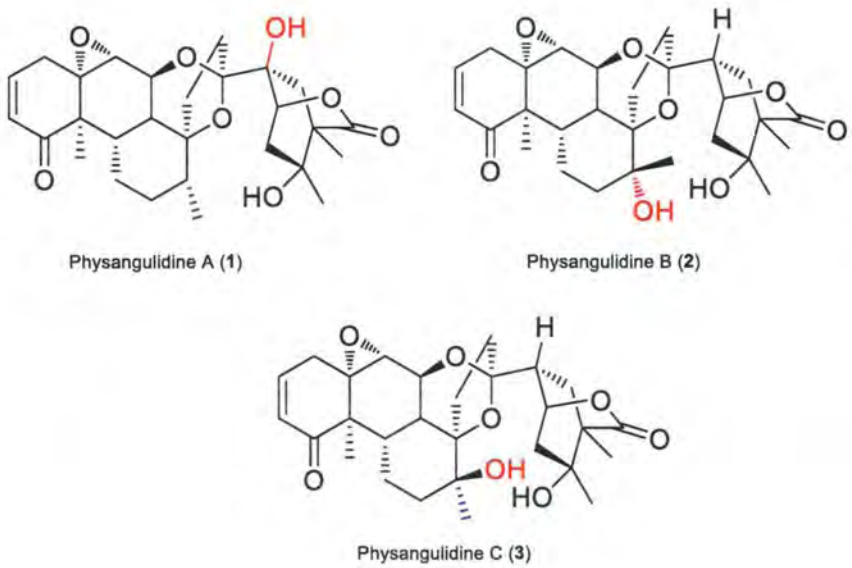


Figure 9. Structures of Physangulidines A (**1**), B (**2**) and C (**3**)

Important structural keys included two olefinic protons H-2 (δ 6.08, dd, *J*=9.8, 2.8 Hz, 1H) and H-3 (δ 6.86, ddd, *J*=9.8, 6.3, 2.8 Hz, 1H) conjugated to carbonyl carbon C-1 (δ 201.825), consistent with an α,β-unsaturated ketone.[86b, c, 86f] This moiety is also supported by IR (1714 cm^{-1}) and UV (220 nm).[86b] In addition, a C-5,6 epoxide, and ketal carbon C-17 (δ 109.709) were surmised from the NMR spectra. Another critical structural feature centered around carbonyl carbon C-26 (δ 176.961) and was indicative of an *isolated* bridged δ-lactone moiety, containing two methyls and two hydroxyl groups. The structure and stereochemistry of **1** was determined by X-ray crystallogryaphy (Figure 11) and ROESY 2D NMR analysis.

Compound **1** contains 28 carbons in which C-22 and C-26[89] have been oxygenated to form a δ–lactone putting it into the class of steroids known as withanolides. Withanolides belong to a group of naturally occurring steroids having 28 carbons and derived from an

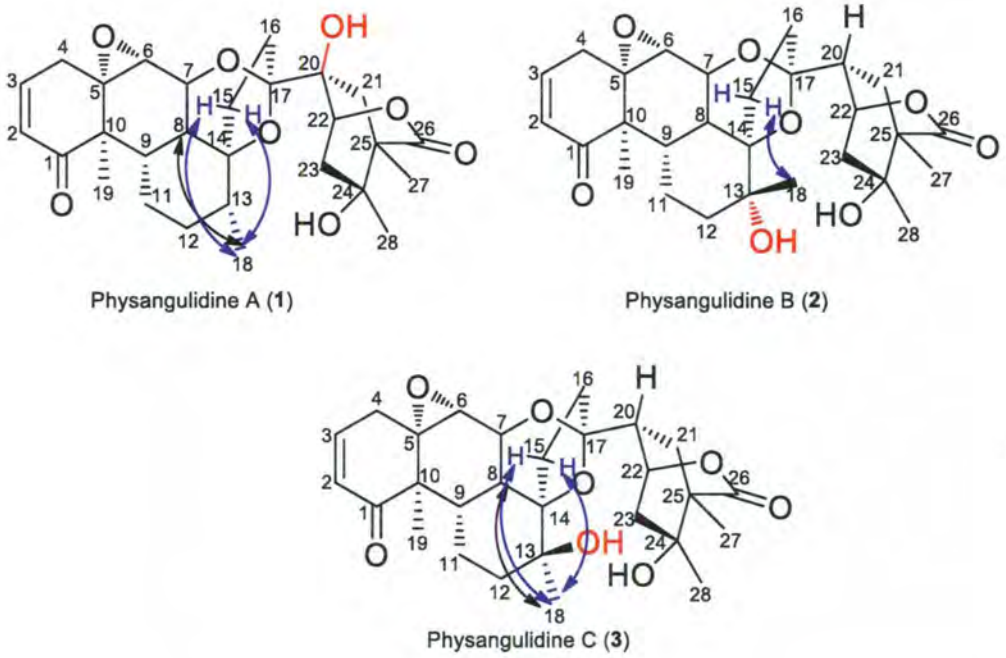


Figure 10. Carbon Numbering and Crucial ROESY Interactions of Physangulidines A (**1**), B (**2**) and C (**3**)

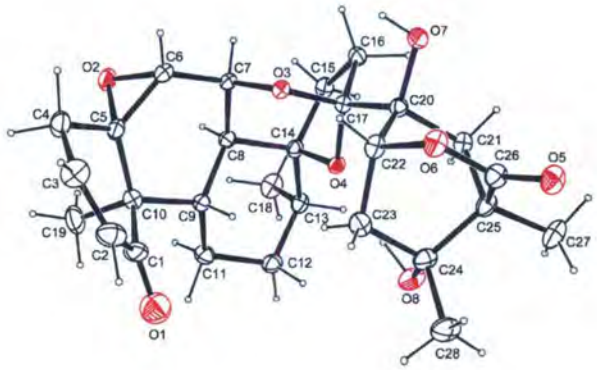


Figure 11. An *ORTEP-3* Diagram of **1** Showing 40% Ellipsoids

Note: H atoms are shown as small spheres of arbitrary radii. Selected bond lengths (Å) and angles (deg): O1-C1, 1.178(5); O5-C26, 1.204(4); O7-C20, 1.418(3); O8-C24, 1.437(4); C13-C18, 1.535(4); C12-C13-C18, 112.5(3). The absolute structure configuration for physangulidine A (**1**) has been reliably determined using Cu radiation including 13 stereocenters which are as follow: (chirality at C5) S, (C6) R, (C7) S, (C8) S, (C9) S, (C10) R, (C13) R, (C14) S, (C17) R, (C20) S, (C22) R, (C24) R, (C25) R.

ergostane skeleton, in which carbons 22 and 26 (Type A) or 23 and 26 (Type B) were oxidized to form lactones (Figure 12).

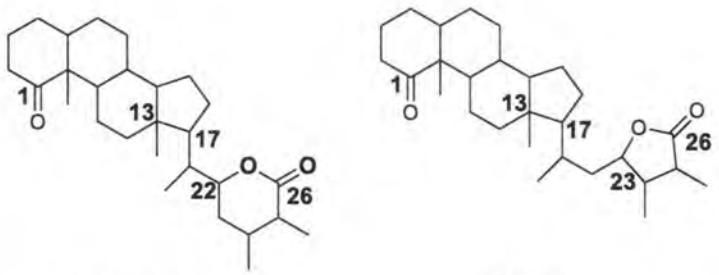


Figure 12. Main structures of Withanolides Have Been Isolated

Although, to date, about 650 withanolides have been isolated from different plant sources,[90] **1** is the first withanolide having a disconnection between C-13 and C-17, which typically forms ring D of the ergostane skeleton.

Physangulidine B (**2**) (mp above 260°C) and physangulidine C (**3**) were also isolated as white needles, and both were found to have the molecular formula of $C_{28}H_{36}O_8$ by HRMS (*m/z* 523.2311 $[M+Na]^+$ for **2**; *m/z* 523.2313 $[M+Na]^+$ for **3**), indicating both are isomers of physangulidine A (**1**). After careful analysis of the NMR data (Table 12 and 13), we found that in the structures of **2** and **3,** C-13 is hydroxylated instead of at C-20 in physangulidine A **(1)**, and that **2** and **3** differed from each other only at the stereochemistry at C-13 (Figure 9).

As with **1**, compounds **2** and **3** also contained the bridged δ lactone moiety and the disconnection between C-13 and C-17. Physangulidine B (**2**) was subjected to X-ray

crystallography, thus confirming the aforementioned C-20 vs C-13 hydroxyl "migration" (Figure 13) and further demonstrated that with the exception of the orientation of the C-13 methyl group, the overall conformation of **1** and **2** were very similar.

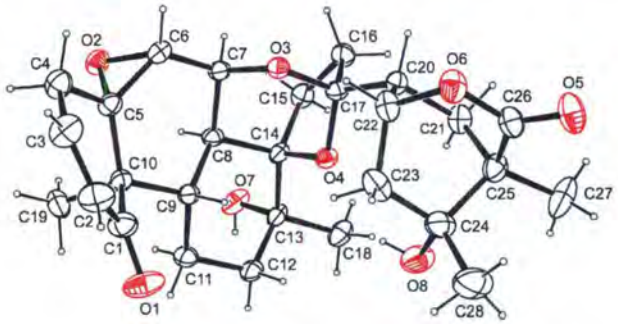


Figure 13. An *ORTEP-3* Diagram of **2** Showing 40% Ellipsoids

Note: H atoms are shown as small spheres of arbitrary radii. Selected bond lengths (Å) and angles (deg): O1-C1, 1.188(5); O5-C26, 1.218(7); O7-C13, 1.433 (5); C13-C18, 1.527(6); O7-C13-C18, 110.4(4); C12-C13-C18, 109.4(4). The absolute structure configuration for physangulidine B (**2**) has been reliably determined using Cu radiation including 13 stereocenters which are as follow: (chirality at C5) S, (C6) R, (C7) S, (C8) S, (C9) S, (C10) R, (C13) R, (C14) R, (C17) R, (C20) R, (C22) R, (C24) R, (C25) R.

Crystals of physangulidine B (**2**) adequate for X-ray diffraction studies were grown from methylene chloride/hexane. $C_{28}H_{36}O_8$: colorless needle, 0.42 x 0.02 x 0.02 mm^3, orthorhombic, space group $P2_12_12_1$, a = 7.6354(9) Å, b = 12.043(2) Å, c = 27.411(5) Å, $\alpha = \beta = \gamma = 90°$, V = 3068.53(18) $Å^3$, D_{calc} = 1.319 Mg/m^3, Z = 4. For 4132 reflections $I > 2\sigma(I)$ [R(int) 0.049] the final anisotropic full matrix least-squares refinement on F^2 for 334 variables converged at R1 = 0.055 and wR2 = 0.08 with a GOF of 1.03. The absolute structure was determined by refinement of the Hooft parameter 0.0(4).

Crystals of physangulidine A (**1**), $C_{28}H_{36}O_8$: colorless prism, 0.42 x 0.22 x 0.09 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.0880(4) Å, b = 10.5957(3) Å, c = 24.5357(11) Å, $\alpha = \beta = \gamma = 90°$, V = 2622.60(18) $Å^3$, D_{calc} = 1.270Mg/m^3, Z = 4. For 5195 reflections I > 2σ(I) [R(int) 0.038] the final anisotropic full matrix least-squares refinement on F^2 for 425 variables converged at R1 = 0.052 and wR2 = 0.118 with a GOF of 1.03 and Hooft parameter of 0.11(6).

Unfortunately, a single crystal of **3** suitable for X-ray crystallography was failed to be isolated, owing to its unstability at room temperature for long time (three weeks). However, the ROESY 2D NMR comparison between **2** and **3** did confirm that the C-18 methyl of physangulidine C is located axially and the hydroxyl group is equatorially positioned on C-13 of **3**, while in physangulidine B (**2**) the C-18 methyl is equatorial on C-13 and the hydroxyl is axial (Figure 9). Accordingly, CH_3-18 shows a strong correlation with H-8 and H-15 (both α and β) in compound **3**, however, CH_3-18 of physangulidine B (2) has only single interaction with H-15β observed in the ROESY spectra. A similar interaction was observed in physangulidine A: CH_3-18 has interaction with H-8 and H-15 (α and β) on ROESY, indicating the preferred axial orientation of the methyl group in both **1** and **3**.

Table 11. All NMR Data of Physangulidine A (**1**)

Position	^{13}C NMR	HSQC	COSY	ROESY	HMBC
1	201.825				3, 4eq, 9, 19
2	129.261	6.08 (dd, *J*=9.8, 2.8 Hz, 1H)	3, 4ax	3	4
3	143.748	6.86(ddd, *J*=9.8, 6.3, 2.8 Hz, 1H)	2, 4eq	2	4
4	32.064	2.95(ax, dt, *J*=18.2, 2.8 Hz, 1H)	Hax: 2	Hax: 19	2, 3, 6, 7
		1.93(eq, dd, *J*=18.2, 6.3 Hz, 1H)	Heq: 3	Heq: 6	
5	62.596				3, 4, 19
6	63.008	3.14(d, *J*=2.1 Hz, 1H)	7	4eq, 7	4, 7
7	67.070	4.32(t, *J*=2.8 Hz, 1H)	6, 8	6, 8, 15α, 16	6, 8
8	33.974	1.45(m, 1H)	7, 9	7, 15α, 18, 19	
9	34.112	1.82(m, 1H)	8	12ax	6, 7, 19
10	47.459				4eq, 19
11	20.488	1.35(ax, dq, *J*=14.0, 2.8 Hz, 1H)		Hax: 18, 19	9, 19
		2.10(eq, m, 1H)		Heq: 12ax, 19	
12	28.535	1.48(ax, m, 1H), 1.73(eq, m, 1H)		Hax: 9, 11eq	11, 18
13	37.345	1.76(m, 1H)	18	18	18
14	90.027				8, 15, 16, 18
15	32.957	1.71(α, m, 1H)	16	Hα: 7, 8, 16, 18	16
		1.85(β, m, 1H)		Hβ: 16, 18, 21ax	
16	31.462	2.17(m, 2H)	15	7, 15, 21ax	
17	109.709				8, 15, 16, 21
18	14.470	0.95(d, *J*=7.0 Hz, 3H)	13	8, 11ax, 13, 15	
19	14.228	1.21(s, 3H)		4ax, 8, 11	4ax
20	75.065				21, 22, 23
21	36.926	2.40(ax, d, *J*=15.4 Hz, 1H)		Hax: 15β, 16, 27	22, 27
		1.45(eq, m, 1H)		Heq: 27	
22	78.743	4.62(dd, *J*=3.5, 1.4 Hz, 1H)	23	23	23
23	40.499	2.41(ax, dd, *J*=16.1, 1.4 Hz, 1H)	22	Hax: 22	28
		2.09(eq, m, 1H)		Heq: 22, 28	
24	69.496				21eq, 22, 23, 27, 28
25	48.461				21, 27, 28
26	176.961				21, 22, 27
27	14.041	1.14(s, 3H)		21	21
28	27.044	1.17(s, 3H)		23eq	23

Table 12. All NMR Data of Physangulidine B (**2**)

Position	^{13}C NMR	HSQC	COSY	ROESY	HMBC
1	201.973				3, 19
2	129.287	6.10(dd, *J*=9.8, 2.8 Hz, 1H)	3, 4ax	3	4
3	143.856	6.88(ddd, *J*=9.8, 6.3, 2.1 Hz, 1H)	2, 4eq	2, 4ax	4
4	31.978	2.96 (ax,dt, *J*=18.2, 2.8 Hz, 1H)	Hax: 2	Hax: 19	2, 3
		1.95 (eq, m, 1H)	Heq: 3	Heq: 3, 6	
5	62.709				3, 4ax, 19
6	62.937	3.11 (d, *J*=2.8 Hz, 1H)	7	4eq, 7	4eq, 7
7	67.063	4.39 (dd, *J*=3.5, 2.8 Hz, 1H)	6, 8	6, 8, 15α, 16α	6
8	35.278	1.68 (m, 1H)	7, 9	7, 15α	15
9	33.338	1.83 (dt, *J*=11.9, 3.8 Hz, 1H)	8, 11	12ax	19
10	47.601				4eq, 19
11	21.632	1.53(ax, m, 1H), 2.17 (eq, m, 1H)	9, 12	Hax: 19	19
12	36.766	1.65 (ax, m, 1H),1.70 (eq, m, 1H)	11	Hax: 9	18
13	71.219				15β, 18
14	88.323				15β, 18
15	27.993	1.79 (α, m, 1H)	16	Hα: 7, 8, 16α	16
		2.17 (β, m, 1H)		Hβ: 16β, 18	
16	33.686	2.07 (α, m, 1H)	15	Hα: 7, 15α	15
		1.94 (β, m, 1H)		Hβ: 15β	
17	108.110				15β, 16, 20, 21
18	23.916	1.21 (s, 3H)		15β	
19	14.291	1.24 (s, 3H)		4ax, 11ax	
20	40.585	2.61 (m, 1H)	21, 22	21eq, 22	15β, 16β, 21, 23eq
21	26.453	2.00(ax, dd, *J*=14.0, 5.6 Hz, 1H)	20	Hax: 27	20, 27
		1.59 (eq, m, 1H)		Heq: 20, 27	
22	74.149	4.76 (dt, *J*=3.5, 2.1 Hz, 1H)	20, 23	20, 23	20, 21
23	40.933	2.03(eq, ddd, *J*=15.4, 3.5, 2.1 Hz, 1H)	22	Hax: 22	20, 28
		2.23 (ax, dd, *J*=15.4, 2.1 Hz, 1H)		Heq: 22, 28	
24	70.651				23, 27, 28
25	47.351				21, 27, 28
26	177.626				21, 22, 23, 27
27	14.284	1.11 (s, 3H)		21	21eq
28	27.399	1.14 (s, 3H)		23eq	

Table 13. All NMR Data of Physangulidine C (**3**)

Position	^{13}C NMR	HSQC	COSY	ROESY	HMBC
1	201.805				3, 9, 19
2	129.310	6.09(dd, *J*=9.8, 3.5 Hz, 1H)	3, 4ax	3	4
3	143.860	6.89(ddd, *J*=9.8, 6.3, 2.1 Hz, 1H)	2, 4eq	2	4
4	31.899	2.95 (ax,dt, *J*=18.2, 2.8 Hz, 1H)	Hax: 2	Hax: 19	2, 3, 6
		1.95 (eq, m, 1H)	Heq: 3	Heq: 6	
5	62.910				3, 4, 19
6	62.963	3.12(d, *J*=2.1 Hz, 1H)	7	4eq, 7	7
7	67.973	4.34(t, *J*=2.8 Hz, 1H)	6, 8	6, 8, 15α, 16α	6
8	36.496	1.40(dd, *J*=11.9, 3.5 Hz, 1H)	7, 9	7, 15α, 18, 19	6, 11ax, 15, 18
9	33.394	1.88(dt, *J*=12.6, 2.8 Hz, 1H)	8	11eq	7, 8, 11, 19
10	47.358				2, 4eq, 19
11	23.897	1.20 (ax, m, 1H)	12	Hax: 12	12
		2.27(eq, m, 1H)		Heq: 9, 12	
12	37.614	1.69(m, 2H)	11	11, 18	18
13	71.066				12, 15β, 18
14	89.003				12, 15β, 16β, 18
15	27.197	1.63(α, m, 1H)	16	Hα: 7, 8, 18	16, 18
		2.31(β, m, 1H)		Hβ: 16β, 18	
16	33.383	2.03(α, m, 1H)	15	Hα: 7	15
		1.97(β, m, 1H)		Hβ: 15β	
17	107.837				15β, 16, 20, 21
18	21.871	1.53 (s, 3H)		8, 12, 15	12
19	14.205	1.19(s, 3H)		4ax, 8	9
20	41.311	2.54(m, 1H)	21, 22	21eq, 22	21, 23eq
21	26.648	2.16(ax, dd, *J*=14.0, 6.3 Hz, 1H)	20	Hax: 27	27
		1.55(eq, dd, *J*=14.0, 11.9 Hz, 1H)		Heq: 20, 27	
22	74.415	4.73(dt, *J*=3.5, 1.4 Hz, 1H)	20, 23	20, 23	20, 21eq, 23eq
23	40.578	2.40(ax, dd, *J*=15.4, 1.4 Hz, 1H)	22	Hax: 22	20, 28
		1.99(eq, m, 1H)		Heq: 22, 28	
24	70.838				21, 22, 23eq, 28
25	47.605				21, 23eq, 27
26	177.574				21, 22, 27
27	14.265	1.14(s, 3H)		21	21
28	28.042	1.19(s, 3H)		23eq	23eq

Physangulidine A (**1**) was found to have significant *in vitro* antiproliferative activity against DU145 cancer cell line in bioassay (GI_{50} estimated to be 3.0 μM) and also RWPE-1 prostate epithelial cell (GI_{50}=2.4 μM). GI_{50} values of physangulidine B (**2**) and physangulidine C (**3**) were found to be very similar and comparatively lower than physangulidine A (**1**).

GI_{50} values of physangulidine B were determined to be 6.0 and 6.8 μM against RWPE-1 and DU145, while in physangulidine C they were 6.6 and 6.0 μM against RWPE-1 and DU145, respectively. Their antiproliferative activities are comparable to, or higher than, related withanolides isolated from *P. angulate*.[86c] Because physangulidine A was the most active and abundant of the three bioactive compounds isolated from *P. angulata*, it was tested on additional cell lines, using 5-fluorouracil as positive control. The results are summarized in Table 14. Compared to 5-fluorouracil, physangulidine A has less antiproliferative activity against nonmalignant 3T3 cell and more antiproliferative activity against HT-29 and K562 cells (Table 14).

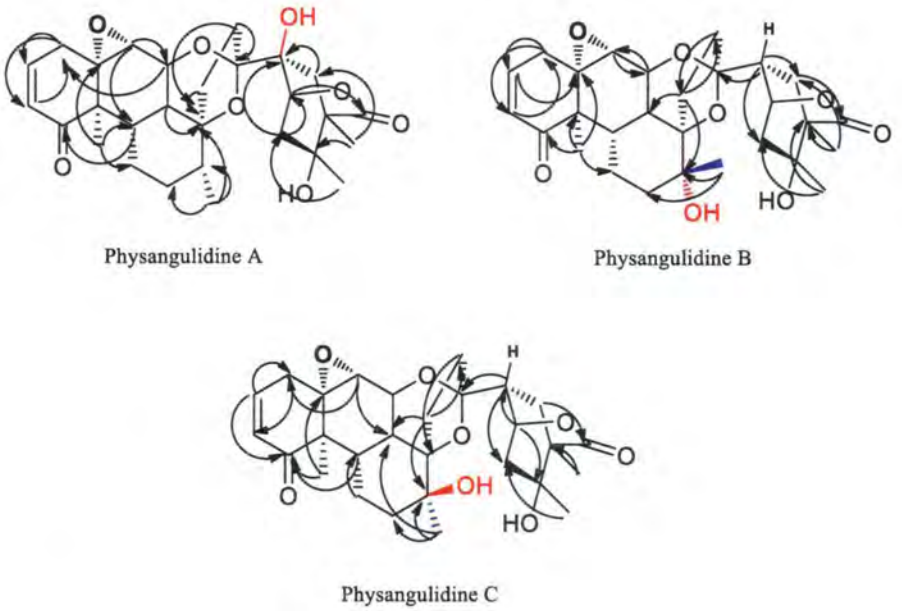
Table 14. GI_{50} Values (μM) of Physangulidine A[a] and 5-Fluororacil on Different Cells

	3T3	H460	HuTu 80	DU145	MCF-7	M-14	HT-29	K562
Physangulidine A	4.12	3.59	4.18	3.56	5.26	4.66	2.73	2.73
5-Fluorouracil	0.28	1.67	4.92	3.11	2.18	5.03	5.92	30.32

[a] GI50 values of physangulidine A in **Table 14** are average values of three tests.
3T3: Nontumorigenic, BALB/c mouse embryo cells. H460: human lung large cell carcinoma.
HuTu 80: human duodenum Adenocarcinoma. DU145: human prostate carcinoma.
MCF-7: human breast adenocarcinoma. M-14: human amelanotic melanoma.
HT-29: human colon adenocarcinoma. K562: human chronic myelogenous leukemia.

In conclusion, we have isolated three new bioactive withanolides, physangulidines A, B and C, from *P. angulata* L. using a bioassay-guided isolation technique. Their structures,

determined by NMR and X-ray crystallography, have an unusual disconnection between C-13 and C-17, a structural feature observed for the first time in the withanolides family.

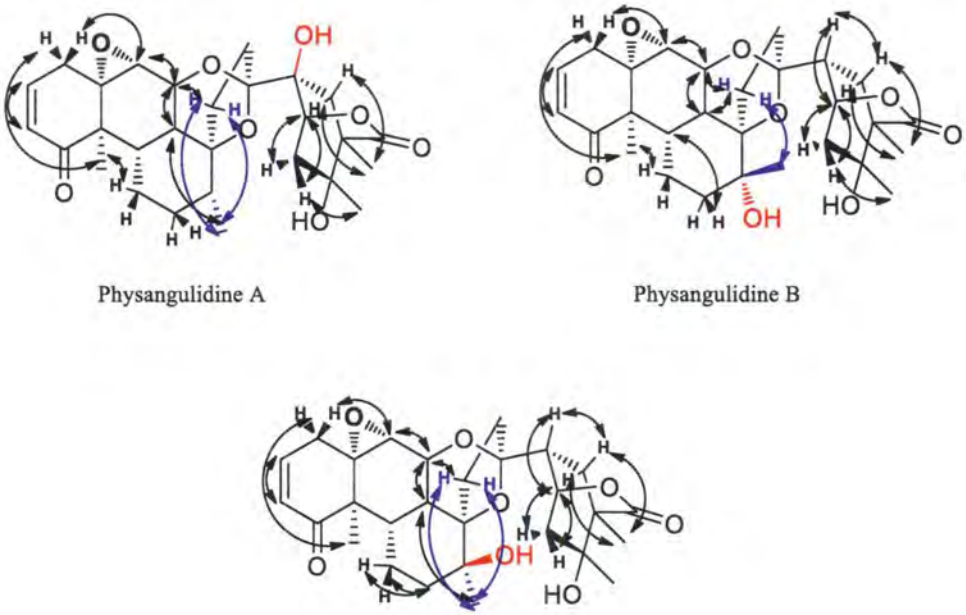


Physangulidine A

Physangulidine B

Physangulidine C

Figure 14. Selected HMBC Interactions in Physangulidines A, B and C



Physangulidine A

Physangulidine B

Physangulidine C

Figure 15. Selected ROESY Interactions in Physangulidines A, B and C

4.3. *Cremastosperma microcarpum* (Annonaceae)

The genus *Cremastosperma* (Annonaceae) is represented by 31 species[91] but has been very poorly investigated phytochemically. There is only one study on C. *polyphlebum*,[92] and no investigation has been conducted on *C. microcarpum*. We investigated *C. microcarpum* and isolated (±)-*trans*-dehydrodiisoeugenol (Figure 16) as the main cytotoxic agent via bioassay-directed fractionation techniques.

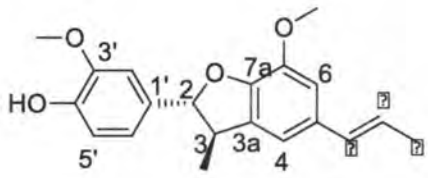


Figure 16. Structure of Trans-dehydrodiisoeugenol

(±)-*Trans*-dehydrodiisoeugenol has been studied previously for its antioxidant and anticancer properties on salivary gland tumor,[93] and it has been recently applied on a skin formulation patent.[94] We found that (±)-*trans*-dehydrodiisoeugenol has moderate cytotoxic activity on different cell lines, compared to a positive control (Doxorubicin, DOXO) (Table 15). (±)-*trans*-Dehydrodiisoeugenol was identified by comparison of its NMR data with literature reports (Table 16).[95]

Table 15. GI_{50} Values (μM) of (±)-*Trans*-dehydrodiisoeugenol[a] and Doxorubicin on Different Cells

Compound	3T3	H460	DU145	MCF-7	M-14	HT-29	K562	Vero
Trans-dehydrodiisoeugenol	63.4	60.5	85.3	38.7	68.8	93.6	48.8	67.8
DOXO	0.029	0.044	0.055	0.074	0.092	0.13	0.044	0.020

[a] GI_{50} values of (±)-Trans-dehydrodiisoeugenol are average values of two tests.

Table 16. NMR data for (±)–*Trans*-dehydrodiisoeugenol and Literature Data

position	^{1}H NMR (400 MHz)		^{13}C NMR (100 MHz)	
	ref [95a]	*(±)-Trans*-dehydrodiisoeugenol	ref [95b]	*(±)-Trans*-dehydrodiisoeugenol
2	5.14 (d, *J*=9.2 Hz, 1H)	5.08 (d, *J*=9.2 Hz, 1H)	93.79	93.77
3	3.48 (dq, *J*=9.2, 6.7 Hz, 1H)	3.43 (dq, *J*=8.8, 6.6 Hz, 1H)	45.62	45.59
4	6.75-7.00 (m, 1H)	6.75 (s, 1H)	113.31	113.28
5	-	-	132.19	132.18
6	6.75-7.00 (m, 1H)	6.77 (s, 1H)	109.23	109.20
7	-	-	144.15	144.13
1'	-	-	132.08	132.07
2'	6.75-7.00 (m, 1H)	6.96 (s, 1H)	108.92	108.89
3'	-	-	146.67	146.64
4'	-	-	145.77	145.75
5'	6.75-7.00 (m, 1H)	6.88 (m, 1H)	114.08	114.03
6'	6.75-7.00 (m, 1H)	6.88 (m, 1H)	119.96	119.96
OCH_3 (on C3')	3.93 (s, 3H)	3.88 (s, 3H)	55.98	55.96
OCH_3 (7)	3.90 (s, 3H)	3.87 (s, 3H)	55.94	55.91
3a	-	-	133.27	133.25
7a	-	-	146.56	146.55
α	6.40 (d, *J*=15.5 Hz, 1H)	6.34 (d, *J*=15.6 Hz, 1H)	130.92	130.89
β	6.11 (dq, *J*=15.5, 5.2 Hz, 1H)	6.09 (dq, *J*=15.6, 6.4 Hz, 1H)	123.48	123.48
γ	1.92 (d, J=5.2 Hz, 3H)	1.86(dd, J=6.8, 1.6 Hz, 3H)	18.38	18.35
CH_3 (on C3)	1.43 (d, *J*=6.7 Hz, 3H)	1.36 (d, *J*=6.8 Hz, 3H)	17.57	17.54
OH	5.69 (s, 1H)	5.61 (s, 1H)	-	-

4.4. *Hyptis lantanaefolia (Lamiaceae)*

Hyptis is a genus of the *Lamiaceae* family, widely spread in the tropical regions of the Americas. There are 300-400 species which may be annual or perennial, appearing as

small herbs or large shrubs.[96] *H. lantanaefolia* is a very poorly investigated species; there is only one report on the xanthine oxidase inhibitory activity of the ethanol extract of *H. lantanaefolia*.[97] We found that the ethanol extract of *H. lantanaefolia* has high cytotoxic activity and the bioassay-directed fractionation afforded semi-purified chromatographic fractions LHL-14 and LHL-15 both of which had extremely high activities on different cell lines (IC_{50} is lower than 50 ng/mL) (Figure 17). The fractions LHL-14 and LHL-15 are currently under investigation.

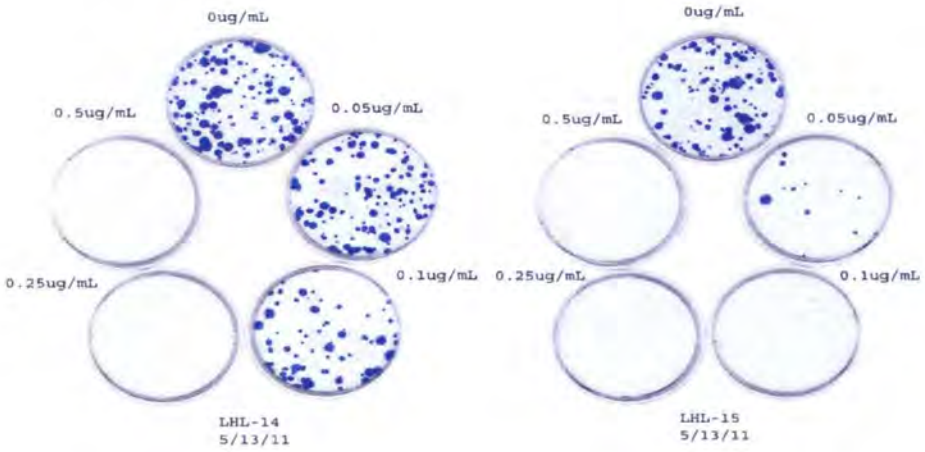


Figure 17. Cytotoxic Activity of Fractions LHL-14 and LHL-15

4.5 *Bocconia intengrifolia (Papaveraceae)*

Bocconia is a small genus in the *Papaveraceae* family, representing 10 species,[98] but up to now there has been no investigation conducted on *B. intengrifolia*. Our collaborators in Peru (Professor Vaisberg's group at UPCH) collected this plant species and found that the ethanol extract had very good cytotoxic activity. Bioassay directed fractionation allowed us to find the most active chromatographic fraction PBI-13, which is currently under investigation.

4.6 Other Plant Species Studied

We have active fractions of the following plant extracts: *Humiria balsamifera* (Humiriaceae), *Rollinia andicola* (Annonaceae), *Hippeastrum puniceum* (Amaryllidaceae), *Aniba riparia* (Lauraceae), and I am instructing other members in Dr. Hammond's group on how to purify them further. Other plant extracts lost their bioactivity during separation, and we failed to isolate any bioactive compounds. These plants are: *Terminalia Amazonia* (Combretaceae), *Piper concinnatoris* (missing), *Paullinia (missing)* (Sapindaceae), *Plukenetia volubillis* (Euphorbiaceae) and *Scutia sp.* (Phammaceae). Their bioactivity loss may be due to two factors: first, the plants were collected from the late 1990's to early 2000's; the active components could have decomposed during the long storage period. Second, the cytotoxic activity we determined could have come from a synergistic effect of different components, and therefore the activity was lost during purification.

4.7. Summary

We have isolated three novel antiproliferative withanolides with an unusual carbon framework, namely, physangulidines A, B and C, isolated from *Physalis angulata* L. using a bioassay-directed isolation technique, and their structures were confirmed by NMR spectroscopy and X-ray crystallography techniques. All three withanolides showed significant antiproliferative activity (GI_{50}<4.0μg/mL) on DU145 and RWPE-1 cells. Compared to 5-fluorouracil, physangulidine A has less antiproliferative activity against nonmalignant 3T3 cell and more antiproliferative activity against HT-29 and K562 cells The antiproliferative mechanism of physangulidine A is currently under investigation.

Similarly, (±)-*trans*-dehydrodiisoeugenol was isolated from *Cremastosperma microcarpum*, as the main cytotoxic and identified by comparison of its NMR data with a literature report. *Hyptis lantanaefolia* and *Bocconia intengrifolia* have been found to contain cytotoxic agents; LHL-14, LHL-15 and PBI-13 are the most cytotoxic fractions. We are working on LHL-14, LHL-15 and PBI-13 to find pure cytotoxic compound(s).

4.8. Experimental Section

General

Plant material was collected in the Aguaruna region of northeastern Perú, from the late 1990's to early 2000's. Methanol for HPLC separation was HPLC grade, and the rest of the solvents were ACS-grade. Column chromatography was carried out using silica gel (230-400 mesh, Silicycle; Quebec, Canada) and octadecyl-functionalized silica gel (C18, 200-400 mesh, Aldrich; St. Louis, MO, USA). HPLC was performed with a Waters 600E equipped with rheodyne injector and a PDA detector, using a Nova-Pak column (Waters, 6μm, 7.8x300 mm, flow rate 1.0 mL/min) or a SymmetryPrep C_{18} column (Waters, 7μm, 300x19 mm, flow rate 4.0 mL/min) and water and methanol as solvent system. NMR spectra of physangulidines A, B and C were collected at 25.0 °C in $CDCl_3$ at 699.81 MHz in a 5 mm $^{1}H(^{13}C/^{15}N)$ (^{13}C enhanced) Cold Probe on a VNMRS700 Varian (Agilent) Spectrometer. ^{1}H NMR spectra of physangulidines A, B and C were recorded at 700 MHz, while their ^{13}C NMR spctra were recorded at 175 MHz. UV spectra of physangulidines A and B were recorded in methanol by a Varian Cary 50 Bio UV-Visible Spectrophotometer. FTIR spectra of physangulidines A and B were recorded in ATR (attenuated total reflection) solid mode using a Perkin Elmer Spectrum 100. Melting

points of physangulidines A and B were measured in a DigiMelt PMA 160 melting point apparatus. Crystallographic data of physangulidines A and B were collected by an Agilent Technologies/Oxford Diffraction Gemini CCD diffractometer at 293 K using CuKα radiation. Crystallographic data of physangulidines A (CCDC-858987) and B (CCDC-858988) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

NMR spectra of (±)-*trans*-dehydrodiisoeugenol were collected at 25.0 °C in $CDCl_3$ in a Varian Inova 400 MHz Spectrometer. ^1H NMR spectrum of (±)-*trans*-dehydrodiisoeugenol was recorded at 400 MHz, while its ^{13}C NMR spectrum was recorded at 100 MHz. Cytotoxic activity of *Physalis angulata*, fractions and physangulidine A, B and C were evaluated by MTT assay. Cytotoxic activity of other plant extracts was evaluated using the sulforhodamine B (SRB) assay method.

The MTT assay

The DU145 and RWPE-1 cell lines were purchased from American Type Tissue Collection (ATCC, Manassas, VA). The DU145 cell line represents human hormone-insensitive metastatic prostate cancer cells and RWPE-1 is derived from histologically normal human prostate epithelial cells that were immortalized by transfection with HPV-18 DNA. Cells were maintained in standard culture in a humidified incubator at 37°C with 5% CO_2. DU145 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) (GIBCO, Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum (FBS, 15 min at 65°C, GIBCO) and 1% penicillin/streptomycin (10,000 units each per 1 mL; GIBCO). RWPE-1 cells were cultured in Keratinocyte SFM medium (GIBCO) containing Human Keratinocyte Growth Supplement (GIBCO). For

antiproliferative activity assays, cells were plated in 96 well plates (1,000 cells per well) and were treated the following day by addition of the experimental fraction or vehicle as control. Plant extracts or fractions were resuspended in dimethylsulfoxide (DMSO) to give a concentration of 2 mg/mL and then diluted in cell culture medium then added to triplicate wells to give final concentrations of 4, 2, 1, 0.5, 0.25, or 0 μg/mL. Cells were cultured for 5 days and then relative cell number was determined using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, as described previously.[99] The GI_{50} value (the concentration required for 50% inhibition of cell proliferation) was estimated from the resulting dose response graphs.

The Sulforhodamine B (SRB) assay method[100]

To determine the cytotoxicity of the compounds, cells were plated into 96-well tissue culture plates and in their corresponding growth medium at approximately 10% confluency (BALB/3T3 at 3,500 cells/well, Vero at 2,500 cells/well, H460 at 1,500 cells/well, M-14 at 5,000 cells/well, DU145 at 3,500 cells/well, MCF-7 at 5,000 cells/well, HT-29 at 3,000 cells/well, and K562 at 4,000 cells/well), and incubated at 37°C in a 5% CO_2 and 95 % air humidified atmosphere for 24 h to allow cells to attach. A plate containing each of these cells was fixed in situ with trichloroacetic acid (TCA) in order to obtain the cell values at cero time before adding the compounds. The rest of the plates containing the different cell lines received serial dilutions of the compound to be tested at the following final concentrations: 62.5, 15.625, 3.90625, and 0.97656 μg/mL. The plates were then incubated at 37 °C in a 5% CO_2 and 95 % air humidified atmosphere for 48 h. The assay was terminated by the addition of cold TCA. TCA treated plates were incubated at 4 °C for 1 hour and then washed five times with tap water to

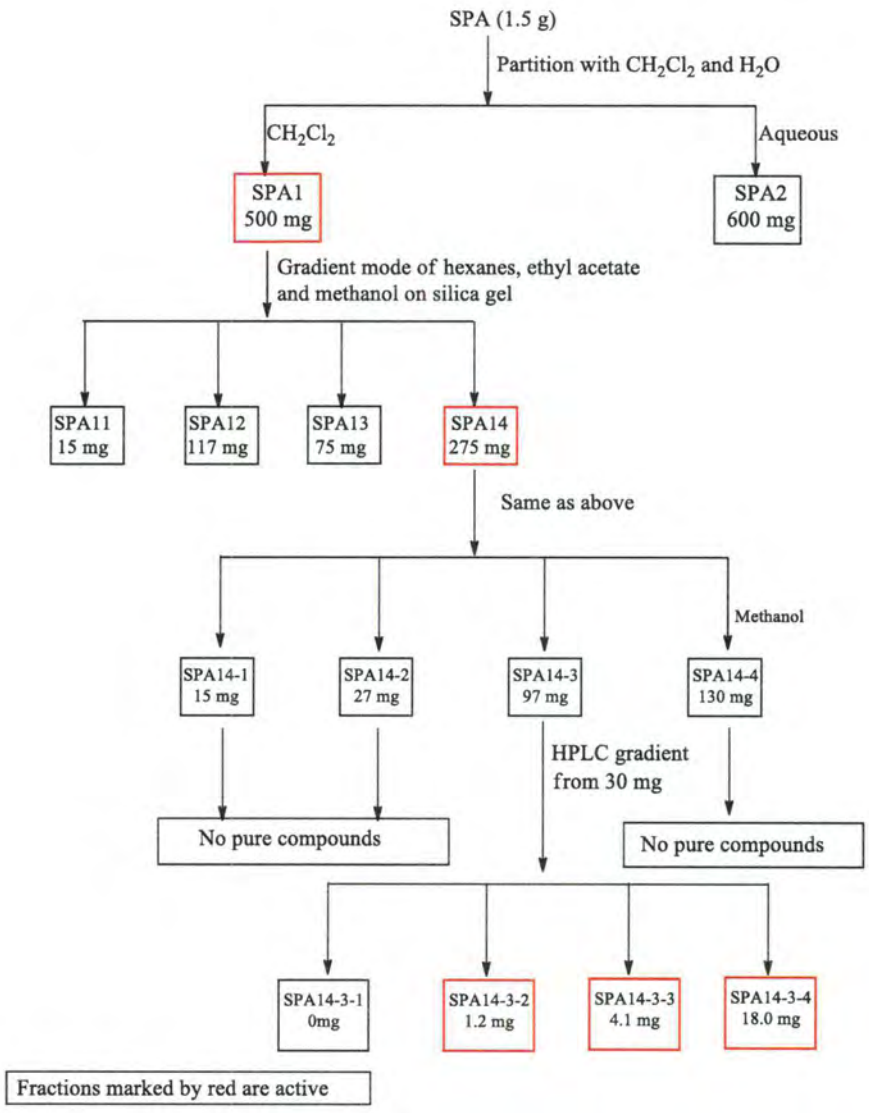
remove TCA and air dried. Background optical densities were measured in wells incubated with growth medium without cells. TCA-fixed cells were stained for 20 minutes with 0.4% (w/v) SRB dissolved in 1% acetic acid. At the end of the staining period unbound dye was removed by washing four times with 1% acetic acid. After air drying the plates, bound dye was solubilized with 10 mM Tris base (pH 10.5) and the absorbance read on an automated plate reader at a wavelength of 550 nm. The GI_{50} value was defined as the concentration of test sample resulting in a 50% reduction of absorbance as compared with untreated controls that received a serial dilution of the solvent in which the test samples were dissolved, and was determined by linear regression analysis.

For K562 cells, which grow in suspension, instead of fixing and staining with SRB, cells were counted using a Coulter counter.

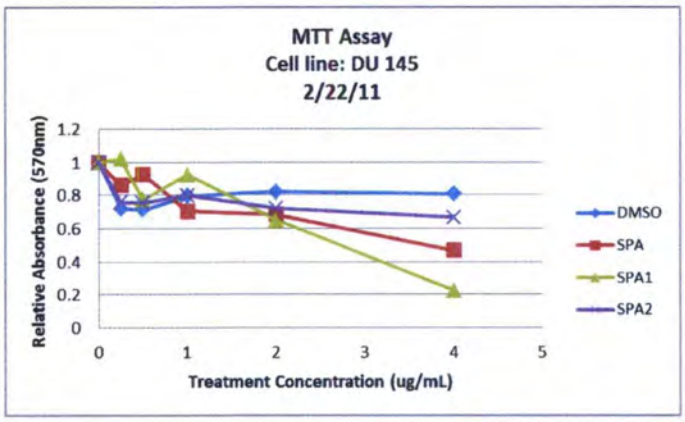
Physalis angulata

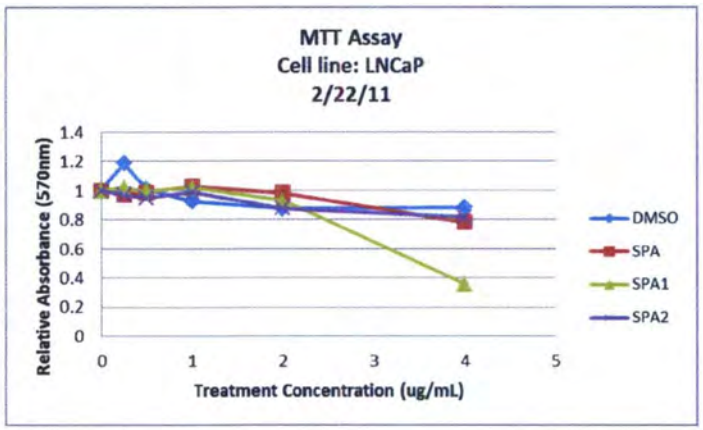
Leaves, stem and fruits of *Physalis angulata* L were collected in Rio Domingusa. Kuith/Barranquita, Amazonas Department, Northeastern Perú, and identified by the team led by Walter Lewis (voucher number: 18597, extract number: 1159) in April 3, 2002. 46 g of the dried and grounded material was extracted by ethanol (1 L, 95%) at room temperature for 7 days to give 6.26 g extract, which was denoted as SPA. An aliquot (1.5 g) of SPA was partitioned between dichloromethane (40 mL) and water (40 mL), which afforded two fractions, namely organic (SPA1, 500 mg) and aqueous (SPA2, 600 mg) fraction (Bioassay directed fractionation, Scheme 21). In vitro cytotoxic study showed that organic fraction (SPA1) is active (Figure 18), and which was separated on silica gel chromatography and eluted by hexane, ethyl acetate and methanol in gradient mode to

give further four more fractions, SPA11 (15 mg), SPA12 (117 mg), SPA13 (75 mg) and SPA14 (275 mg). Then the most active SPA14 (Figure 19) was subjected to the same chromatography separation as above to further give four fractions: SPA14-1 (15 mg), SPA14-2 (27 mg), SPA14-3 (97 mg) and SPA14-4 (130 mg). Unfortunately, we failed to isolate any pure compound from SPA14-1, SPA14-2 and SPA14-4. SPA14-3 (30 mg) was separated on HPLC reverse phase C18 column eluted in gradient mode of methanol and water (from 80% methanol to 100% methanol) and detected at 254 nm, yielding SPA14-3-1 (0 mg), SPA14-3-2 (1.2 mg) (physangulidine B), SPA14-3-3 (4.1 mg) (physangulidine C) and SPA14-3-4 (18 mg) (physangulidine A). All three of them showed cytotoxic activity against DU145 and RWPE-1 (Figure 20). Their structures were determined by NMR spectra analysis and X-ray crystallography.



Scheme 21. Bioassay Directed Fractionation of *P. angulata* L





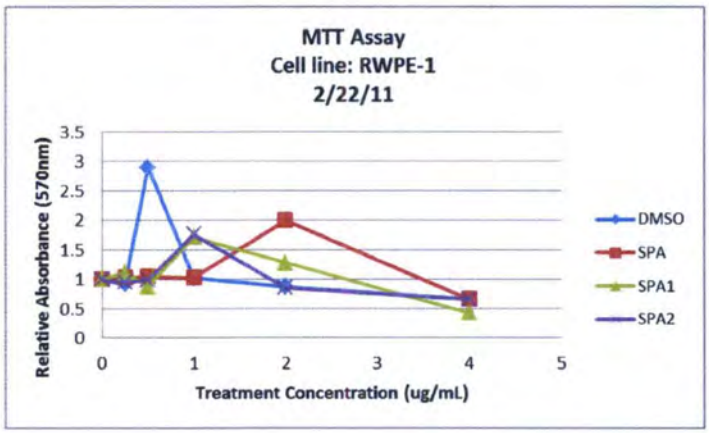
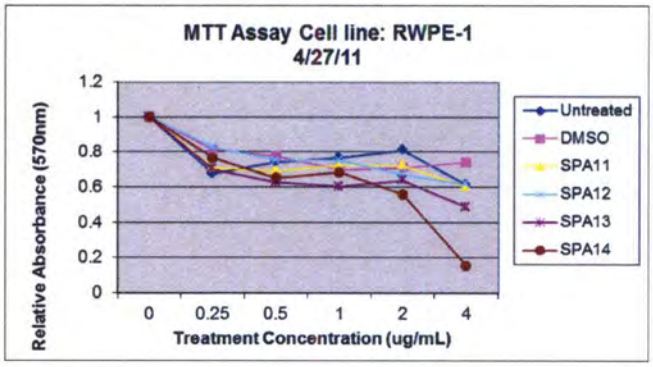
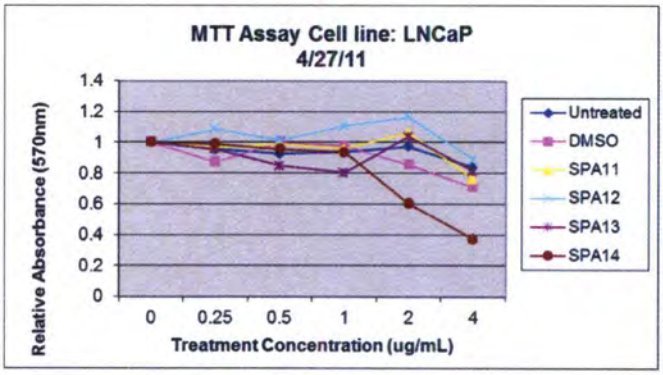
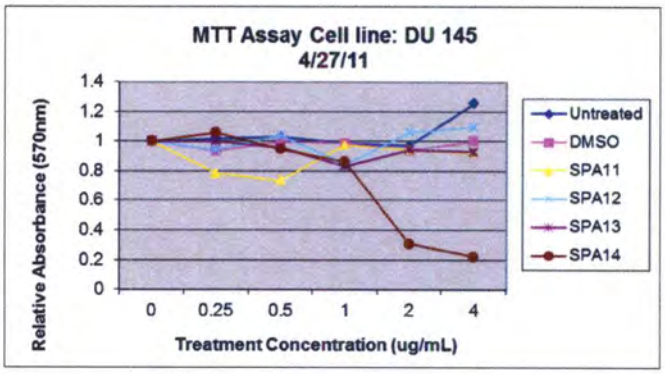


Figure 18. Cytotoxic Activity of SPA, SPA1 and SPA2







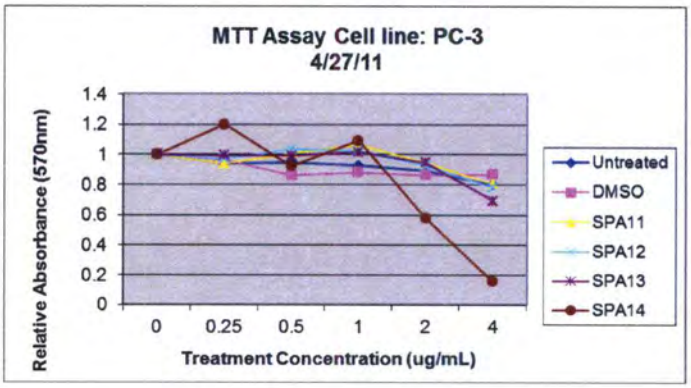
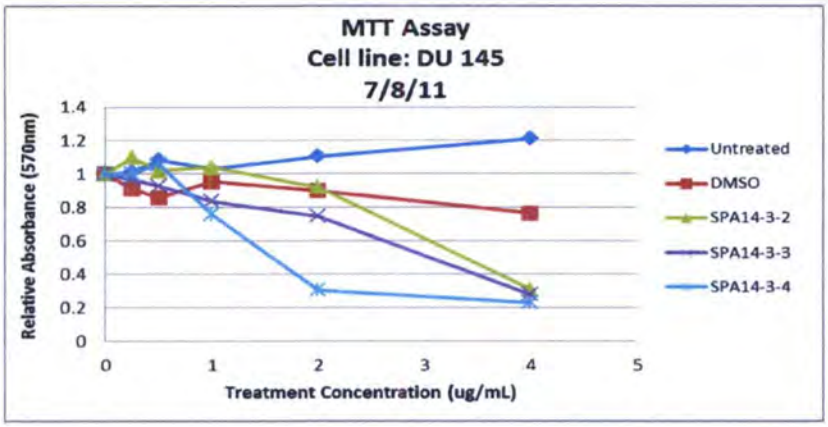


Figure 19. Cytotoxic Activity of SPA11, SPA12, SPA13 and SPA14



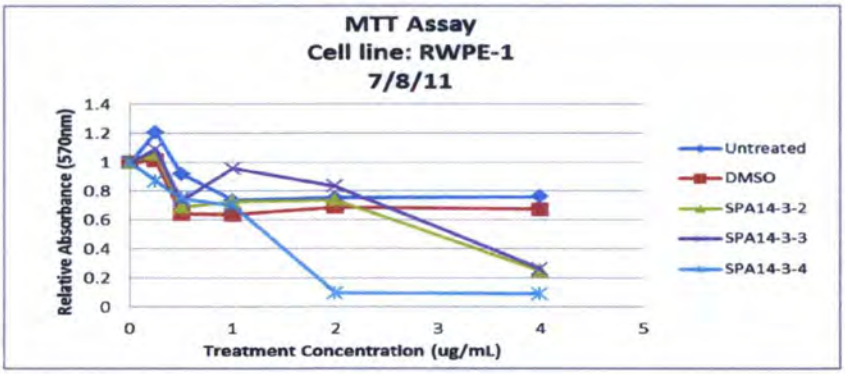
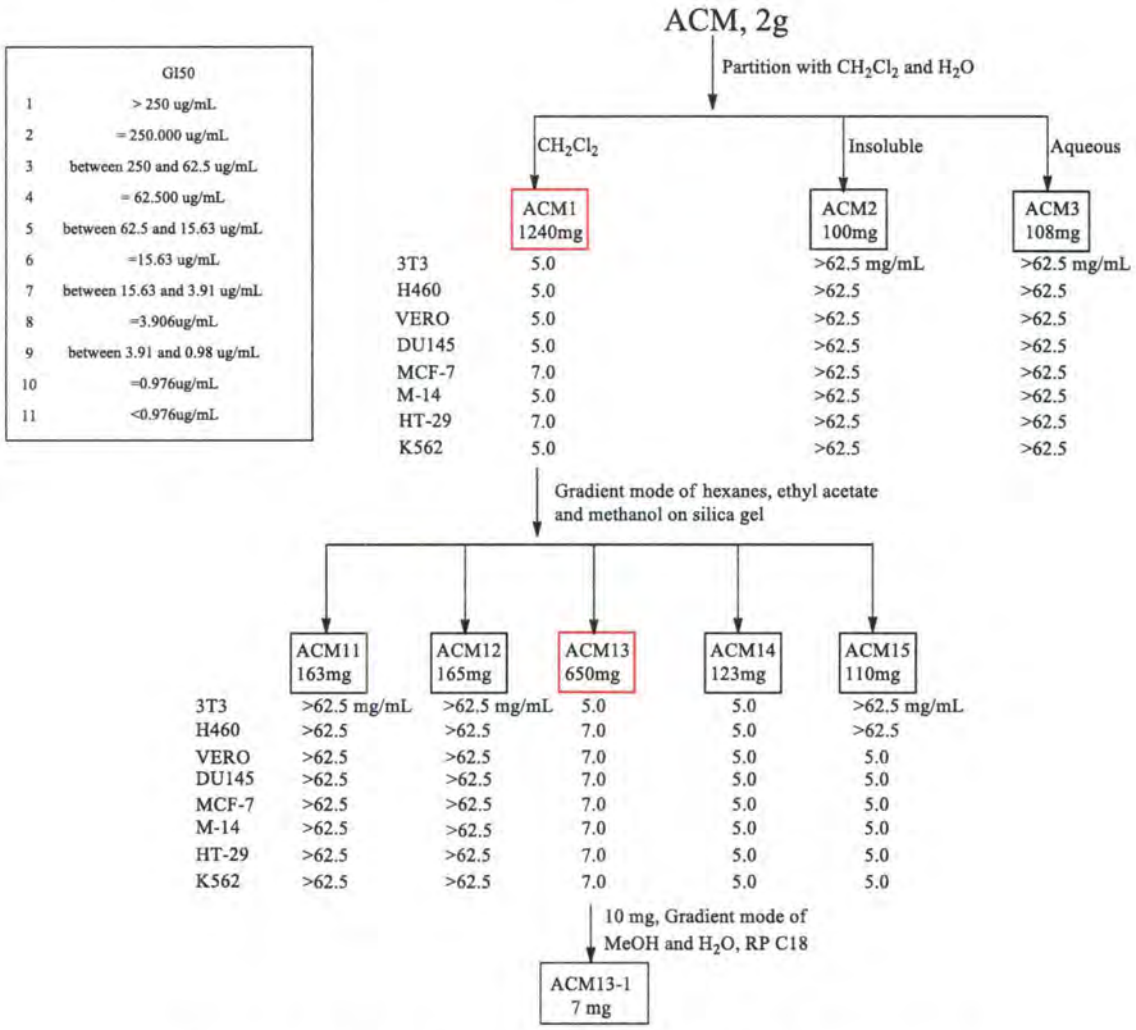


Figure 20. Cytotoxic Activity of SPA14-3-2, SPA14-3-3 and SPA14-3-4

Cremastosperma microcarpum

Leaflets and stems of *C. microcarpum* were collected at Copallin, province of Bagua, Amazonas Department, Perú, in May 1999 (voucher number: 19759, extract number: 2967). Air-dried and ground leaflets and stems of *C. microcarpum* (50 g) were extracted with ethanol (1 L, 95%) at room temperature for 7 days. The ethanolic solution was concentrated to dryness under reduced pressure to yield 3.66 g of extract, denoted as ACM. An aliquot (2.0 g) was partitioned between dichloromethane (45 mL) and water (45 mL), which afforded an organic fraction (ACM1, 1240 mg), insoluble residue

(ACM2, 100 mg) and an aqueous fraction (ACM3, 108 mg). *In vitro* cytotoxic studies indicated that ACM1 was the only active fraction. Hence, it was purified on silica gel chromatography and eluted with hexanes, ethyl acetate and methanol in gradient mode to yield five sub-fractions: ACM11 (163 mg), ACM12 (165 mg), ACM13 (650 mg), ACM14 (123 mg) and ACM15 (110 mg). An aliquot of ACM13 (10 mg) was the most cytotoxic fraction, and An aliquot (10 mg) was further chromatographed using a reverse phase C18 column in a solvent gradient of methanol-water (80%, V/V) to pure methanol, yielding (±)-*trans*-dehydrodiisoeugenol (7.0 mg) (Scheme 22).



	GI50
1	> 250 ug/mL
2	= 250.000 ug/mL
3	between 250 and 62.5 ug/mL
4	= 62.500 ug/mL
5	between 62.5 and 15.63 ug/mL
6	=15.63 ug/mL
7	between 15.63 and 3.91 ug/mL
8	=3.906ug/mL
9	between 3.91 and 0.98 ug/mL
10	=0.976ug/mL
11	<0.976ug/mL

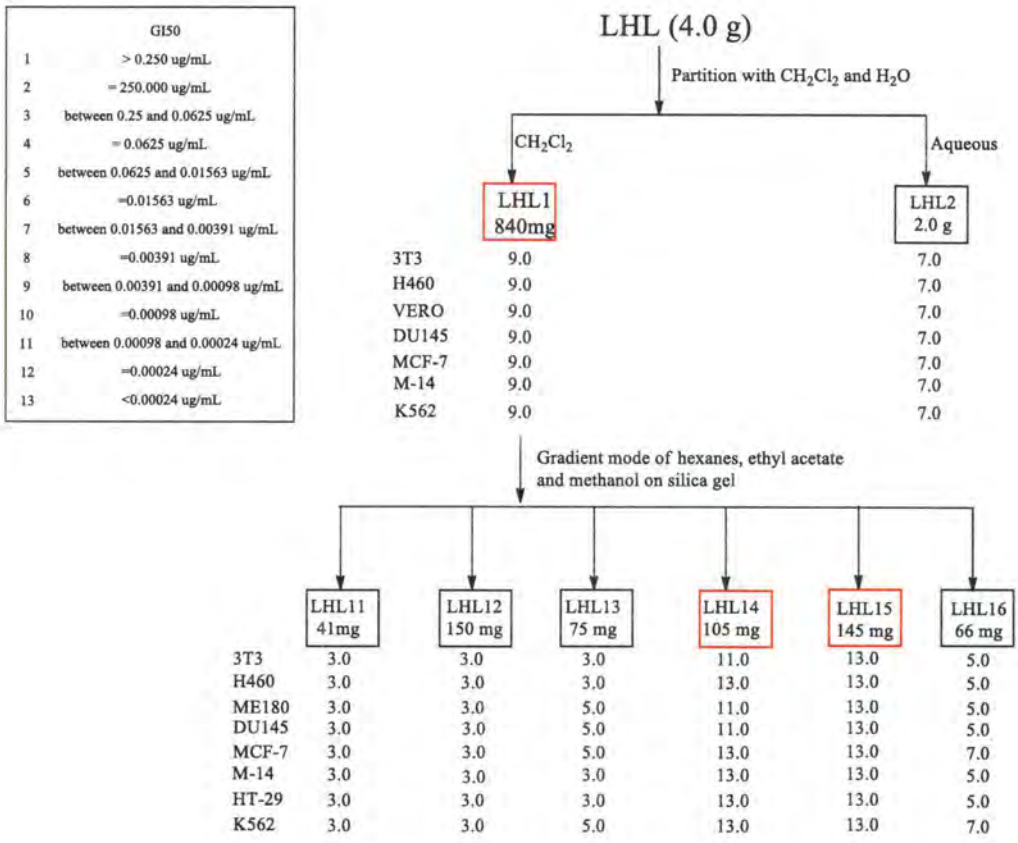
	ACM1 1240mg	ACM2 100mg	ACM3 108mg
3T3	5.0	>62.5 mg/mL	>62.5 mg/mL
H460	5.0	>62.5	>62.5
VERO	5.0	>62.5	>62.5
DU145	5.0	>62.5	>62.5
MCF-7	7.0	>62.5	>62.5
M-14	5.0	>62.5	>62.5
HT-29	7.0	>62.5	>62.5
K562	5.0	>62.5	>62.5

	ACM11 163mg	ACM12 165mg	ACM13 650mg	ACM14 123mg	ACM15 110mg
3T3	>62.5 mg/mL	>62.5 mg/mL	5.0	5.0	>62.5 mg/mL
H460	>62.5	>62.5	7.0	5.0	>62.5
VERO	>62.5	>62.5	7.0	5.0	5.0
DU145	>62.5	>62.5	7.0	5.0	5.0
MCF-7	>62.5	>62.5	7.0	5.0	5.0
M-14	>62.5	>62.5	7.0	5.0	5.0
HT-29	>62.5	>62.5	7.0	5.0	5.0
K562	>62.5	>62.5	7.0	5.0	5.0

Scheme 22. Bioassay Directed Fractionation of *C. microcarpum*

Hyptis lantanaefolia

Leaves, stem and flower of *H. lantanaefolia* were collected at road from Chiple to Cutervo, province of Jaén, Cajamarca Department, Perú in Oct 6, 2005. (Voucher number: 19547, extract number: 2352). Dried leaflets, stems and flower of H. lantanaefolia (70 g) were extracted with ethanol (1L, 95%) at room temperature for 7 days. The ethanolic solution was concentrated to dryness under reduced pressure to yield the extract (5.12 g), denoted as LHL. An aliquot of LHL (4.0 g) was partitioned between dichloromethane (60mL) and water (65 mL), affording an organic fraction (LHL1, 840 mg) and an aqueous fraction (LHL2, 2.0 g) (Scheme 23). LHL1 was more active on different cell

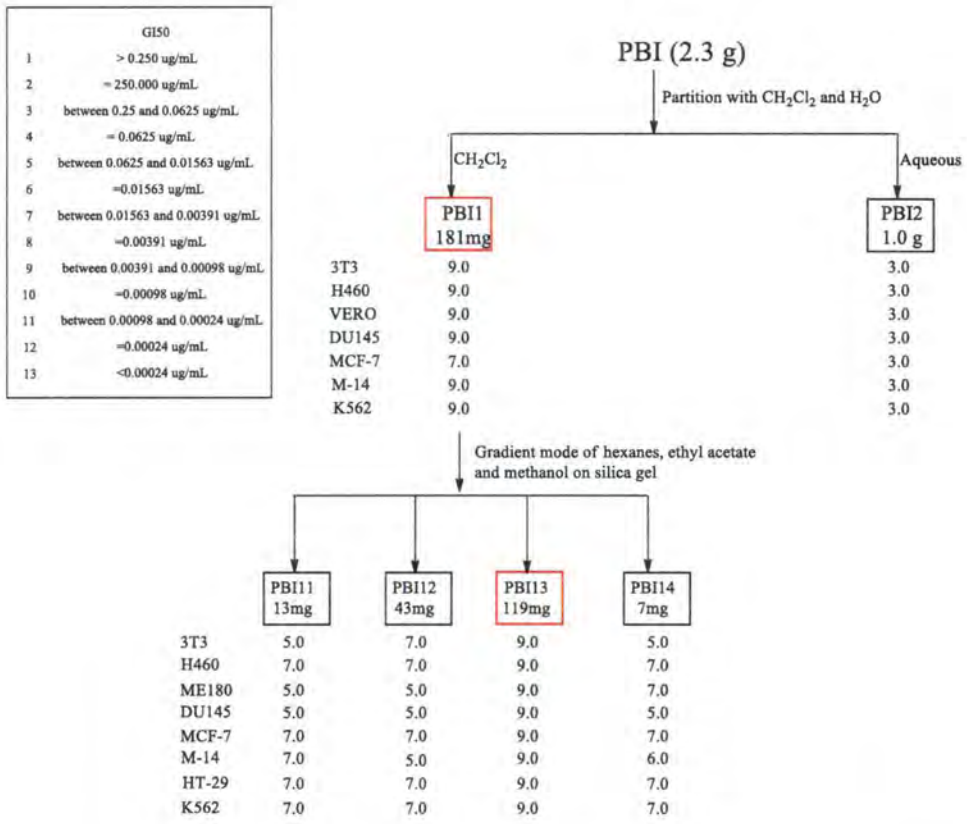


Scheme 23. Bioassay Directed Fractionation of *H. lantanaefolia*

lines than LHL2, and LHL1 was further subjected to silica gel chromatographic separation to give six fractions: LHL11 (41 mg), LHL12 (150 mg), LHL13 (75 mg), LHL14 (105 mg), LHL15 (145 mg) and LHL16 (66 mg). Of all fractions LHL14 and LHL15 were extremely high in vitro cytotoxic activities. We are currently working on both LHL14 and LHL15 to isolate active agents.

Bocconia intengrifolia

Bark of *B. intengrifolia* was collected on the road from Santo Domingo de la Capilla to San Pedro, province of Cutervo, Cajamarca Department, Perú (Voucher number: 19644, extract number: 2367). Dried and grounded bark of *B. intengrifolia* (50) was extracted by ethanol (1L, 95%) at room temperature for 7 days to give crude extract (4.47 g) after dryness of ethanol. An aliquot of PBI (2.3 g) was partitioned between dichloromethane (50 mL) and water (50 mL), affording an organic fraction (PBI1, 181 mg) and an aqueous fraction (PBI2, 1.5 g) (Scheme 24). *In vitro* cytotoxicity study showed that the organic fraction PBI1 is active; following fractionation of PBI1 on silica gel furnished four fractions: PBI11 (13 mg), PBI12 (43 mg), PBI13 (119 mg) and PBI14 (7 mg), of which PBI13 is most active fraction. PBI13 is currently under investigation.



Scheme 24. Bioassay Directed Fractionation of *B. intengrifolia*

Ongoing plant studies

Bark and leaves of *Humiria balsamifera* (Humiriaceae) were collected in the trail to Quebrada Sunsunza, El Porvenir, Aramango, province of Bagua, Amazonas department, Perú (Voucher number: 19478, extract number: 2278). Dried and grounded bark and leaves of *H. balsamifera* (50 g) were extracted with ethanol (1L, 95%) to give crude extract (6.69 g) after filtration and dryness of ethanol solution. Then, the extract was subjected to simple partition between water and dichloromethane; the bioactive organic layer is currently under study.

Fruits of *Rollinia andicola* (Annonaceae) were collected at El Tigre, Cambio-Pitec, Copallín, province of Bagua, Amazonas Department, Perú (Voucher number: 19877, extract number: 2900). Dried and grounded flowers of *R. andicola* (61 g) were extracted with ethanol (1L, 95%) to give crude extract (7.71 g). The bioactive organic layer is currently under study.

Bulbs of *Hippeastrum puniceum* (Amaryllidaceae) were collected at Kunchin, Imaza, province of Bagua, Amazonas Department, Perú in Aug 9, 2001(Voucher number: 17506, extract number: 435). Dried and grounded *H. puniceum* (43 g) was extracted with ethanol (1L, 95%) to give crude extract (3.36 g). Bioactive organic layer is currently under investigation.

The bark of *Aniba riparia* (Lauraceae) was collected at Wichim, Imaza, province of Bagua, Amazonas Department, Perú in Nov 26, 2002 (Voucher number: 19366, extract number: 2239). Dried and grounded bark of *A. riparia* (50 g) was extracted with ethanol (1L, 95%) to yield crude extract (4.13 g) after dryness. The bioactive organic layer is currently under investigation.

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60. We modified Gogosz's reaction condition by replacing CH_2Cl_2 with $CDCl_3$ considering two reasons: 1) Gold catalyst 4, purchased from Aldrich, is more efficient in $CDCl_3$ than in CH_2Cl_2. 2) Reaction can be easily monitored by ^{1}H-NMR.

61. We chose two steps in one pot reaction, because the gold catalyzed isomerization is not effective in CD_3CN and Selectfluor has low solubility in $CDCl_3$.

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APPENDIX A: LIST OF ABBREVIATIONS

DMP: Dess-Martin Periodinane

DMSO: Dimethylsulfonyl Oxide

dr: diastereomeric ratio

FTIR: Fourier transform infrared spectroscopy

ee: Enantiomeric excess

EI: Electrospray Ionization

EPR: Electron paramagnetic resonance

Eq: Equation

Equiv: Equivalence

h: Hour

HPLC: High performance liquid chromatography

HRMS: High resolution mass spectroscopy

Hz: Hertz

IR: infrared

LDA: Lithium diisopropylamide

M: Molar

m: meta

mg: milligram

min: minute

mL: milliliter

mmol: millimole

NMR: Nuclear magnetic resonance spectroscopy

o: ortho

p: para

ppm: Parts per million

r.t.: room temperature

TBS: *tert*-Butyldimethylsilyl

tert: tertiary

TABF: Tetrabutylammonium flouride

TIPS: Triisopropylsilyl

TMS: Trimethylsilyl

THF: Tetrahydrofuran

TLC: Thin layer chromatography

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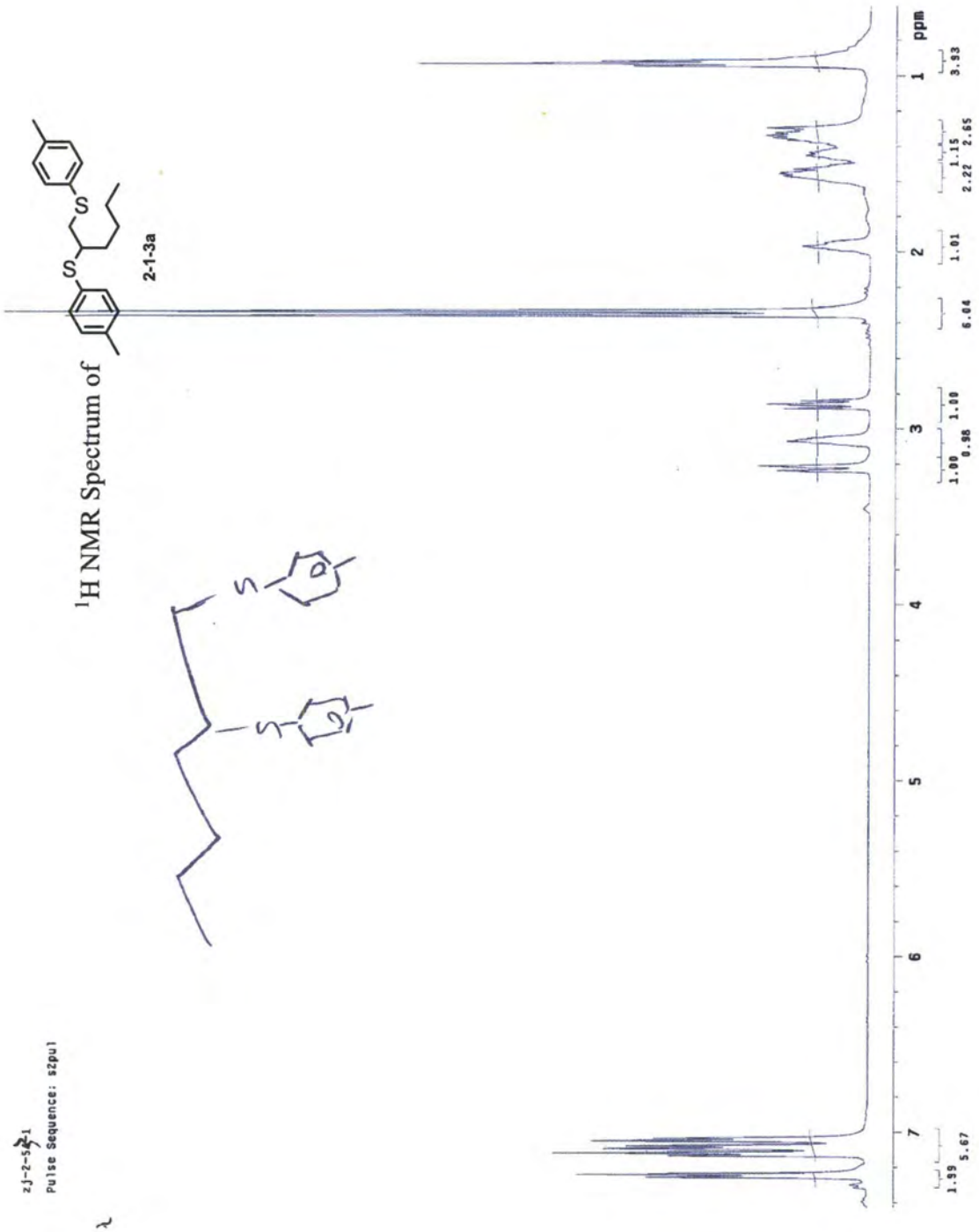
APPENDIX C: NMR SPECTRA FOR NEW COMPOUNDS



zj-2-S3-1

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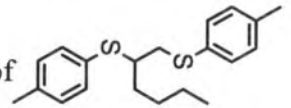
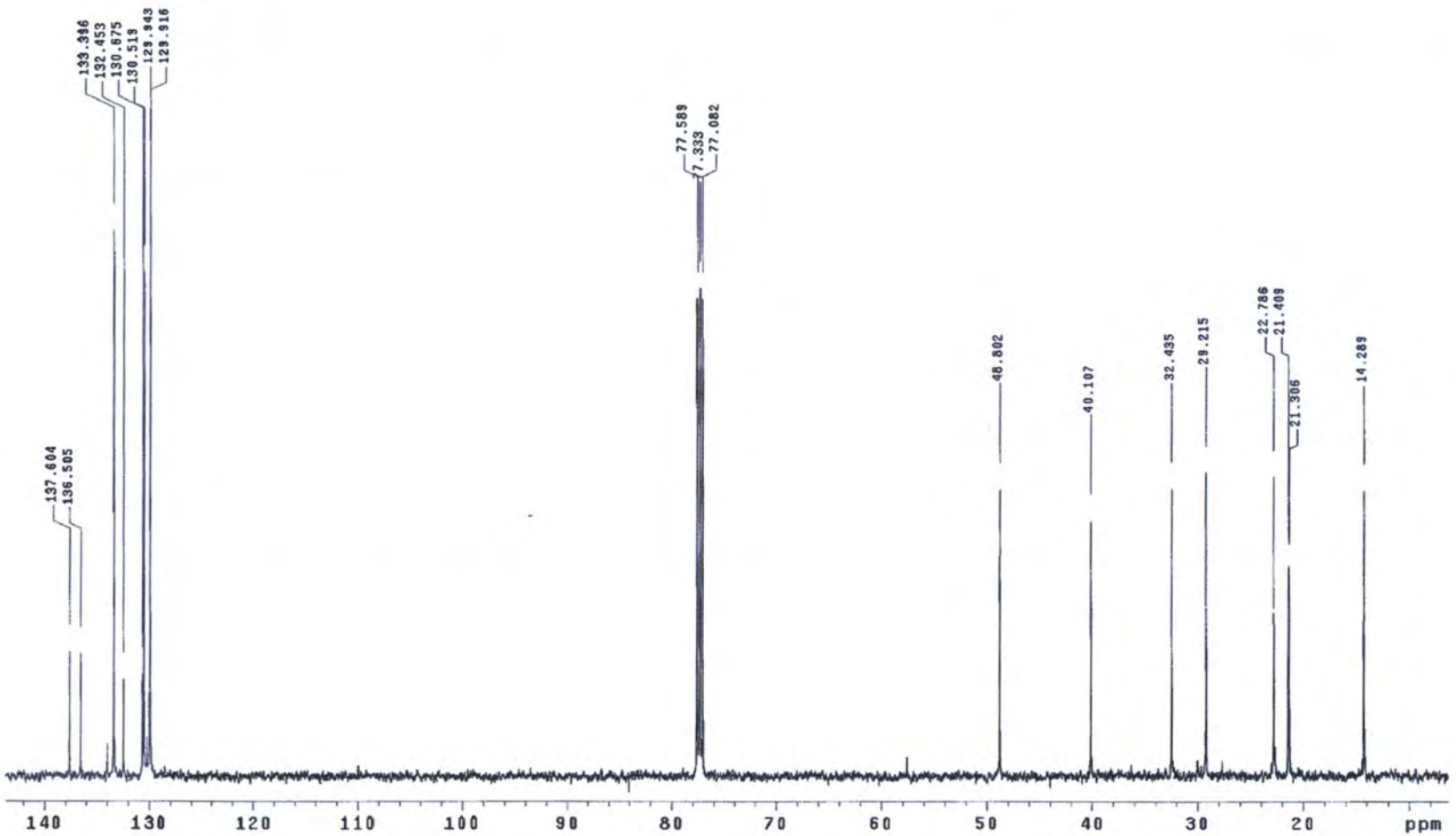
Sample directory:
File: CARBON

Pulse Sequence: s2pul

^{13}C NMR Spectrum of 

2-1-3a



zj-2-53-1

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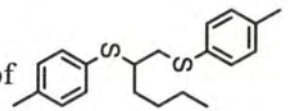
^{13}C NMR Spectrum of 

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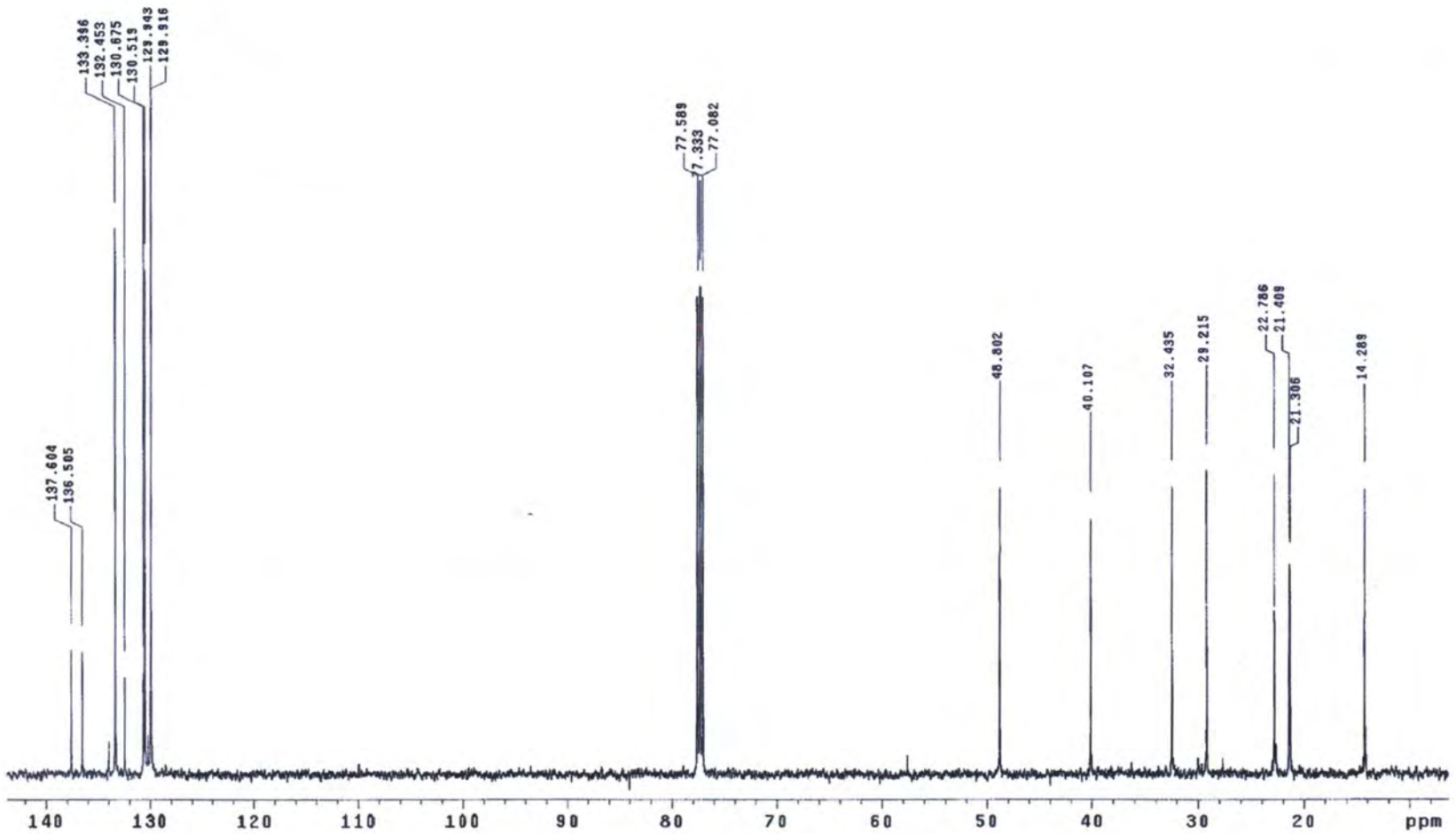
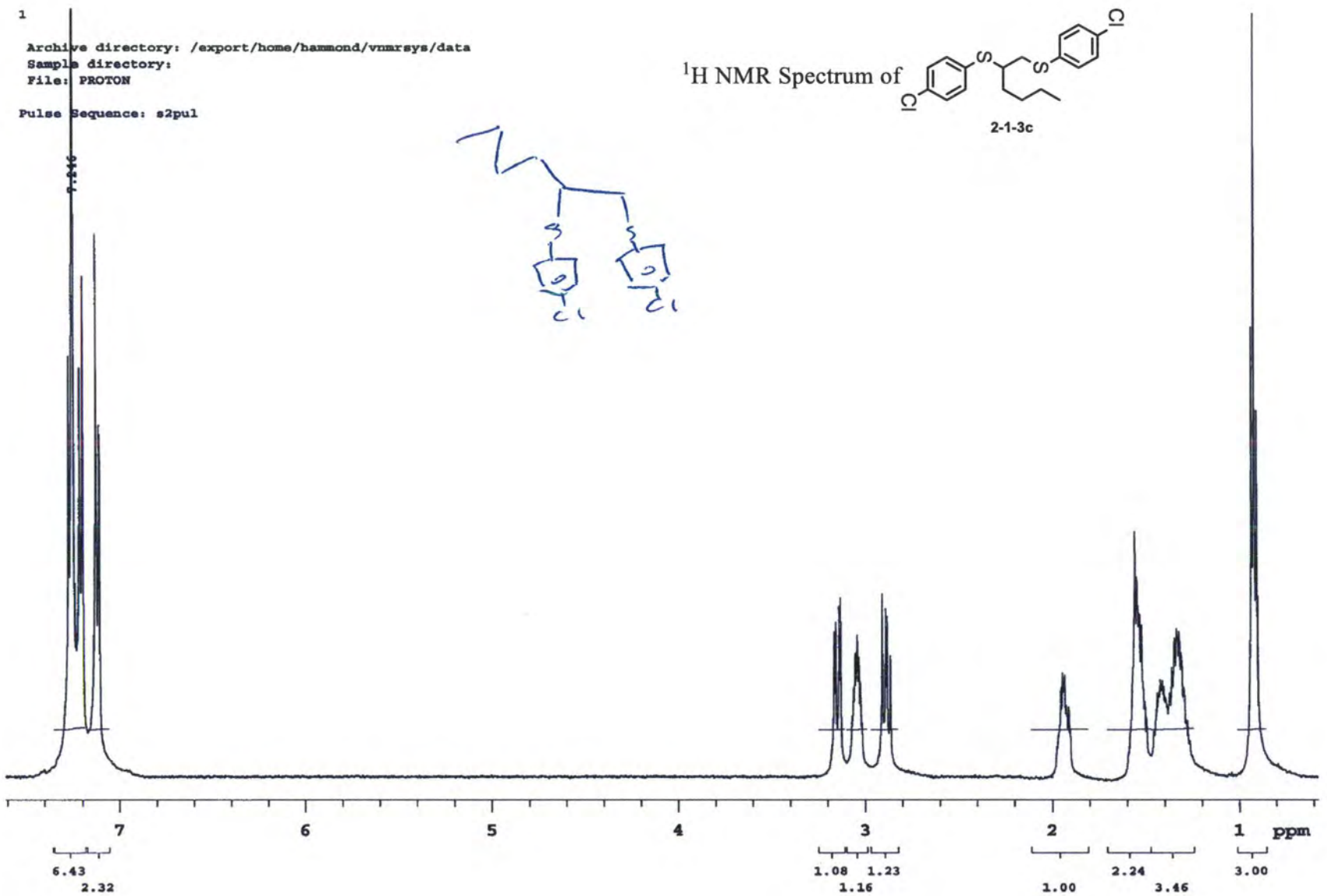
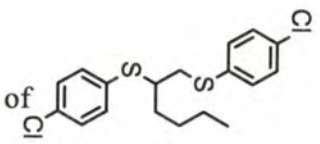



1
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
7.246
^{1}H NMR Spectrum of
2-1-3c
7
6
5
4
3
2
1
ppm
6.43
2.32
1.08
1.23
1.16
1.00
2.24
3.46
3.00

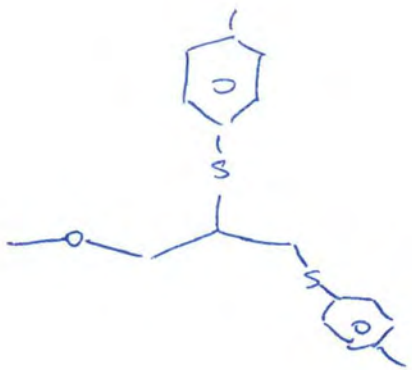
^{13}C NMR Spectrum of

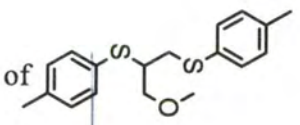


2-1-3c

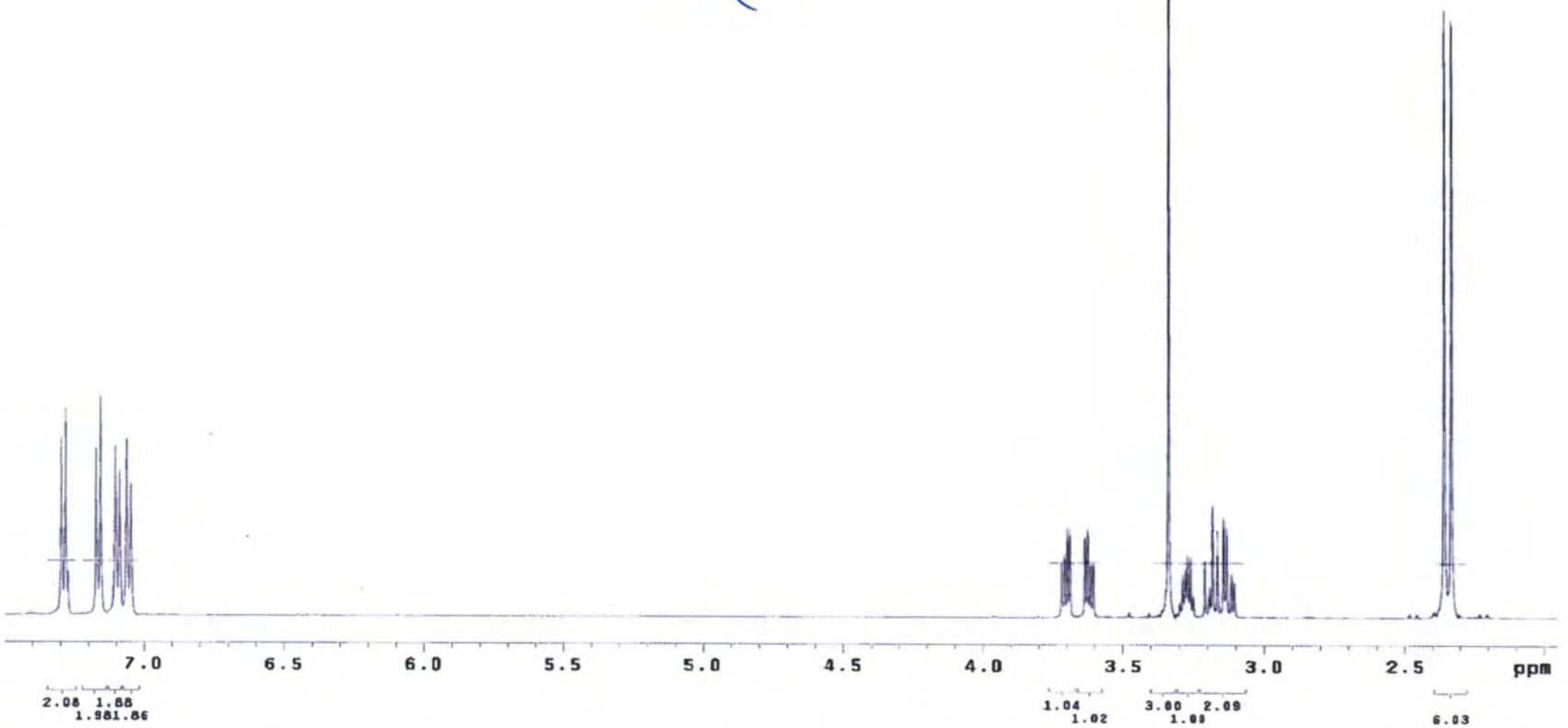
d

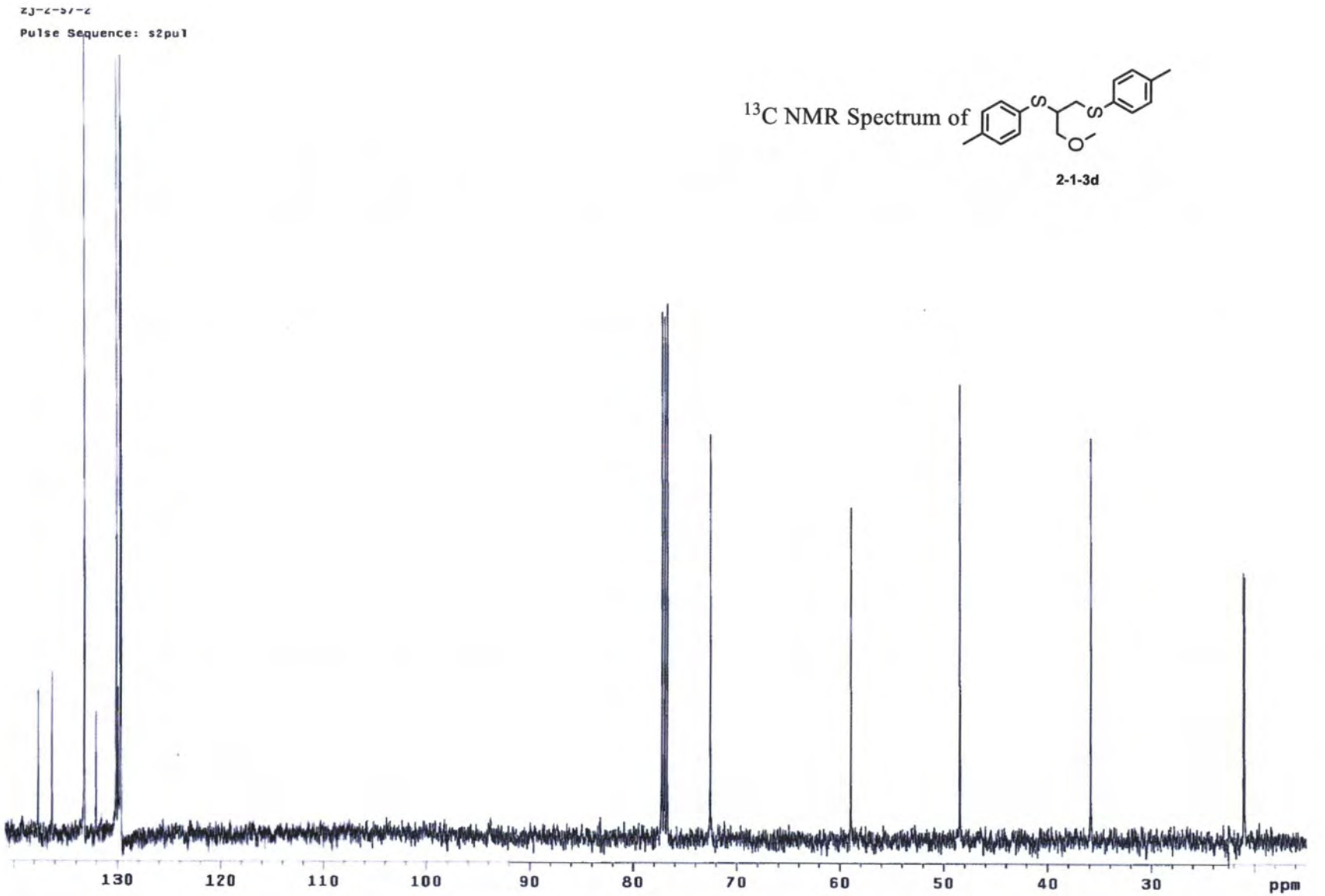
zj-2-57-2
Pulse Sequence: s2pul



^{1}H NMR Spectrum of 

2-1-3d



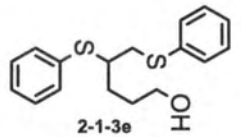


^{13}C NMR Spectrum of

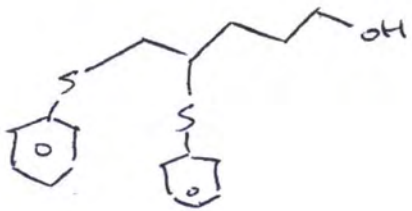
2-1-3d

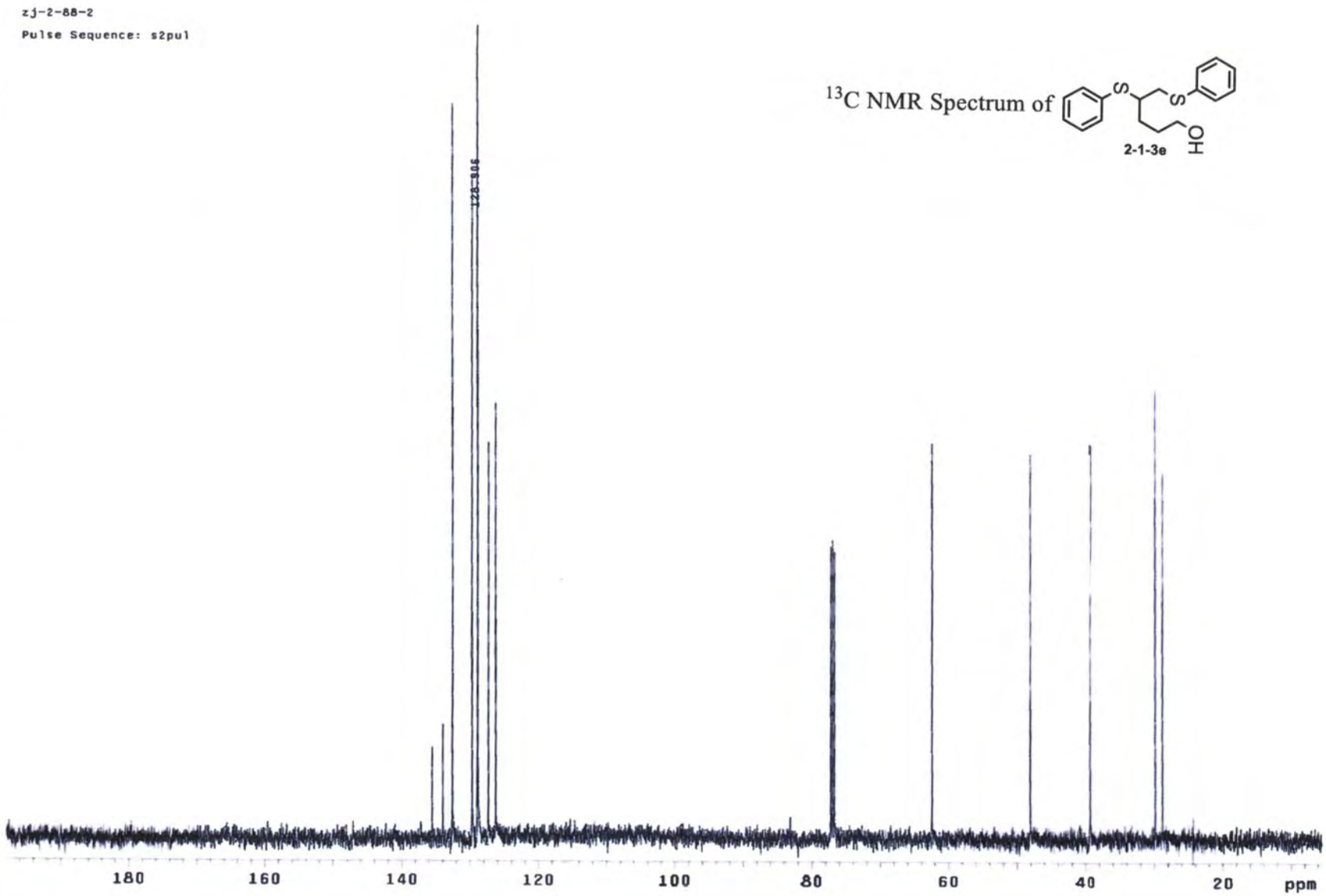
zj-2-88-2

Pulse Sequence: s2pul

^{1}H NMR Spectrum of 

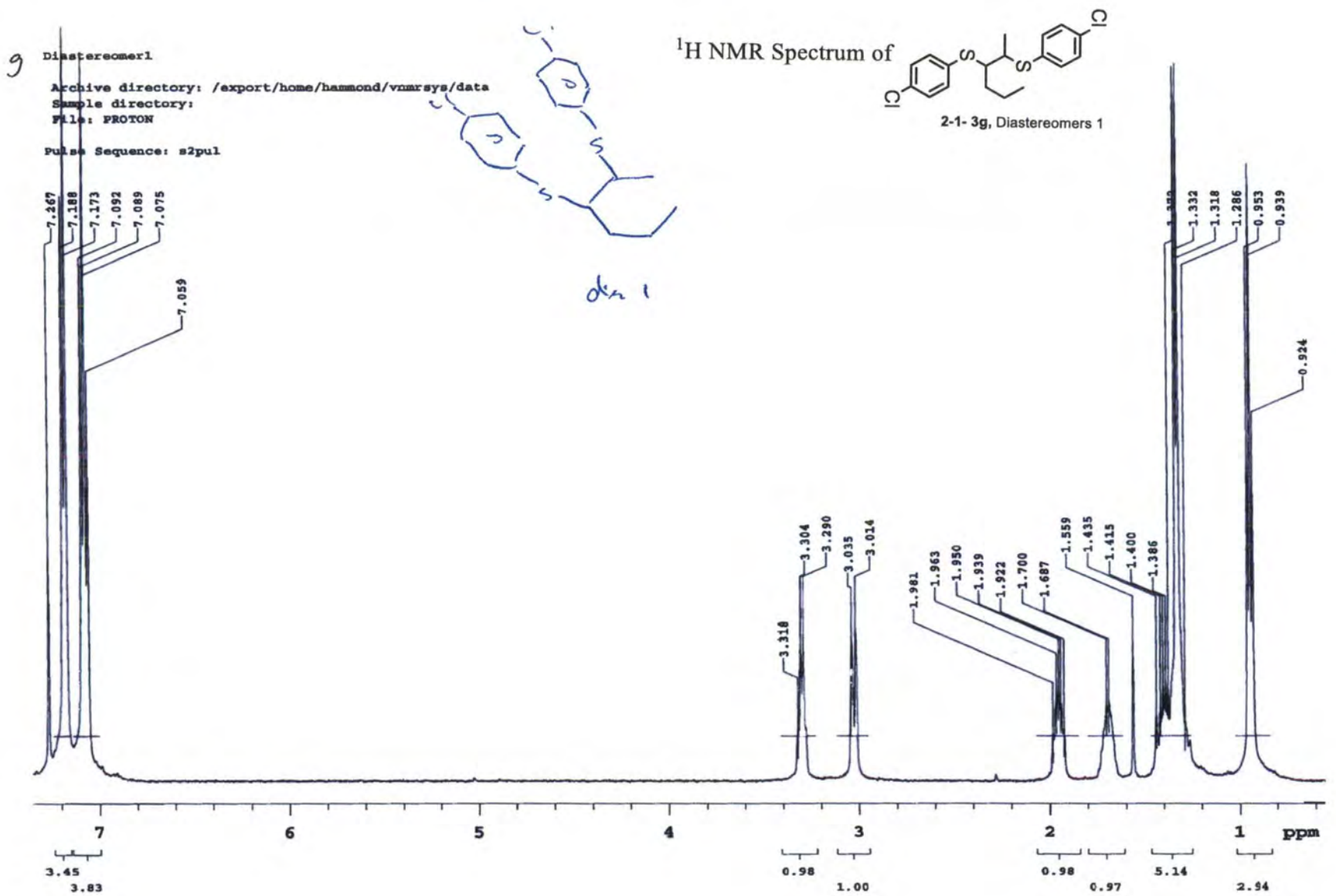
2-1-3e





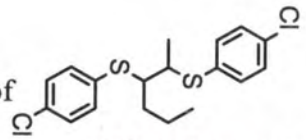
^{13}C NMR Spectrum of

2-1-3e

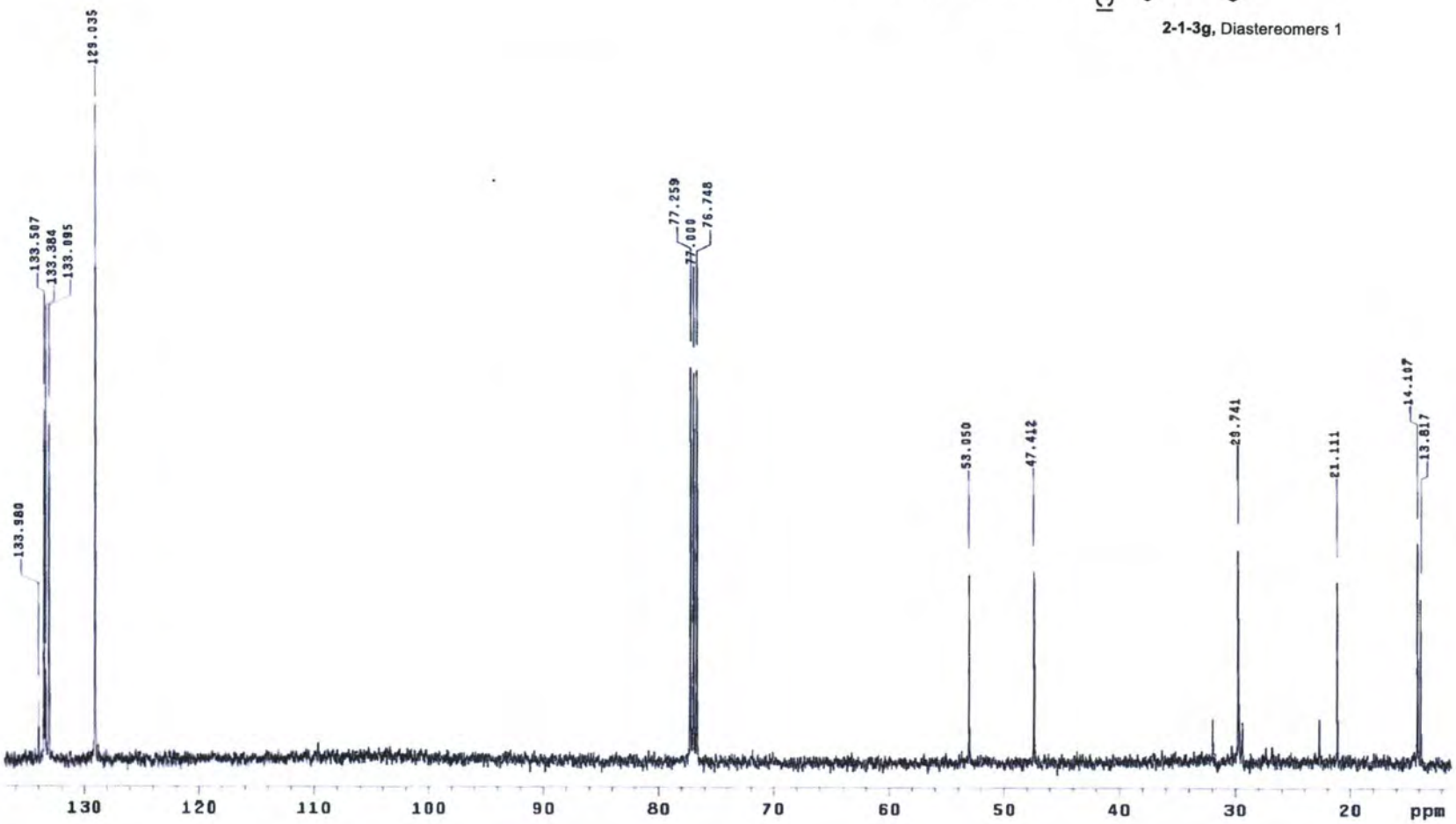

9
Diastereomer1
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
7.267
7.188
7.173
7.092
7.089
7.075
7.059
dia 1
1H NMR Spectrum of
2-1- 3g, Diastereomers 1
3.318
3.304
3.290
3.035
3.014
1.981
1.963
1.950
1.939
1.922
1.700
1.687
1.559
1.435
1.415
1.400
1.386
1.332
1.318
1.286
0.953
0.939
0.924
7
6
5
4
3
2
1
ppm
3.45
3.83
0.98
1.00
0.98
0.97
5.14
2.94

zj-2-60-2-1

Pulse Sequence: s2pul

^{13}C NMR Spectrum of 

2-1-3g, Diastereomers 1

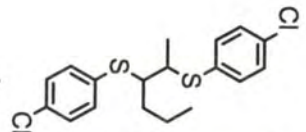


Diastereomer2

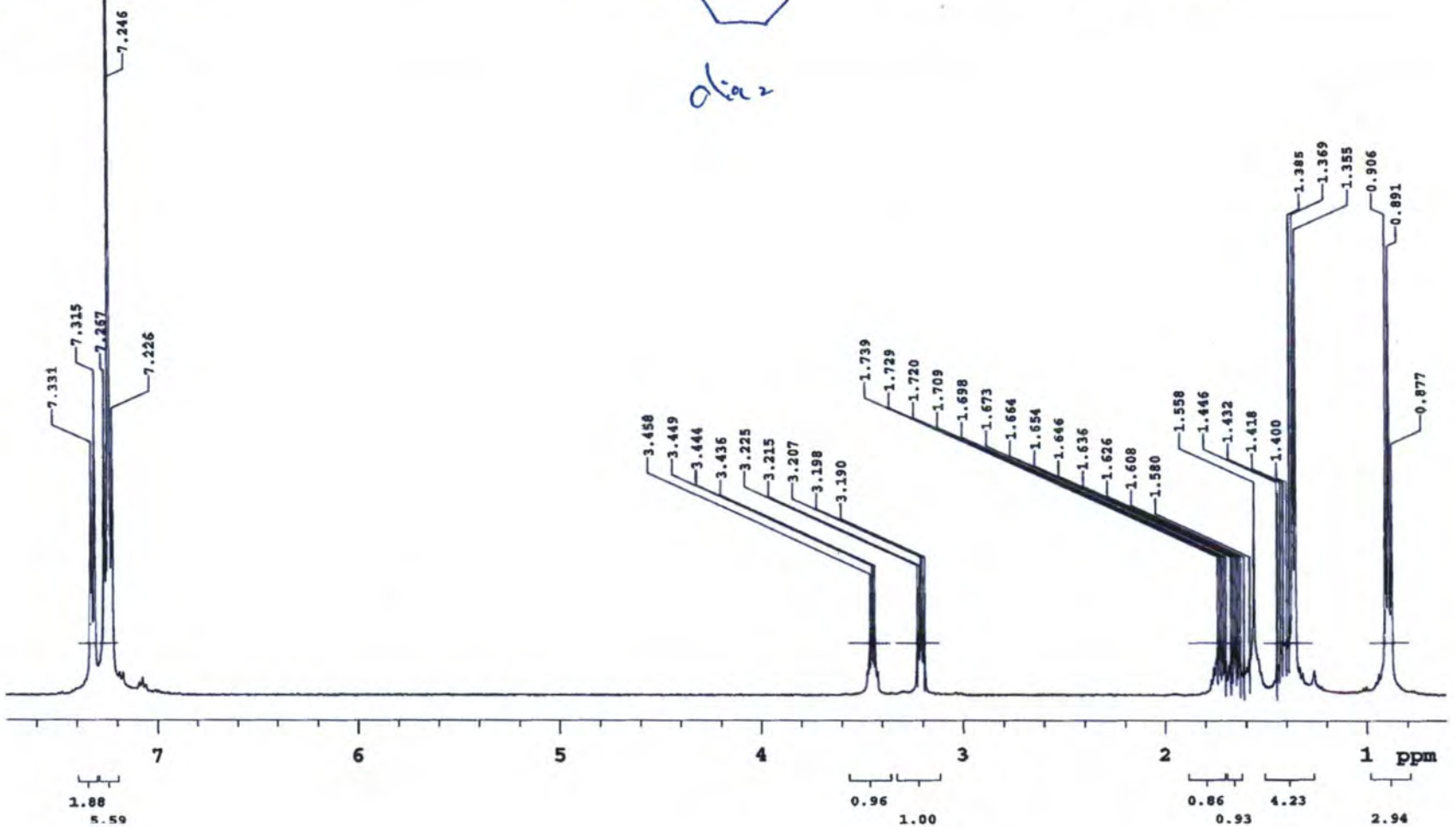
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

^{1}H NMR Spectrum of



2-1-3g, Diastereomers 2

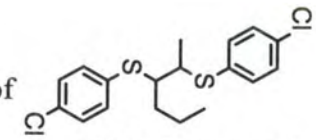


diasteresomer 2

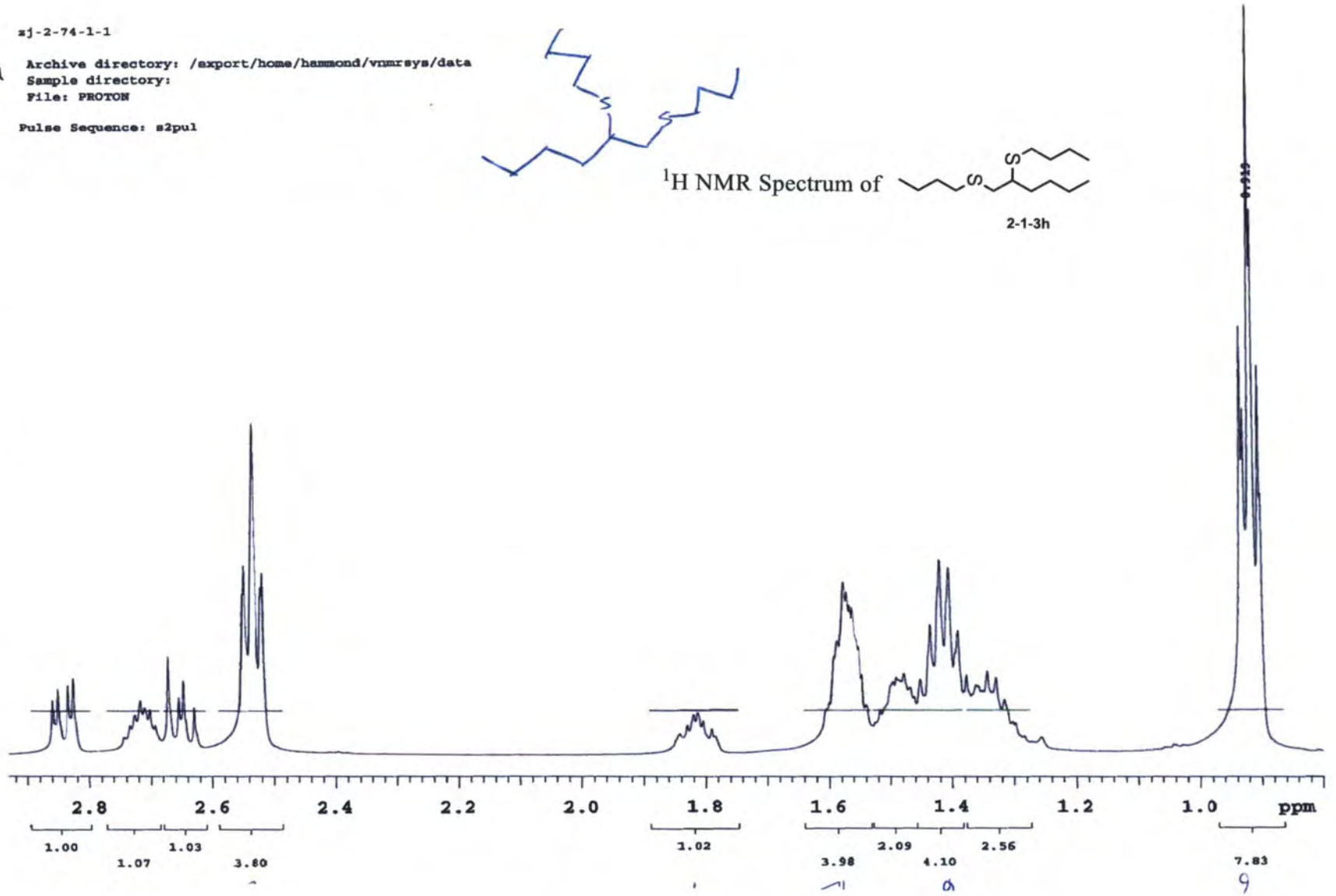
9

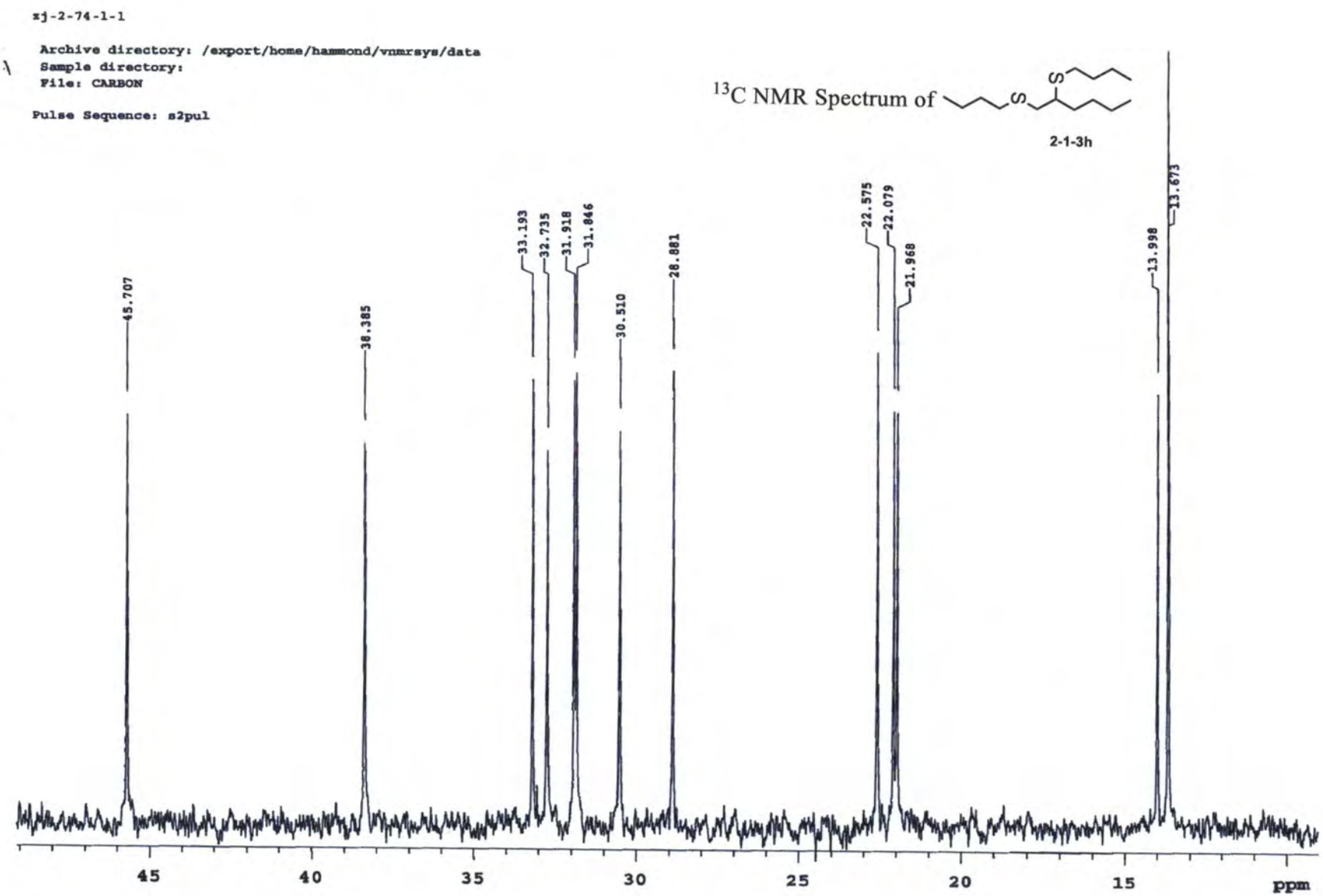
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: CARBON

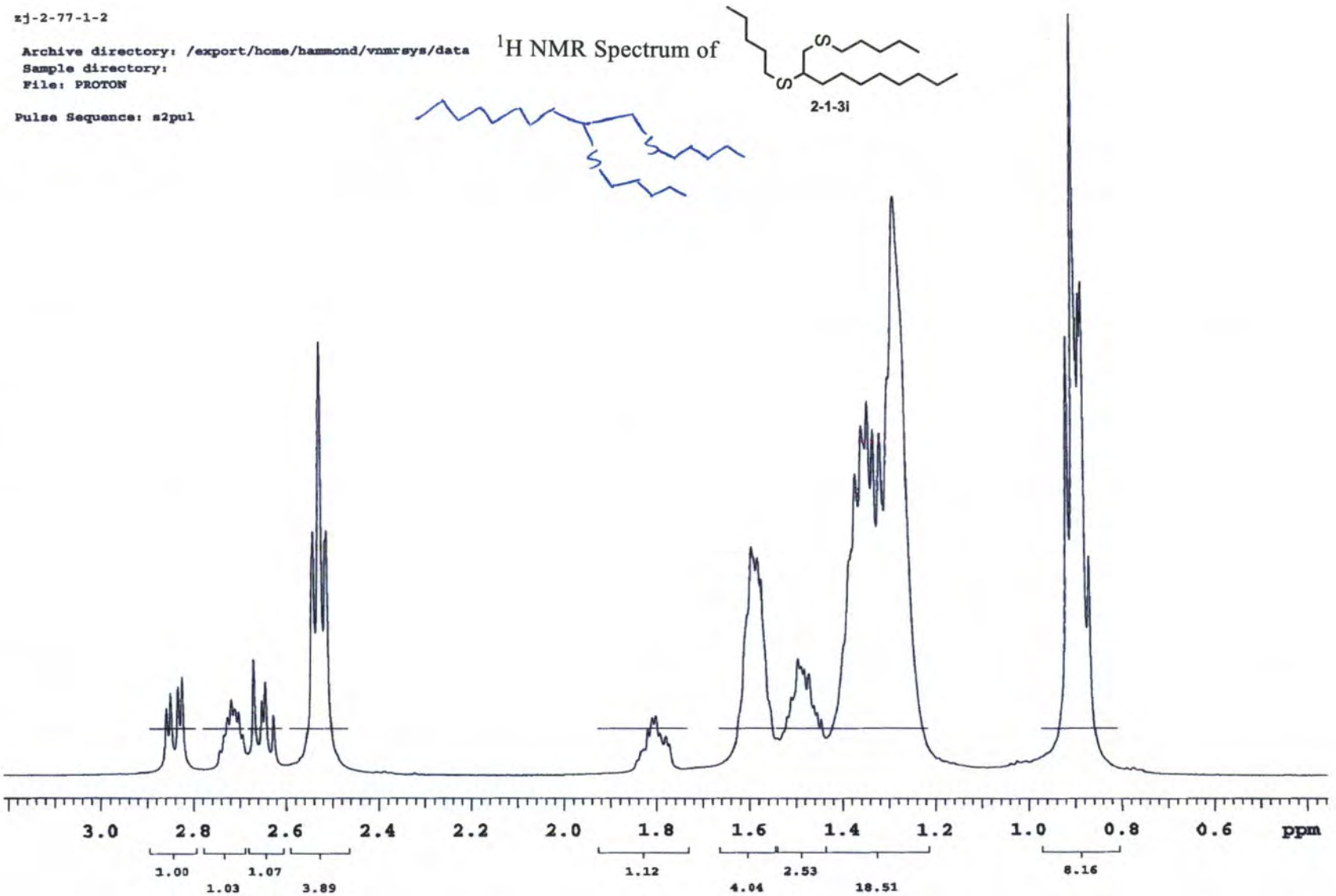
Pulse Sequence: s2pul

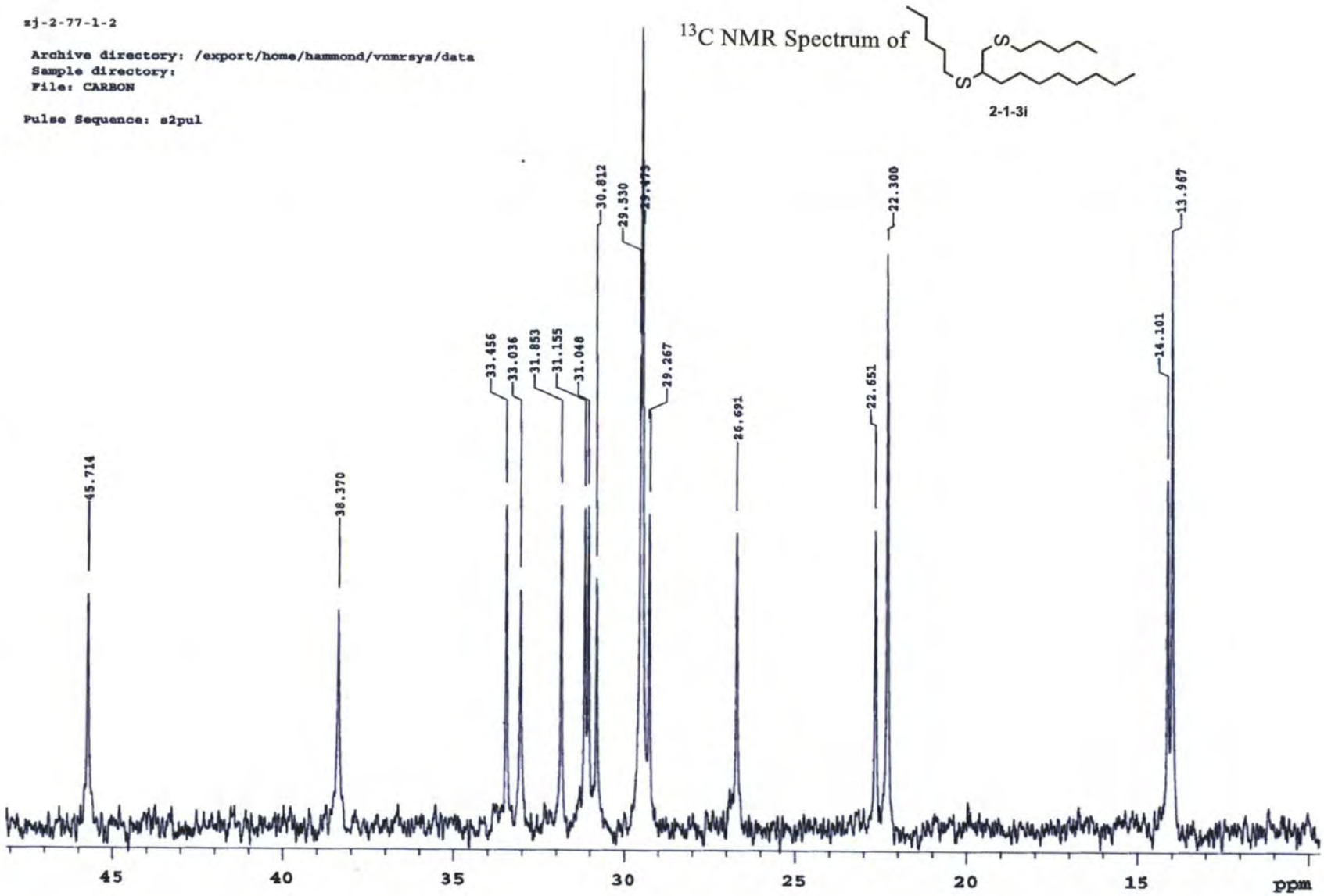
^{13}C NMR Spectrum of 

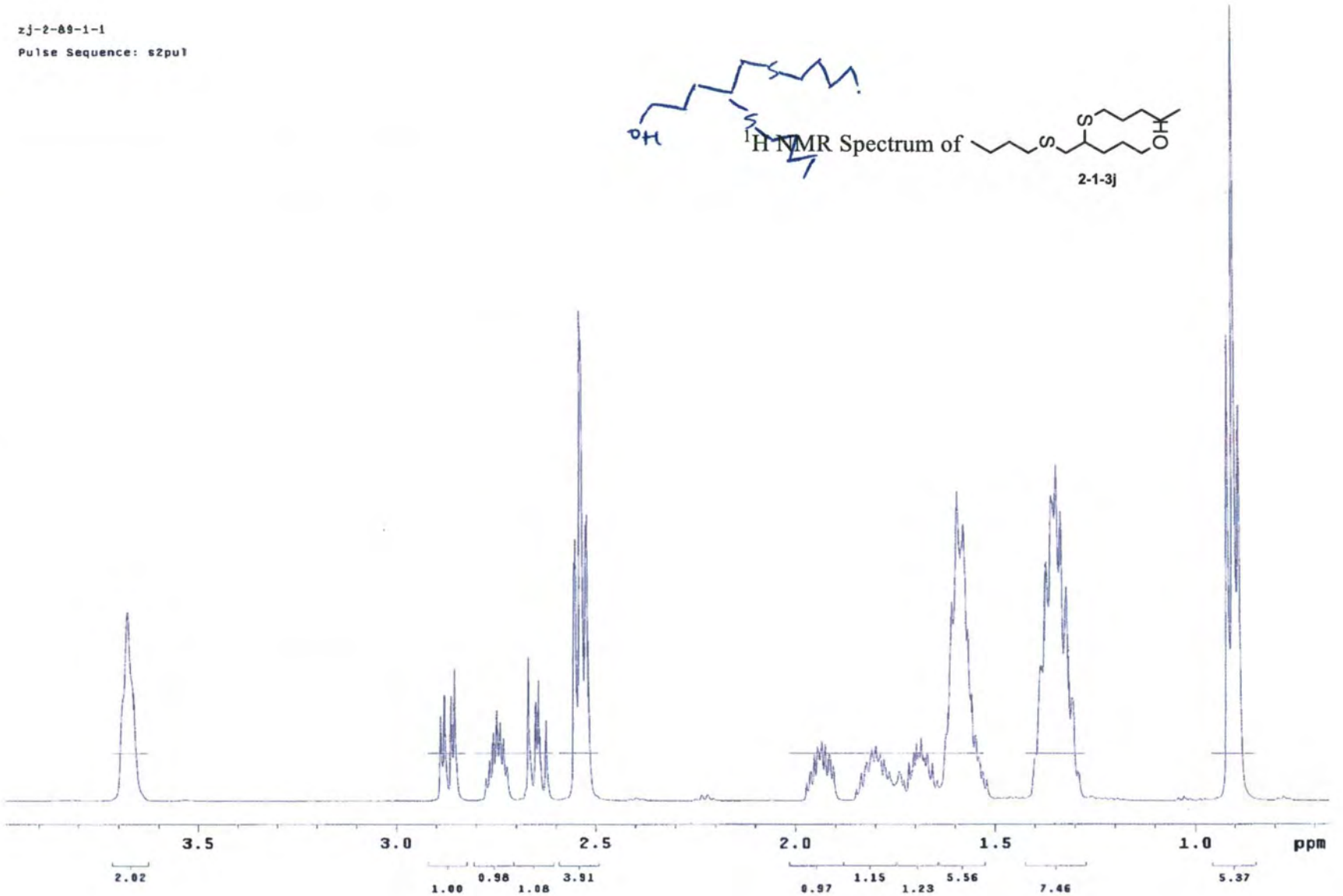
2-1-3g, Diastereomers 2


zj-2-74-1-1
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
^{1}H NMR Spectrum of
2-1-3h
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
1.00
1.07
1.03
3.80
1.02
3.98
2.09
4.10
2.56
7.83


zj-2-74-1-1
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
^{13}C NMR Spectrum of
2-1-3h
45.707
38.385
33.193
32.735
31.918
31.846
30.510
28.881
22.575
22.079
21.968
13.998
13.673
45
40
35
30
25
20
15
ppm

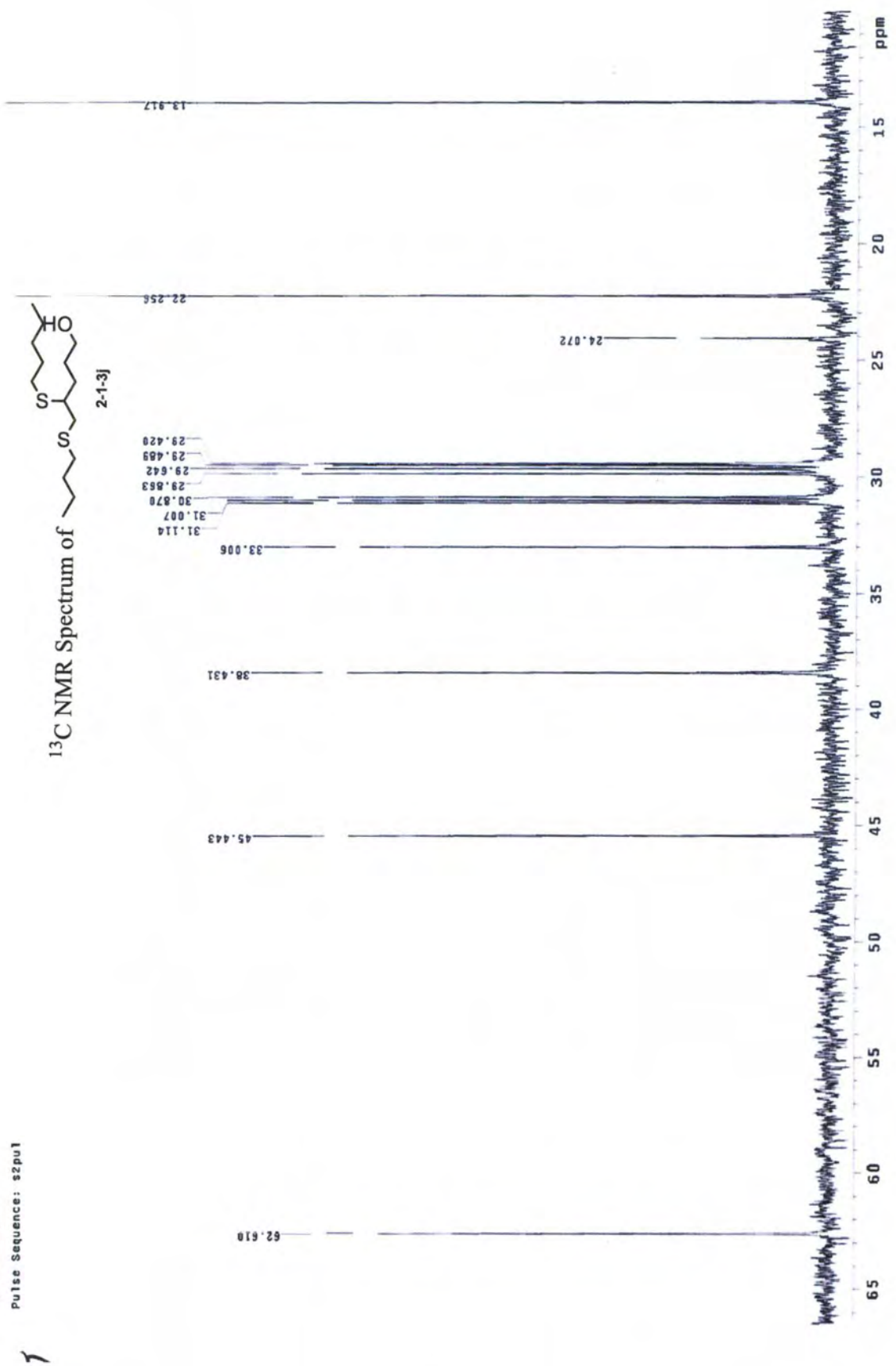

zj-2-77-1-2
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
^{1}H NMR Spectrum of
2-1-3i
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
ppm
1.00
1.03
1.07
3.89
1.12
4.04
2.53
18.51
8.16


zj-2-77-1-2
Archive directory: /export/home/hammond/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
13C NMR Spectrum of
2-1-3i
45.714
38.370
33.456
33.036
31.853
31.155
31.048
30.812
29.530
29.267
26.691
22.651
22.300
14.101
13.967
45
40
35
30
25
20
15
ppm

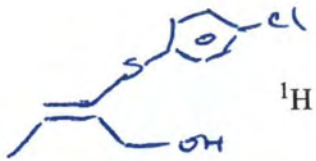


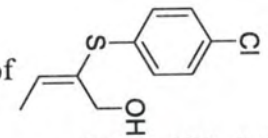
^{1}H NMR Spectrum of

2-1-3j


zj-2-89-1-1
Pulse Sequence: s2pul
^{13}C NMR Spectrum of
2-1-3j
13.917
22.256
24.072
29.420
29.489
29.642
29.863
30.870
31.007
31.114
33.006
38.431
45.443
62.618
ppm

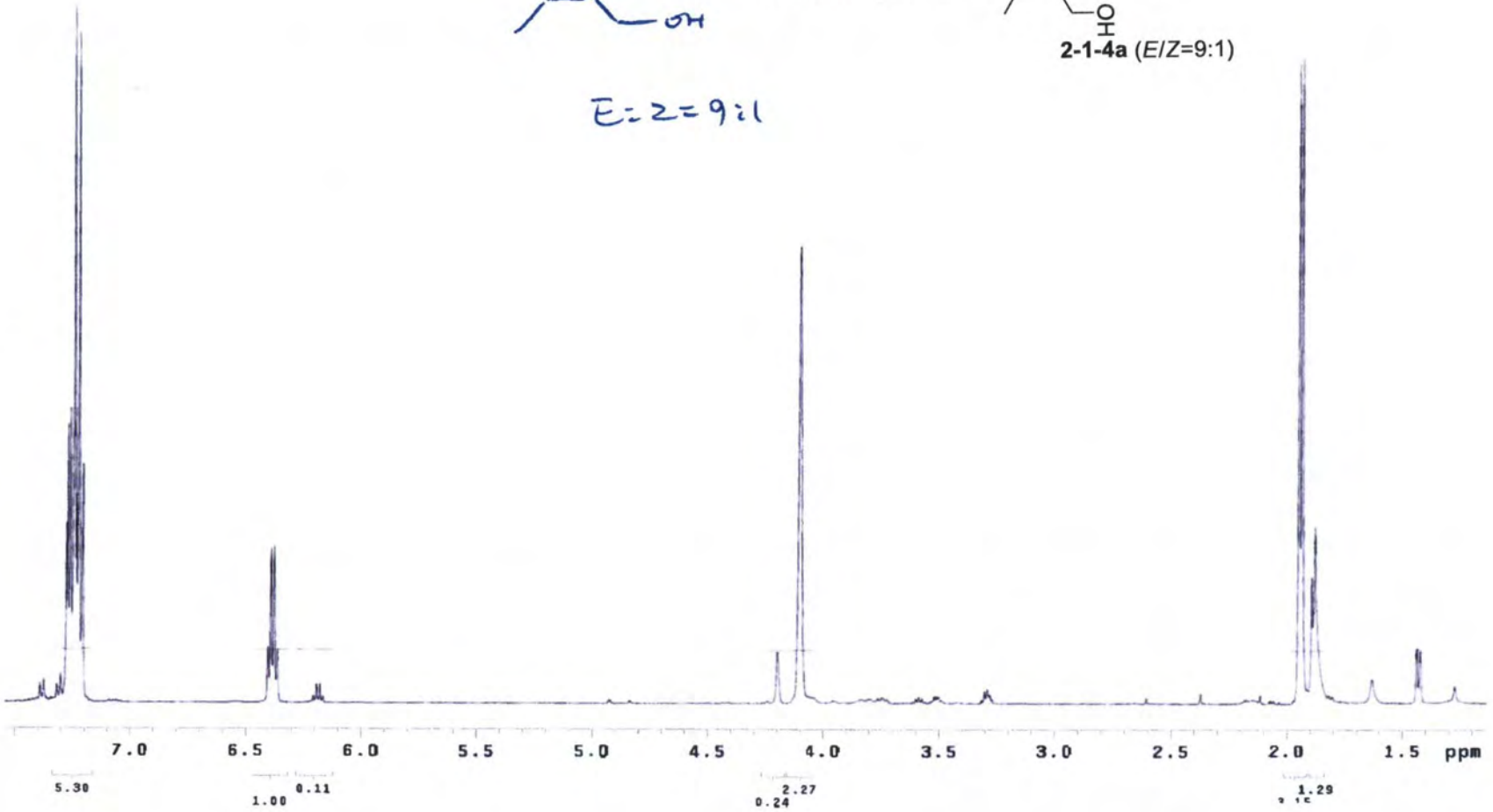
zj-2-93-2
Pulse Sequence: s2pul



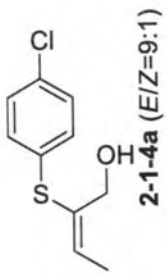
^{1}H NMR Spectrum of 

2-1-4a (*E*/*Z*=9:1)

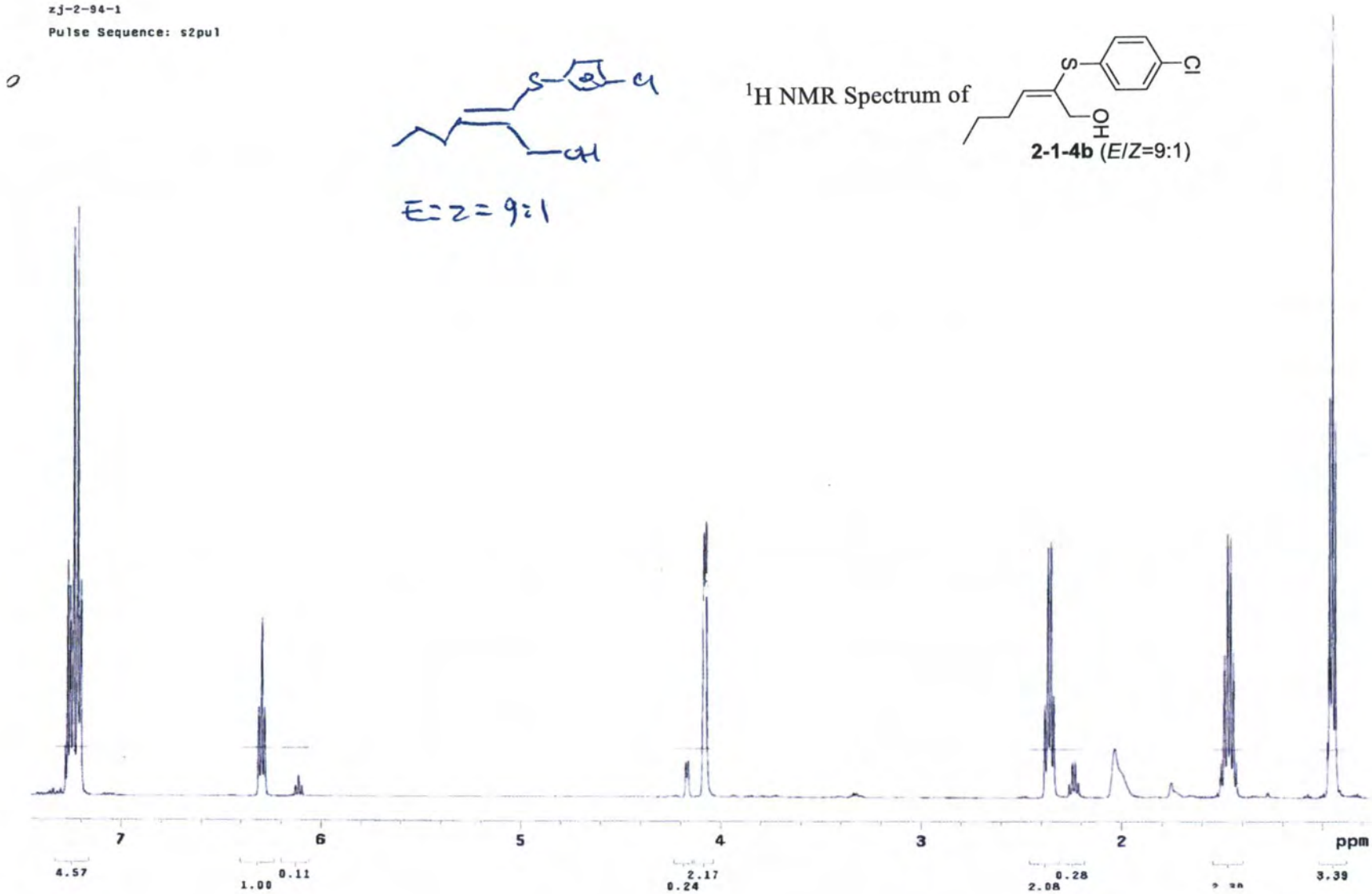
E:Z=9:1



^{13}C NMR Spectrum of



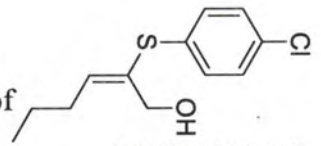
2-1-4a (*E*/*Z*=9:1)



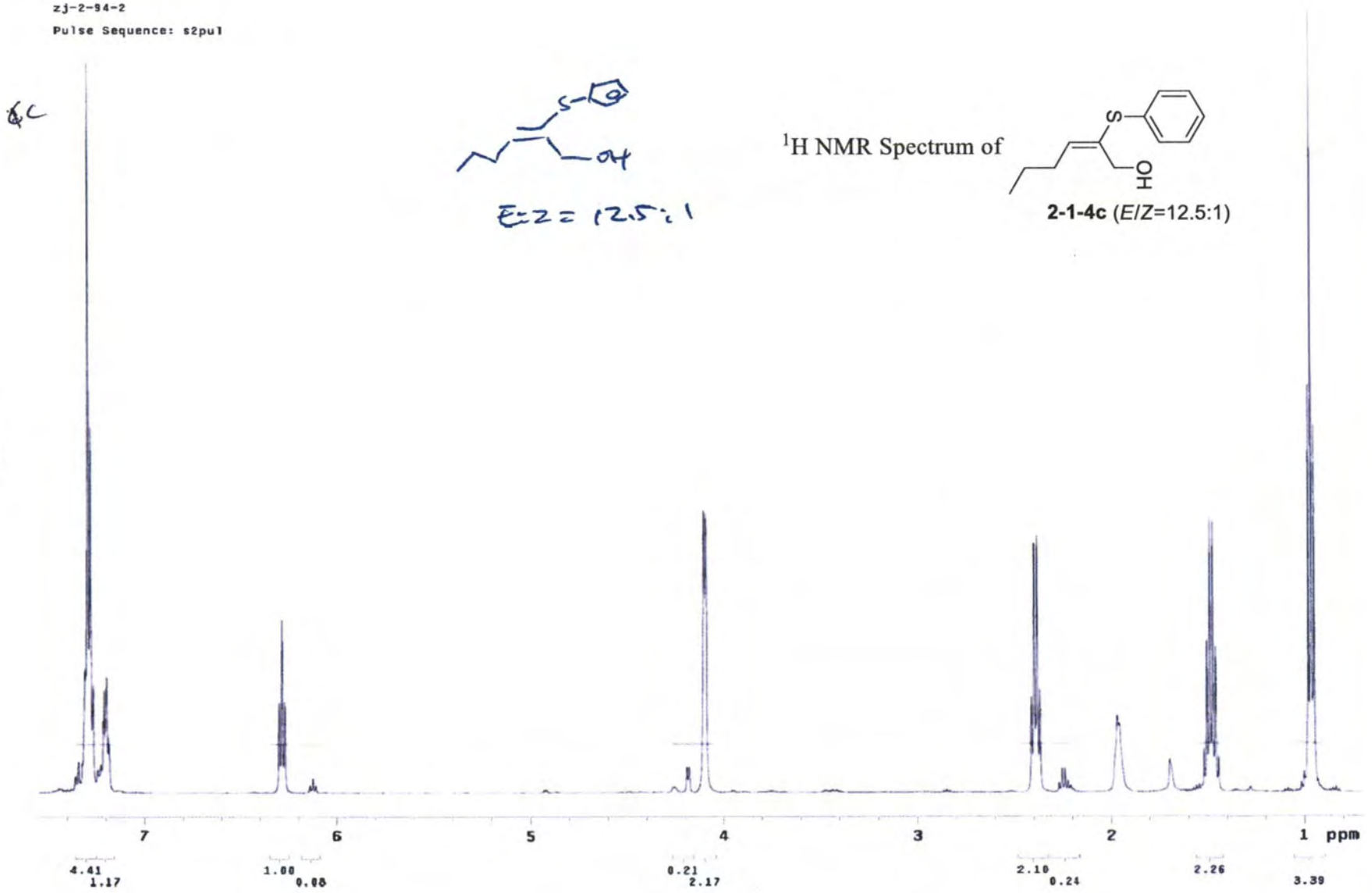
^{1}H NMR Spectrum of

2-1-4b (*E*/*Z*=9:1)

^{13}C NMR Spectrum of



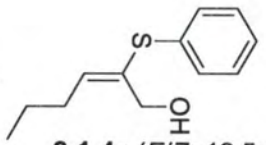
2-1-4b (*E*/*Z*=9:1)



^{1}H NMR Spectrum of

2-1-4c (*E*/*Z*=12.5:1)

^{13}C NMR Spectrum of

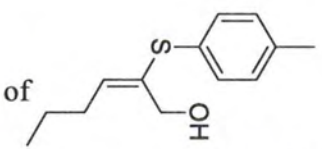


2-1-4c (*E*/*Z*=12.5:1)

zj-2-95-1
Pulse Sequence: s2pul

d

^{1}H NMR Spectrum of

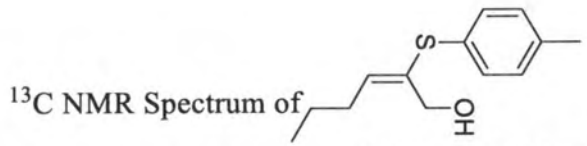


2-1-4d (*E*/*Z*=12.5:1)

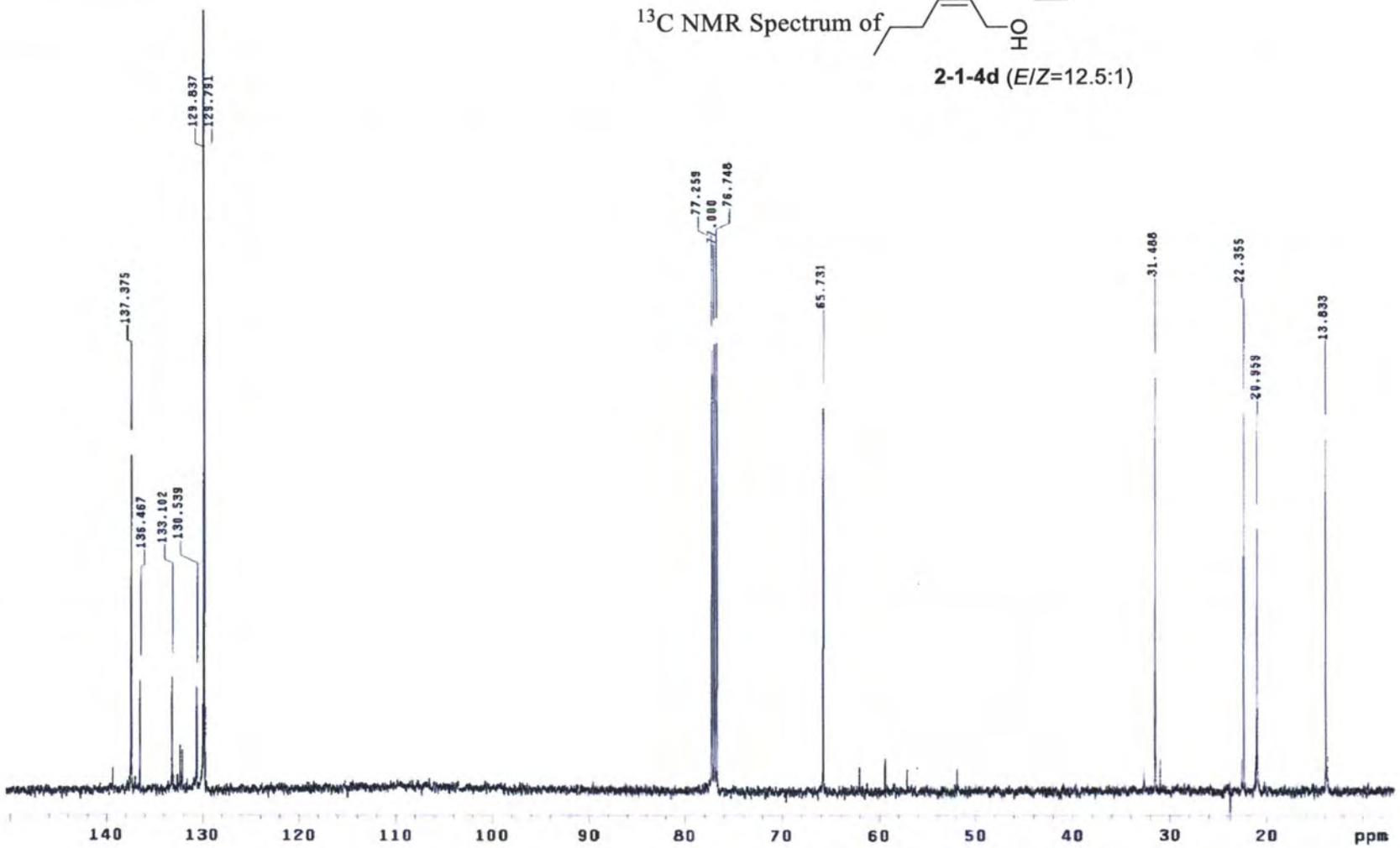
zj-2-95-1
Pulse Sequence: s2pul

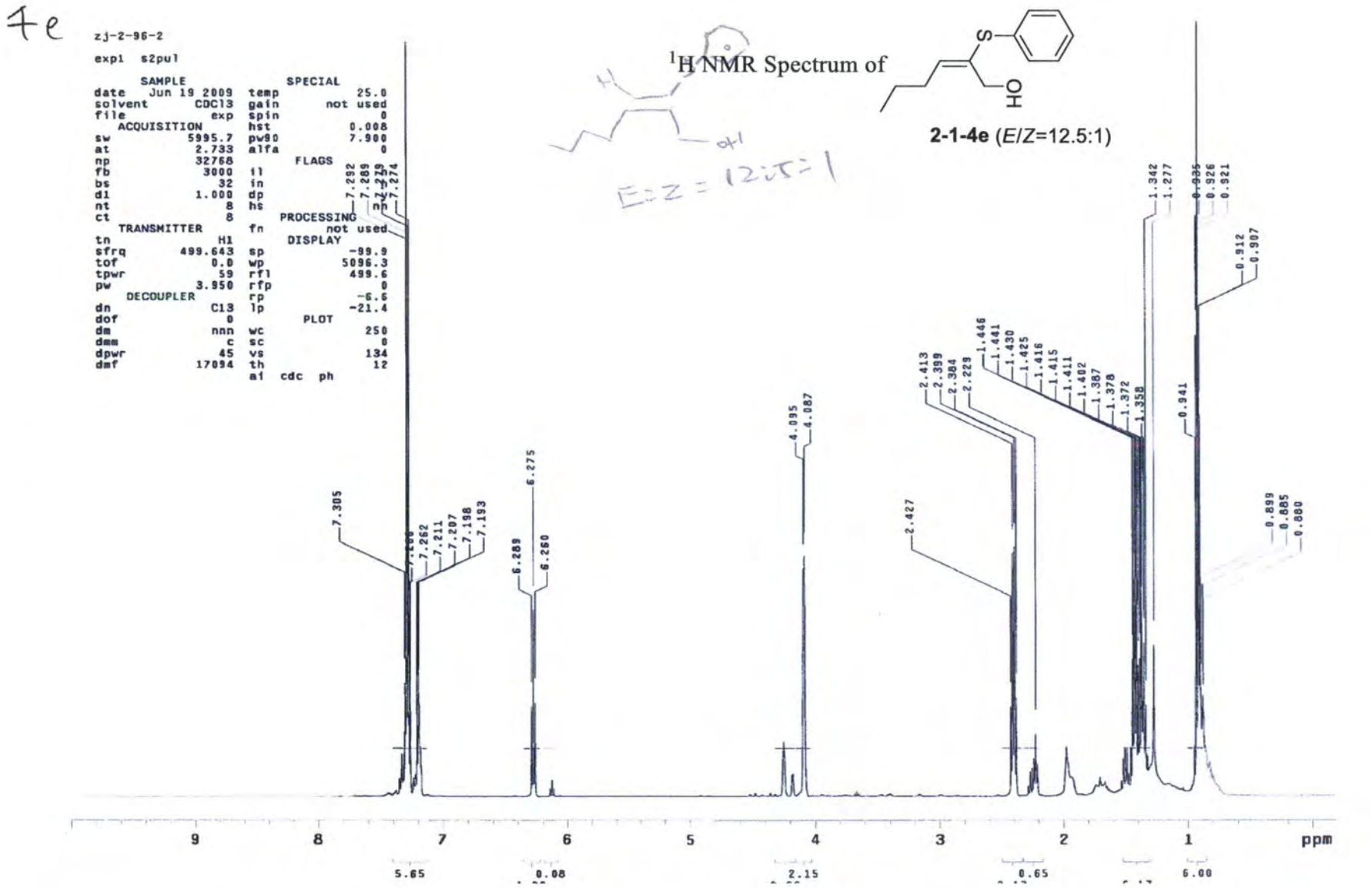
4d

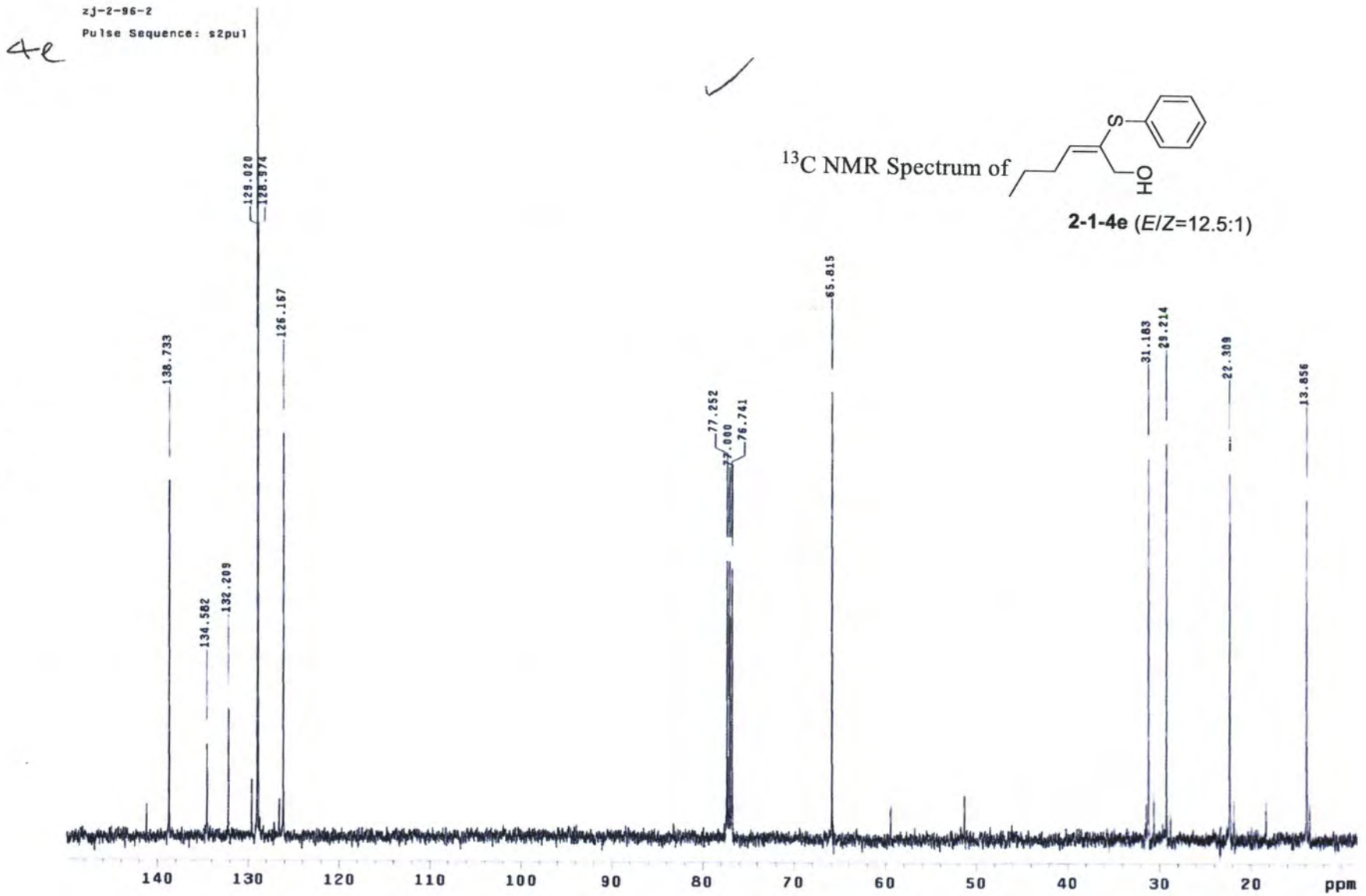
^{13}C NMR Spectrum of



2-1-4d (*E*/*Z*=12.5:1)




4e
zj-2-96-2
exp1 s2pul
SAMPLE
date Jun 19 2009
solvent CDCl3
file exp
ACQUISITION
sw 5995.7
at 2.733
np 32768
fb 3000
bs 32
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 499.643
tof 0.0
tpwr 59
pw 3.950
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 45
dmf 17094
SPECIAL
temp 25.0
gain not used
spin 0
hst 0.008
pw90 7.900
alfa 0
FLAGS
PROCESSING
fn not used
DISPLAY
sp -99.9
wp 5096.3
rfl 499.6
rfp 0
rp -6.6
lp -21.4
PLOT
wc 250
sc 8
vs 134
th 12
ai cdc ph
1H NMR Spectrum of
2-1-4e (E/Z=12.5:1)
E:Z = 12:1
7.305
7.262
7.211
7.207
7.198
7.193
6.275
6.289
6.260
4.095
4.087
2.427
2.413
2.399
2.384
2.229
1.446
1.441
1.430
1.425
1.416
1.415
1.411
1.402
1.387
1.378
1.372
1.358
1.342
1.277
0.941
0.935
0.926
0.921
0.912
0.907
0.899
0.885
0.880
9
8
7
6
5
4
3
2
1
ppm
5.65
0.08
2.15
0.65
6.00



^{13}C NMR Spectrum of

2-1-4e (*E*/*Z*=12.5:1)

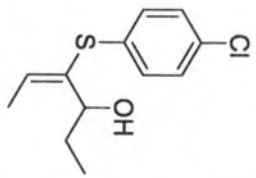
^{1}H NMR Spectrum of

2-1-4f (*E*/*Z*=17:1)

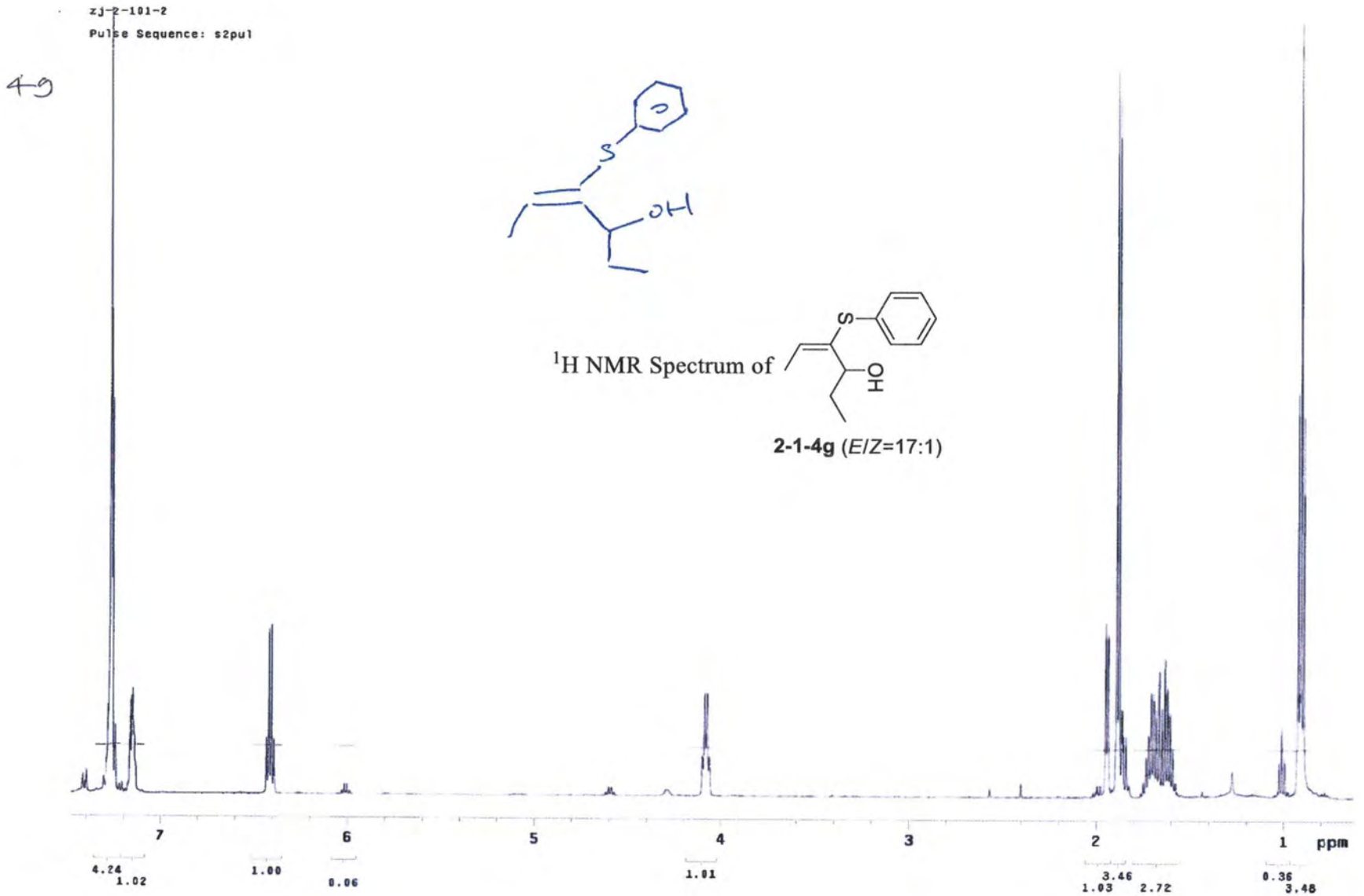
zj-2-101-1

Pulse Sequence: s2pul

^{13}C NMR Spectrum of

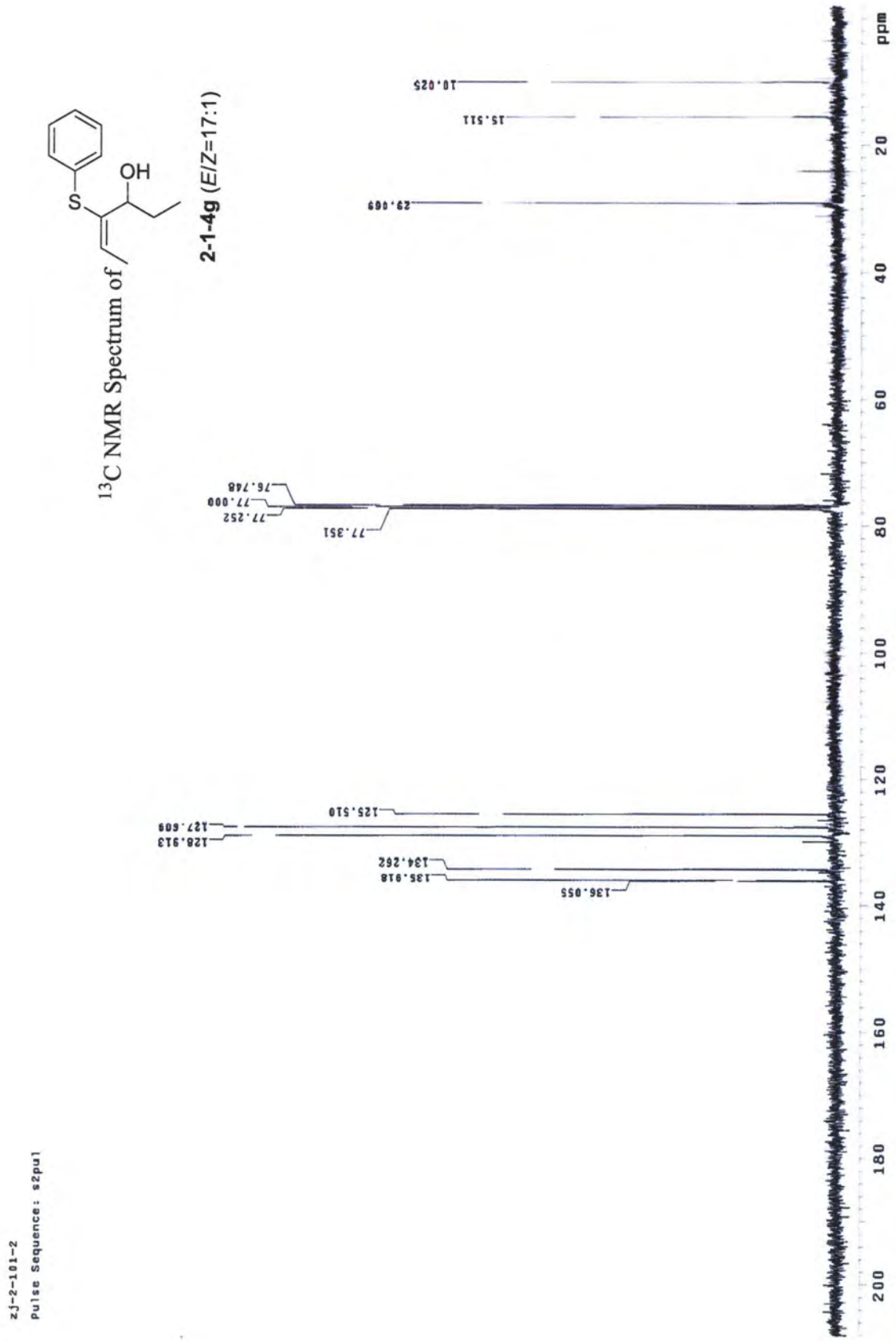


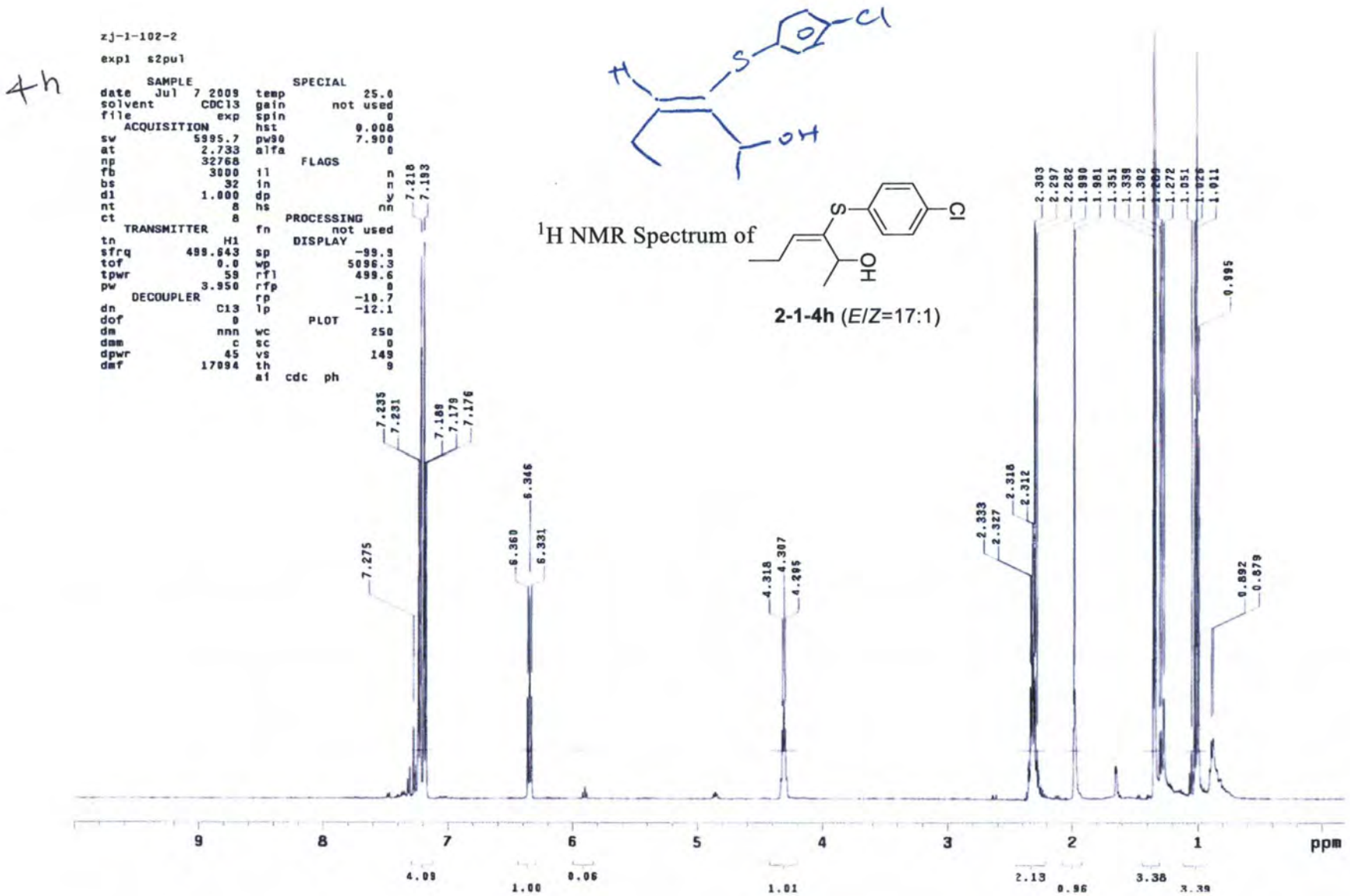
2-1-4f (*E*/*Z*=17:1)



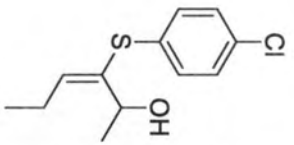
^{1}H NMR Spectrum of

2-1-4g (*E*/*Z*=17:1)


^{13}C NMR Spectrum of
2-1-4g (E/Z=17:1)
OH
S
10.025
15.511
29.069
76.748
77.000
77.252
77.351
125.510
127.609
128.913
134.262
135.918
136.055
ppm
zj-2-101-2
Pulse Sequence: s2pul


4h
zj-1-102-2
expl s2pul
SAMPLE
date Jul 7 2009
solvent CDCl3
file exp
ACQUISITION
sw 5995.7
at 2.733
np 32768
fb 3000
bs 32
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 499.643
tof 0.0
tpwr 59
pw 3.950
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 45
dmf 17094
SPECIAL
temp 25.0
gain not used
spin 0
hst 0.008
pw90 7.900
alfa 0
FLAGS
il
in
dp
hs nscan
PROCESSING
fn not used
DISPLAY
sp -99.9
wp 5096.3
rfl 499.6
rfp 0
rp -10.7
lp -12.1
PLOT
wc 250
sc 0
vs 149
th 9
ai cdc ph
1H NMR Spectrum of
2-1-4h (E/Z=17:1)
ppm

^{13}C NMR Spectrum of



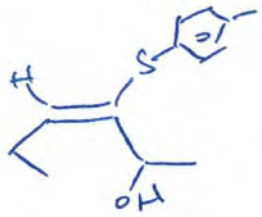
2-1-4h (*E*/*Z*=17:1)

1i

zj-2-103-2

expl s2pul

SAMPLE		SPECIAL	
date	Jul 9 2009	temp	25.0
solvent	CDCl3	gain	not used
file	exp	spin	0
ACQUISITION		hst	0.008
sw	5995.7	pw90	7.900
at	2.733	alfa	0
np	32768	FLAGS	
fb	3000	il	n
bs	32	in	n
dl	1.000	dp	y
nt	8	hs	nn
ct	8	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	499.643	sp	286.0
tof	0.0	wp	3442.7
tpwr	59	rfl	499.6
pw	3.950	rfp	0
DECOUPLER		rp	-5.8
dn	C13	lp	-22.5
dof	0	PLOT	
dm	nnn	wc	250
dmm	c	sc	0
dpwr	45	vs	116
dmf	17094	th	6
		ai cdc ph	

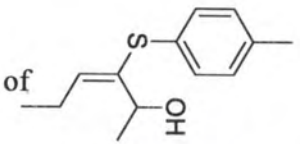


E:Z = 20:1

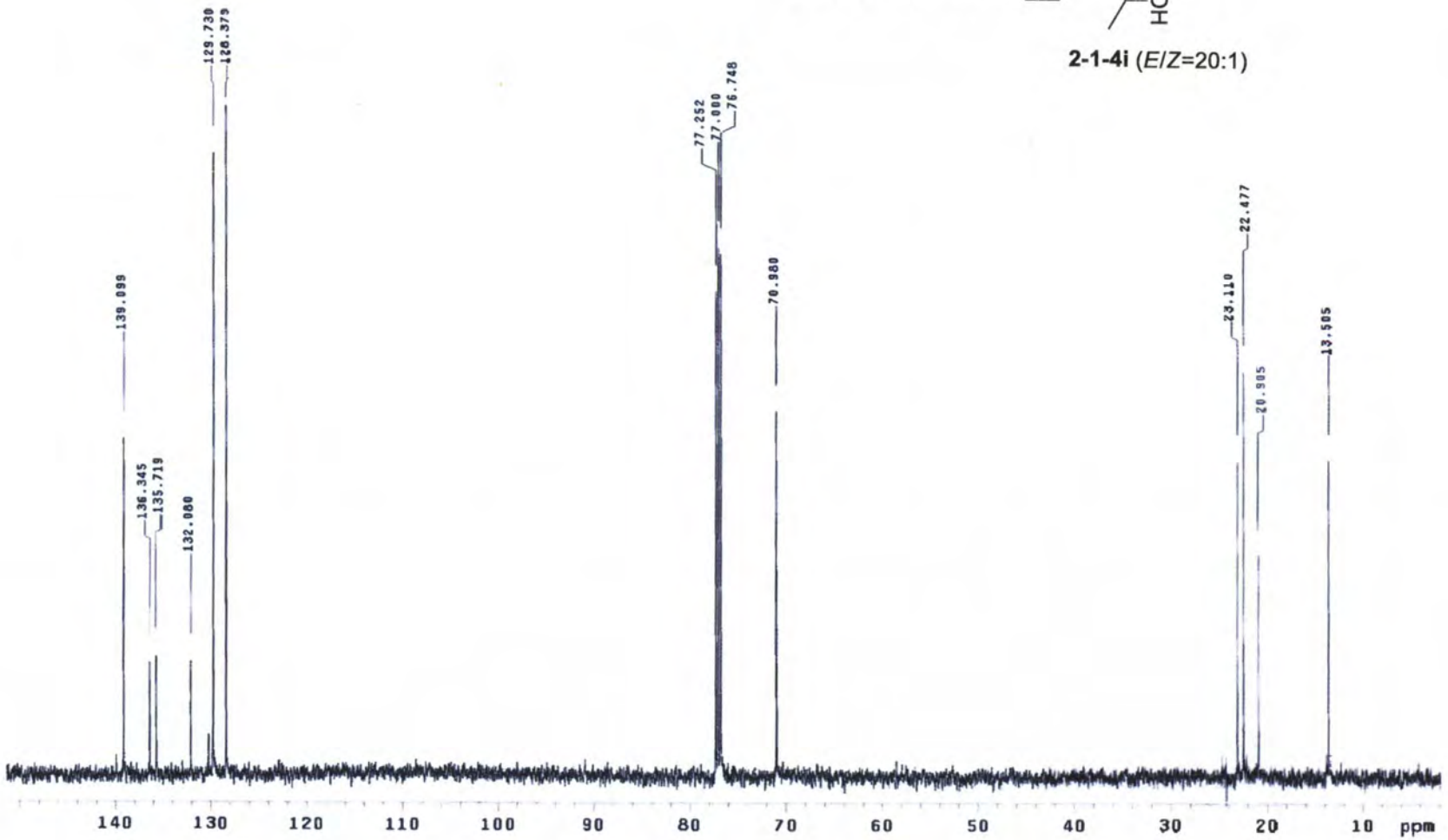
zj-2-103-2

Pulse Sequence: s2pul

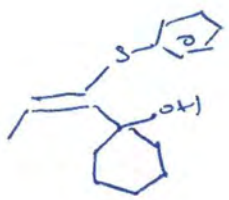
Av

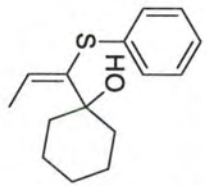
^{13}C NMR Spectrum of 

2-1-4i (*E*/*Z*=20:1)

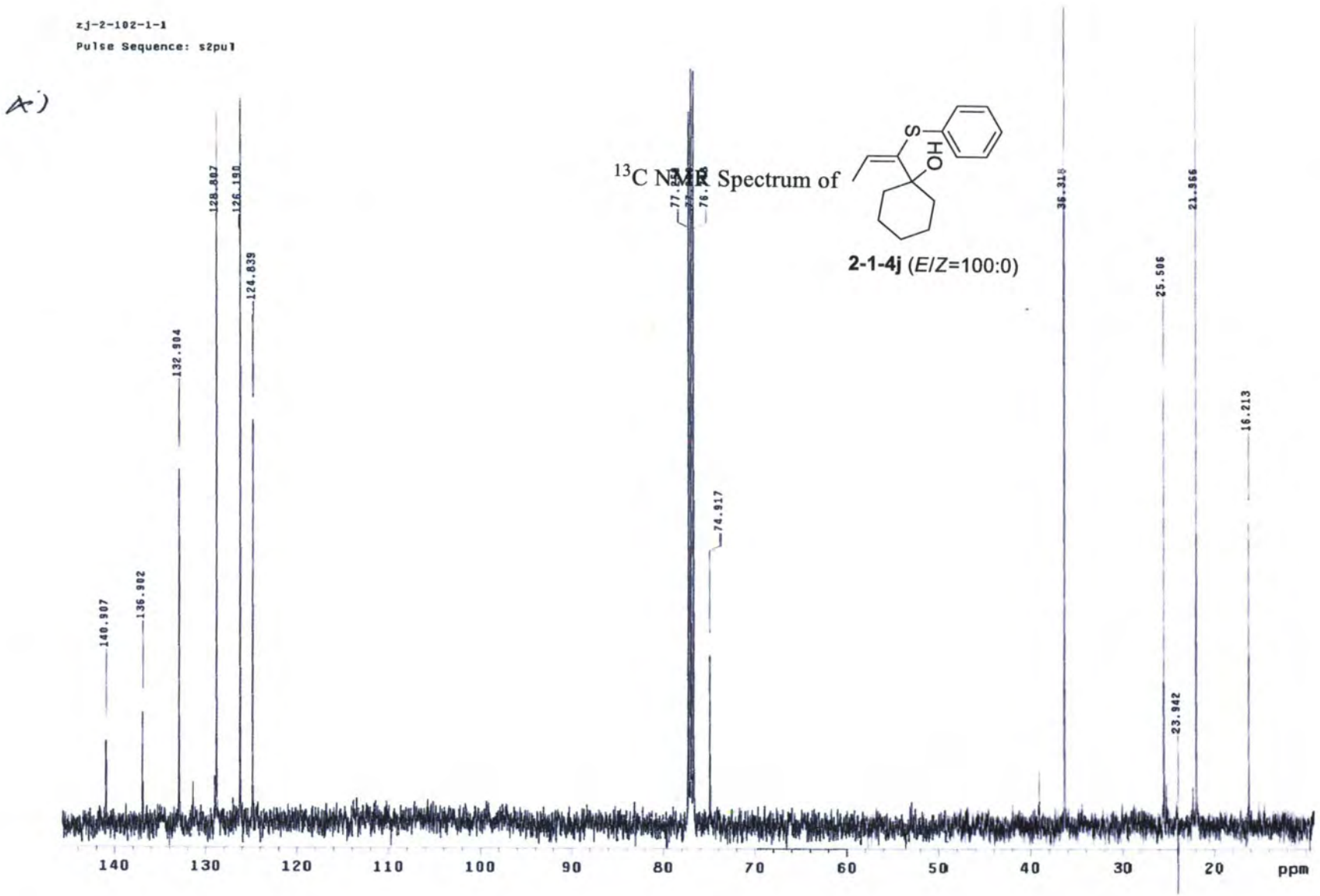


4j



^{1}H NMR Spectrum of 

2-1-4j (*E*/*Z*=100:0)

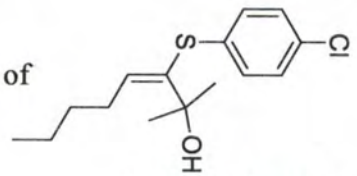


^{13}C NMR Spectrum of

2-1-4j (*E*/*Z*=100:0)

zj-2-104-1
Pulse Sequence: s2pul

4k

^{1}H NMR Spectrum of 

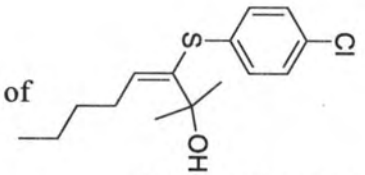
2-1-4k (*E*/*Z*=100:0)

zj-2-104-1

Pulse Sequence: s2pul

AK

^{13}C NMR Spectrum of

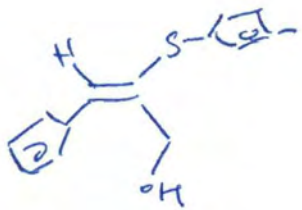


2-1-4k (*E*/*Z*=100:0)

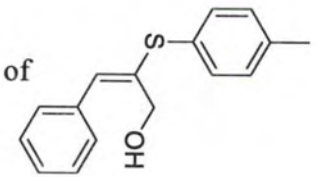
zj-2-105-2

Pulse Sequence: s2pul

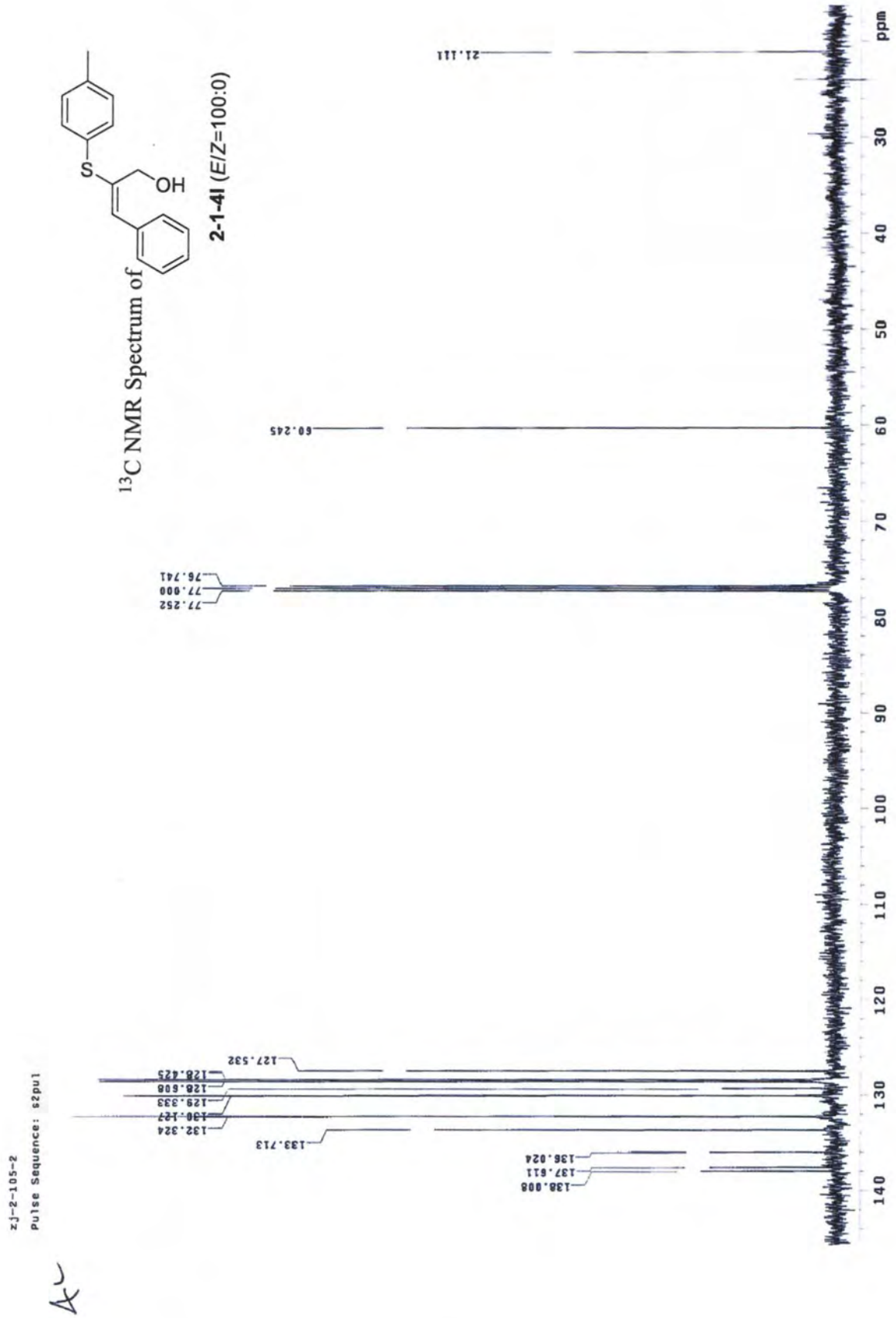
4L

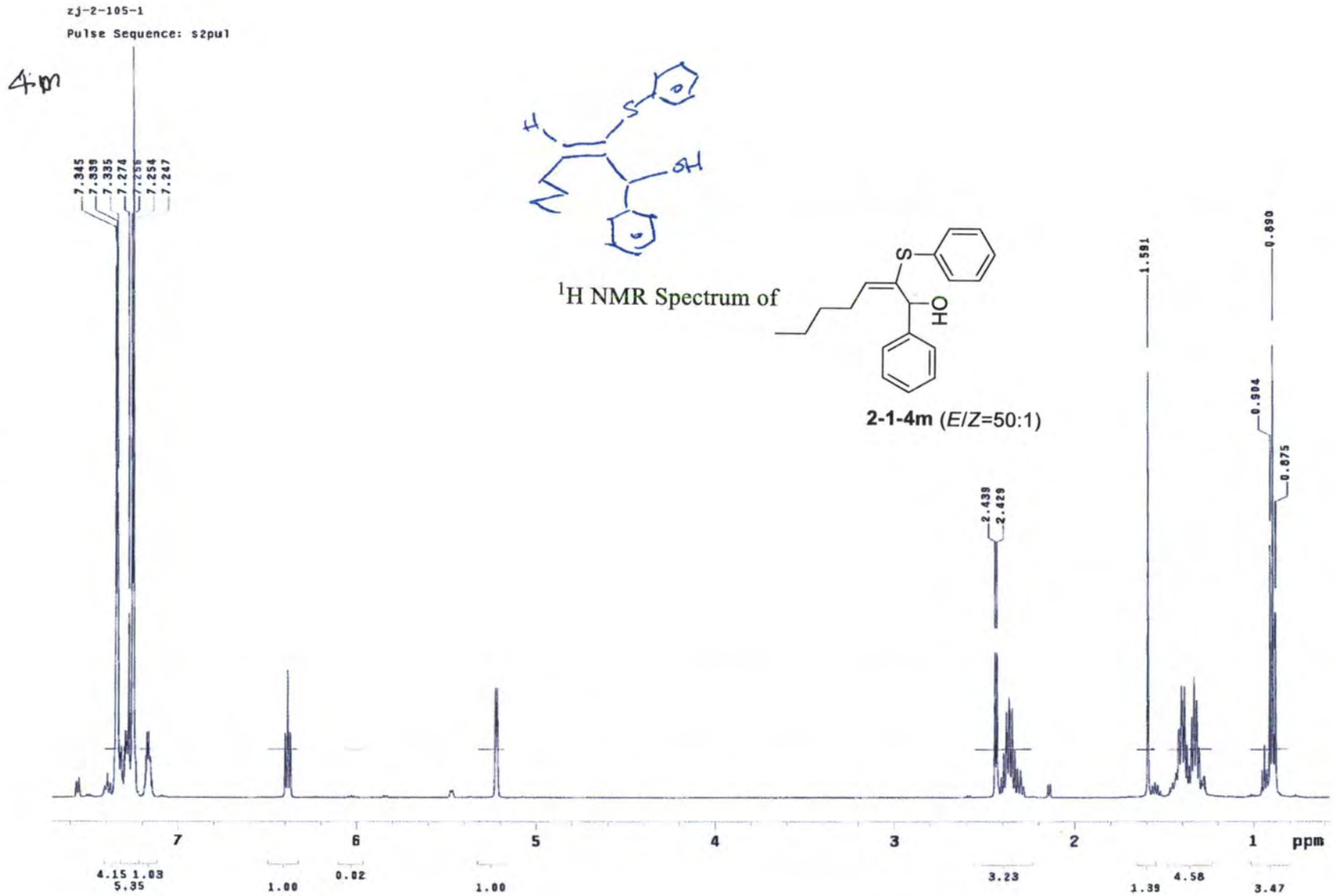


^{1}H NMR Spectrum of



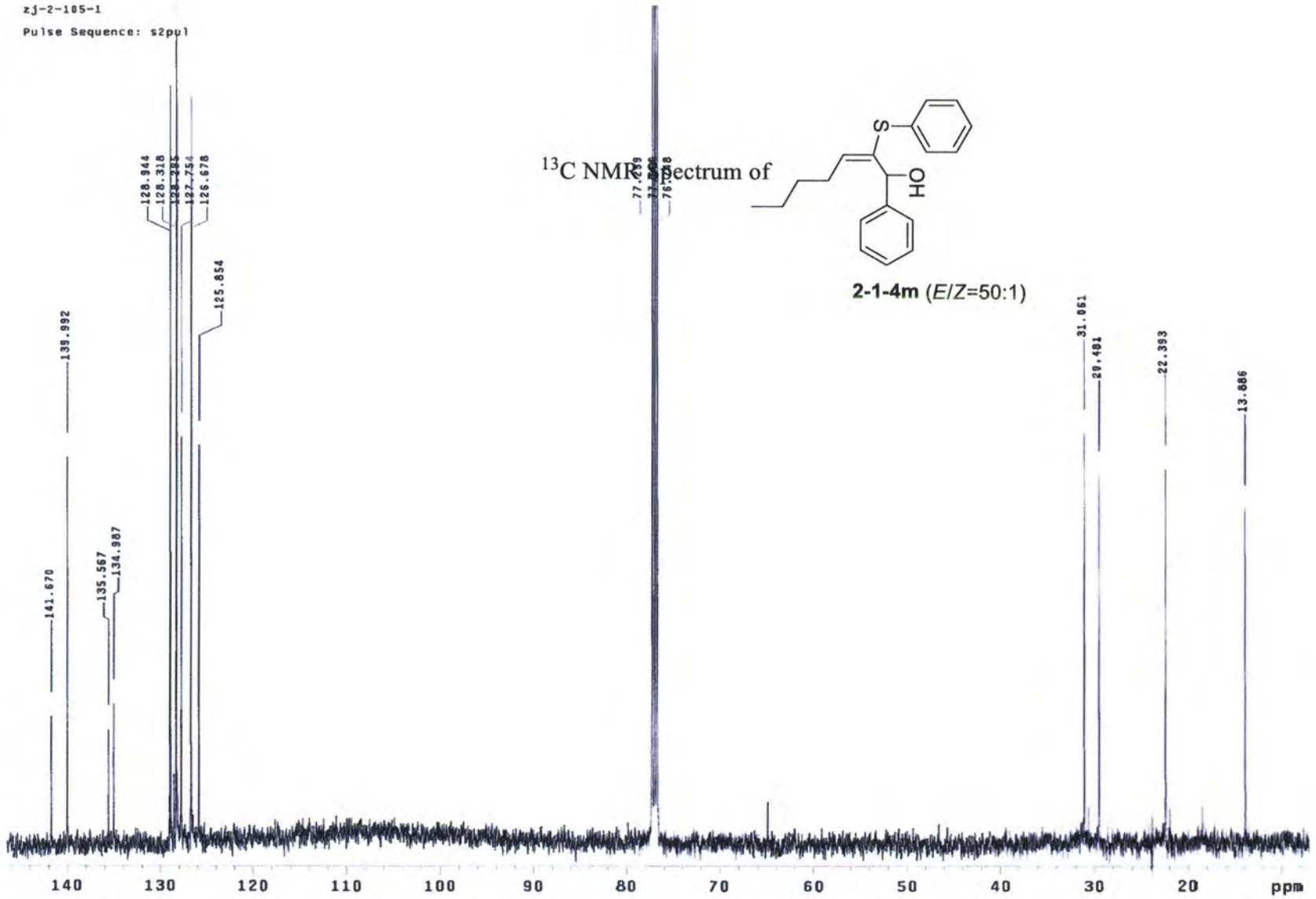
2-1-4l (*E*/*Z*=100:0)


^{13}C NMR Spectrum of
2-1-4l (E/Z=100:0)
S
OH
21.111
60.245
77.252
77.000
76.741
127.532
128.425
128.608
129.333
130.127
132.324
133.713
136.024
137.611
138.008
ppm
zj-2-105-2
Pulse Sequence: s2pul



^{1}H NMR Spectrum of

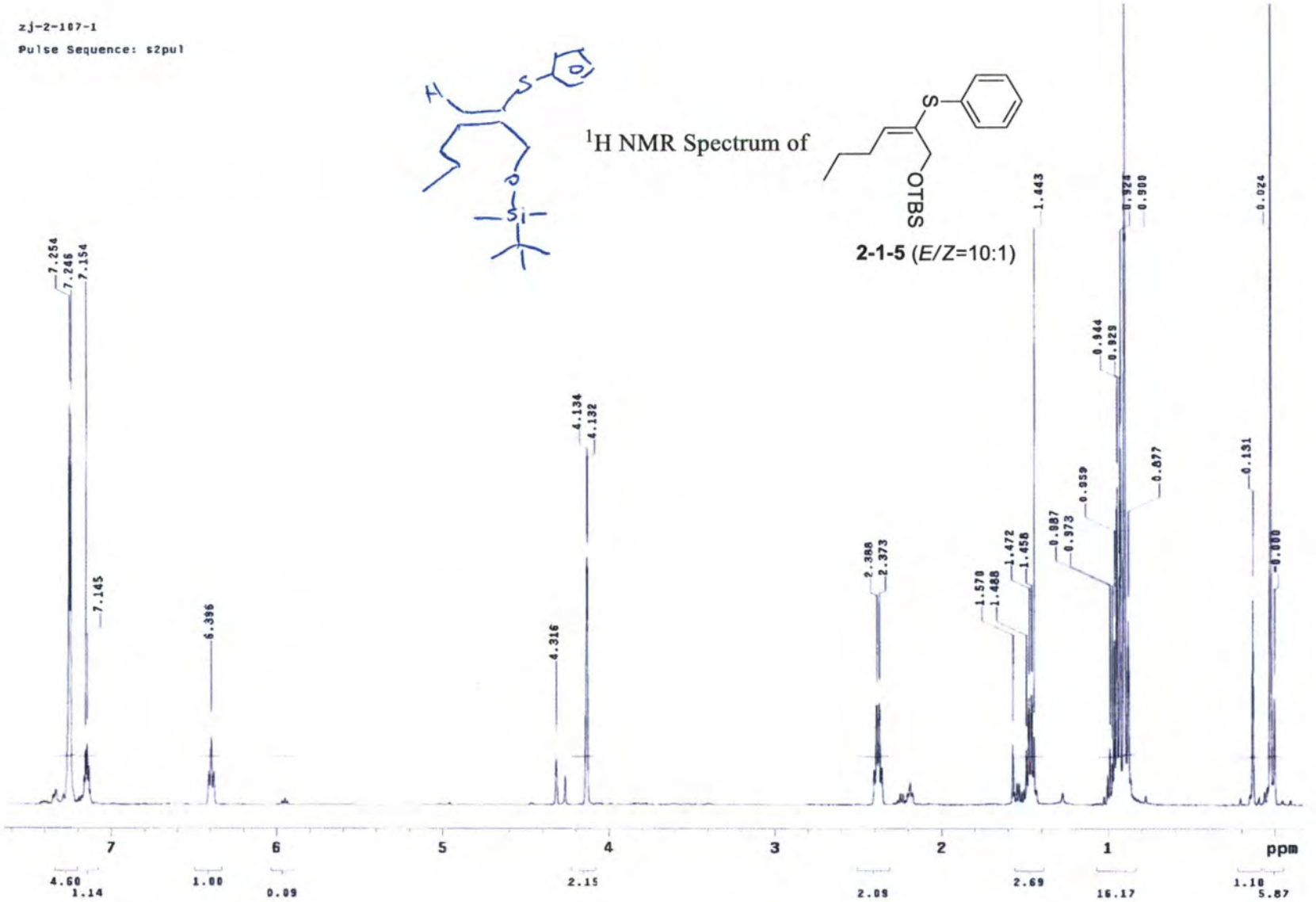
2-1-4m (*E*/*Z*=50:1)



^{13}C NMR spectrum of

2-1-4m (*E*/*Z*=50:1)

5

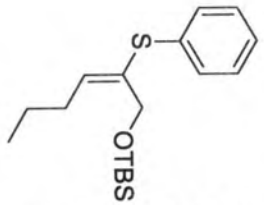


^{1}H NMR Spectrum of

2-1-5 (*E*/*Z*=10:1)

zj-2-107-1
Pulse Sequence: s2pul

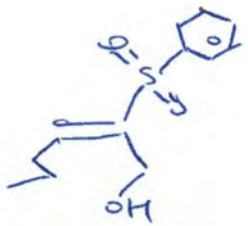
^{13}C NMR Spectrum of



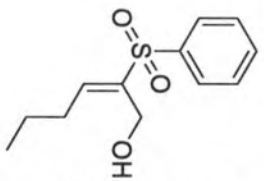
2-1-5 (*E*/*Z*=10:1)

zj-2-109-1

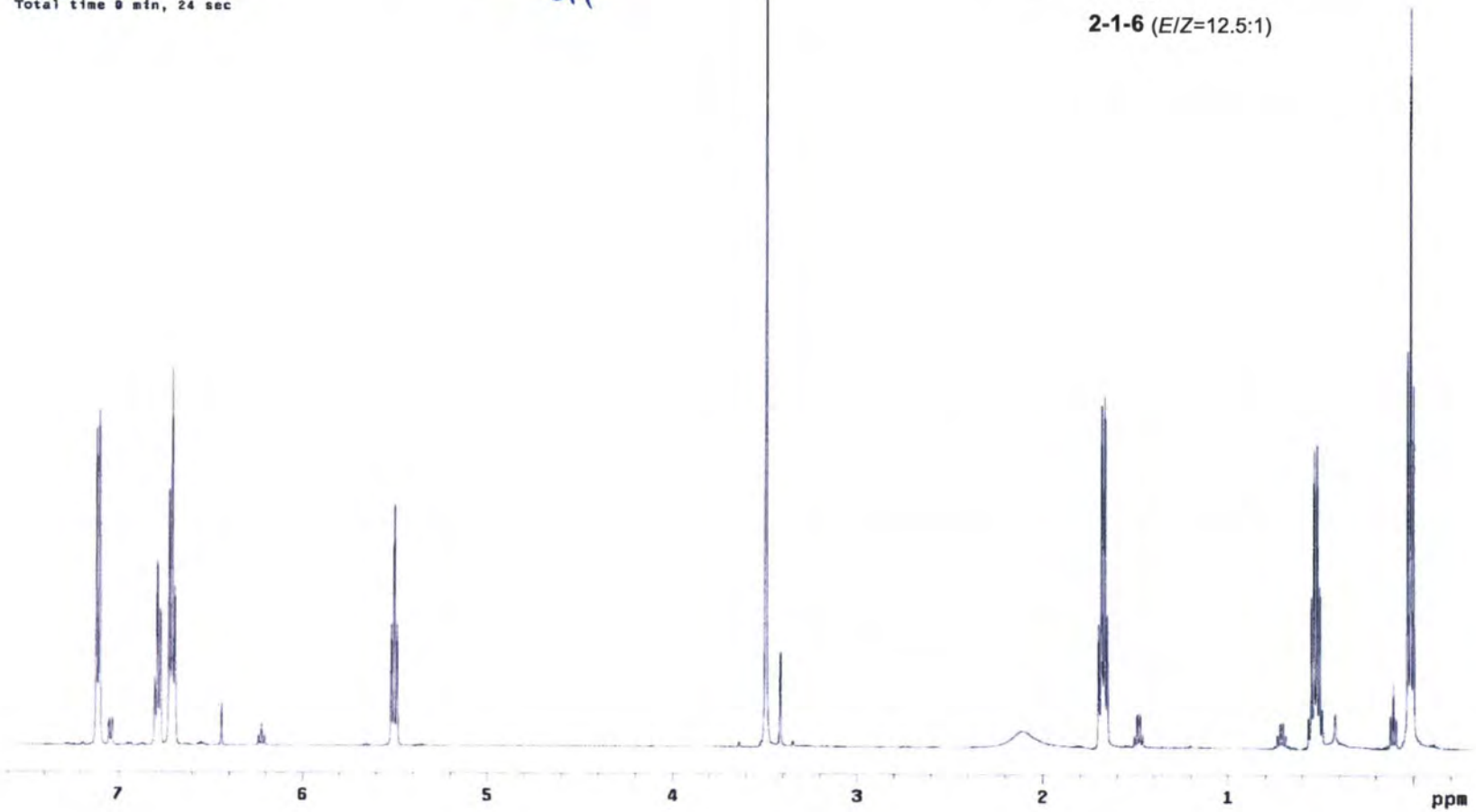
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-500 "ulnmr3"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 3997.2 Hz
8 repetitions
OBSERVE H1, 499.6405729 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 24 sec



^{1}H NMR Spectrum of

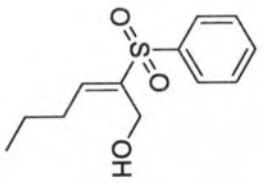


2-1-6 (*E*/*Z*=12.5:1)



6

^{13}C NMR Spectrum of



2-1-6 (*E*/*Z*=12.5:1)

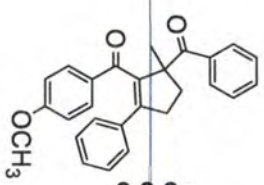
Sample: ZJ-3-61-1
Sample ID: ZhuangJ_20100917_11
File: ZhuangJ_20100917_11/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603207 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



2-2-2a

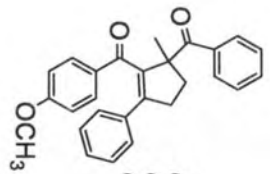
Sample: ZJ-3-61-1
Sample ID: ZhuangJ_20100917_12
File: ZhuangJ_20100917_12/data/Carbon_01.fid

Pulse Sequence: s2pul

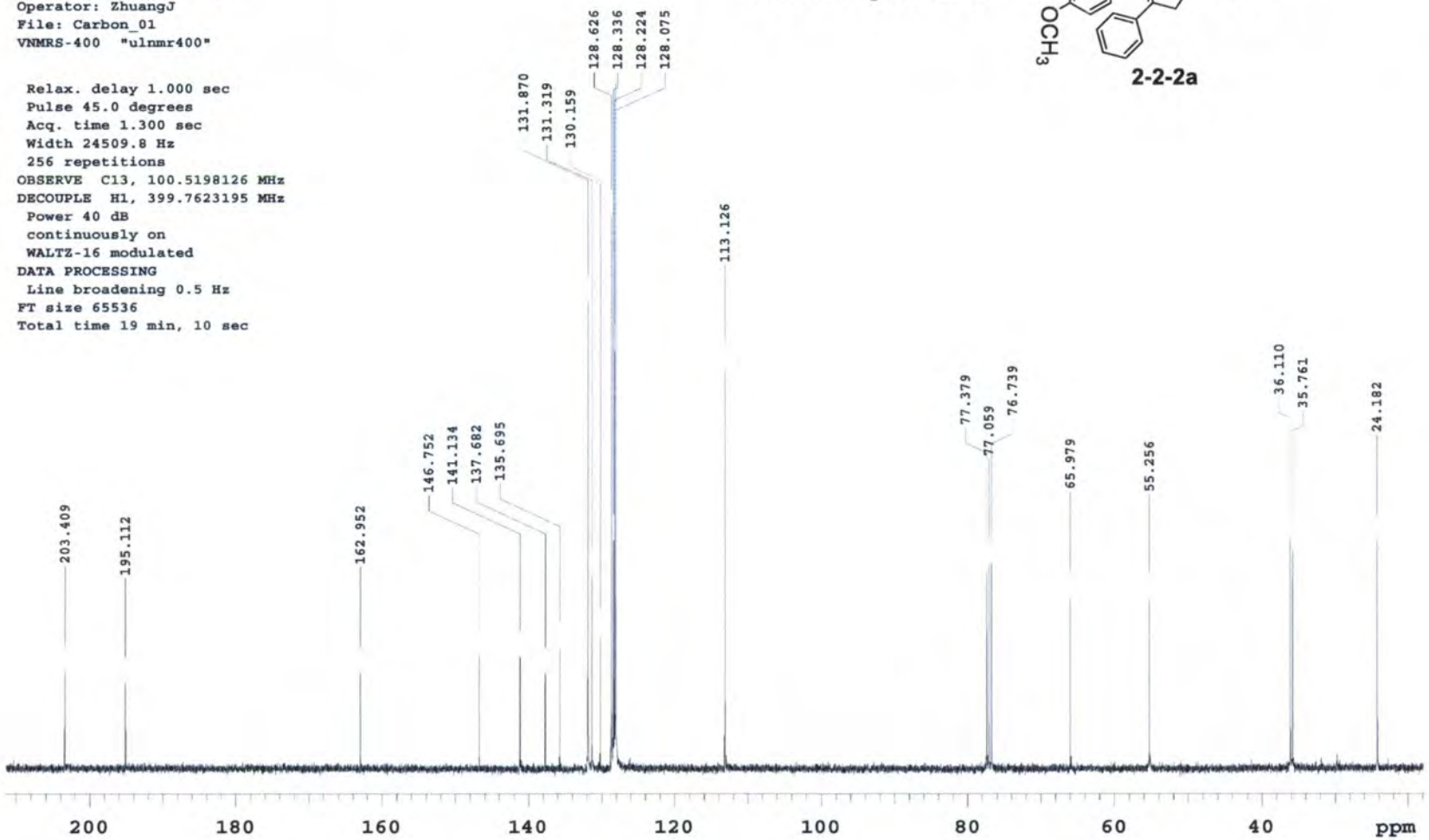
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
256 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min, 10 sec

^{13}C NMR Spectrum of



2-2-2a



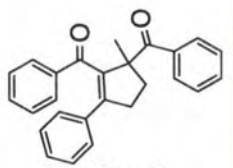
Sample: Zj-3-63-1
Sample ID: ZhuangJ_20100922_08
File: ZhuangJ_20100922_08/data/Proton_01.fid

Pulse Sequence: s2pul

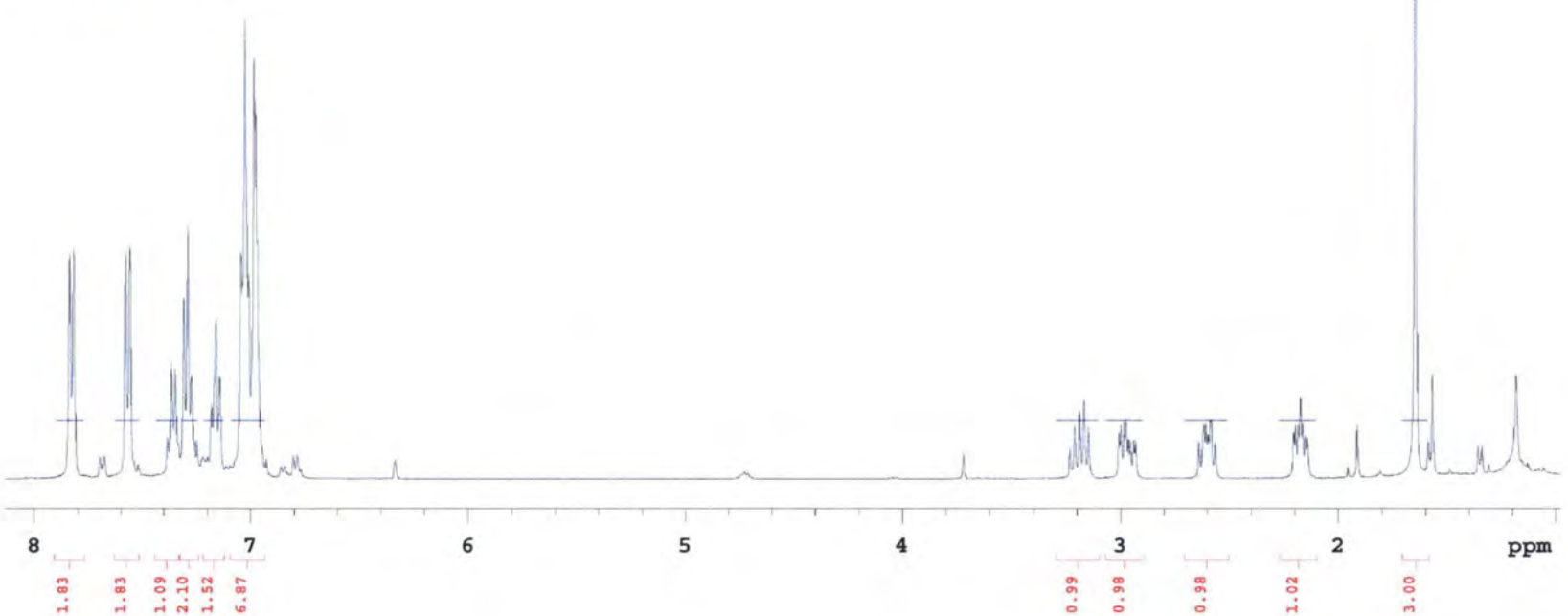
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603522 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



2-2-2b

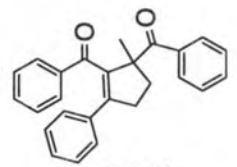


Sample: zj-3-63-1
Sample ID: ZhuangJ_20100922_10
File: ZhuangJ_20100922_10/data/Carbon_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
1000 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min, 21 sec

^{13}C NMR Spectrum of 

2-2-2b

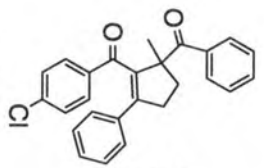
Sample: zj-3-64-1
Sample ID: ZhuangJ_20100924_01
File: ZhuangJ_20100924_01/data/Proton_01.fid

Pulse Sequence: s2pul

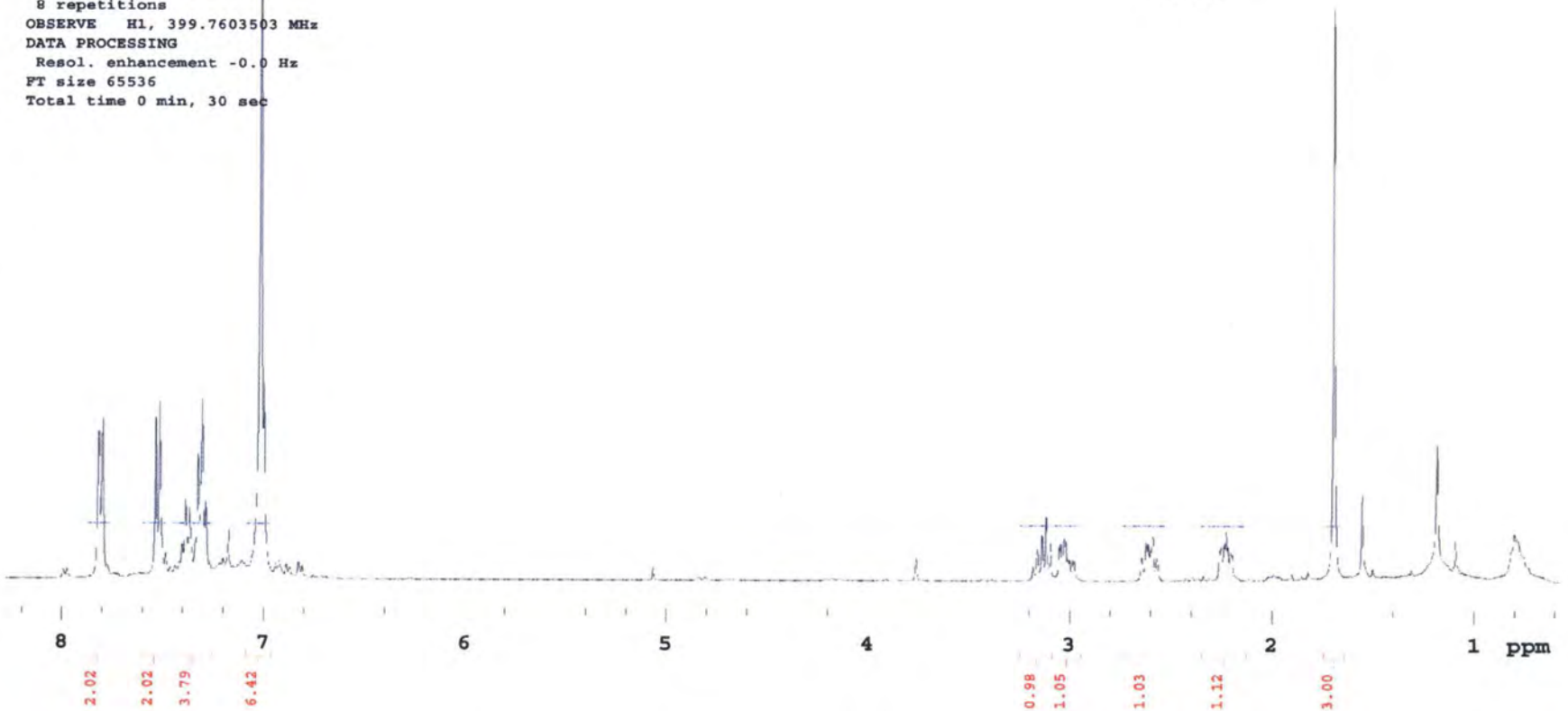
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603503 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



2-2-2c



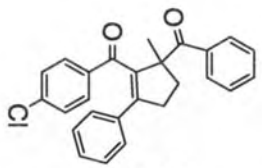
Sample: zj-3-64-1
Sample ID: ZhuangJ_20100924_02
File: ZhuangJ_20100924_02/data/Carbon_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
64 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min, 21 sec

^{13}C NMR Spectrum of



2-2-2c

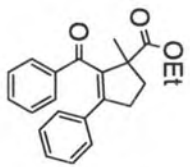
Sample: ZJ-3-65-2
Sample ID: ZhuangJ_20101001_06
File: ZhuangJ_20101001_06/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603207 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



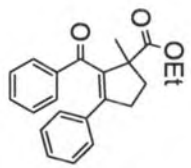
2-2-2d

Sample: ZJ-3-65-2
Sample ID: ZhuangJ_20101001_09
File: /home/walkup/vnmrsys/data/auto_2010.09.27/ZhuangJ_20101001_09/data/Carbon_01.fid

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #37, Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
8000 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 6 min, 45 sec

^{13}C NMR Spectrum of



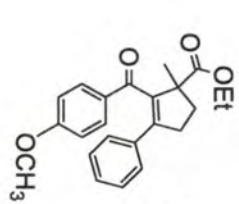
2-2-2d

Sample: ZJ-3-68-2
Sample ID: ZhuangJ_20101006_07
File: ZhuangJ_20101006_07/data/Proton_01.fid

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603207 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



2-2-2e

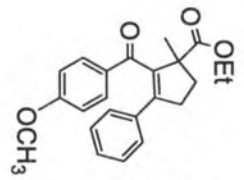
Sample: ZJ-3-68-2
Sample ID: ZhuangJ_20101006_08
File: ZhuangJ_20101006_08/data/Carbon_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
64 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 6 min, 45 sec

^{13}C NMR Spectrum of



2-2-2e

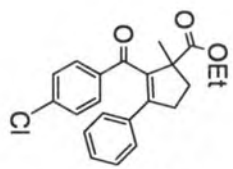
Sample: ZJ-3-70-1
Sample ID: ZhuangJ_20101018_04
File: ZhuangJ_20101018_04/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
INOVA-500 "ulnmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7994.4 Hz
8 repetitions
OBSERVE H1, 499.5404224 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec

^{1}H NMR Spectrum of



2-2-2f

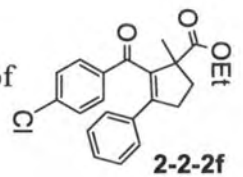
Sample: ZJ-3-70-2
Sample ID: ZhuangJ_20101018_05
File: ZhuangJ_20101018_05/data/Carbon_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
INOVA-500 "ulnmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
64 repetitions
OBSERVE C13, 125.6346841 MHz
DECOUPLE H1, 499.6429206 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 8 hr, 20 min, 22 sec

^{13}C NMR Spectrum of



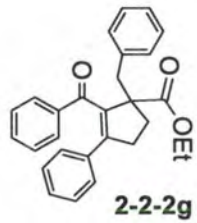
2-2-2f

Sample: ZJ-3-74-1
Sample ID: ZhuangJ_20101023_06
File: ZhuangJ_20101023_06/data/Proton_01.fid

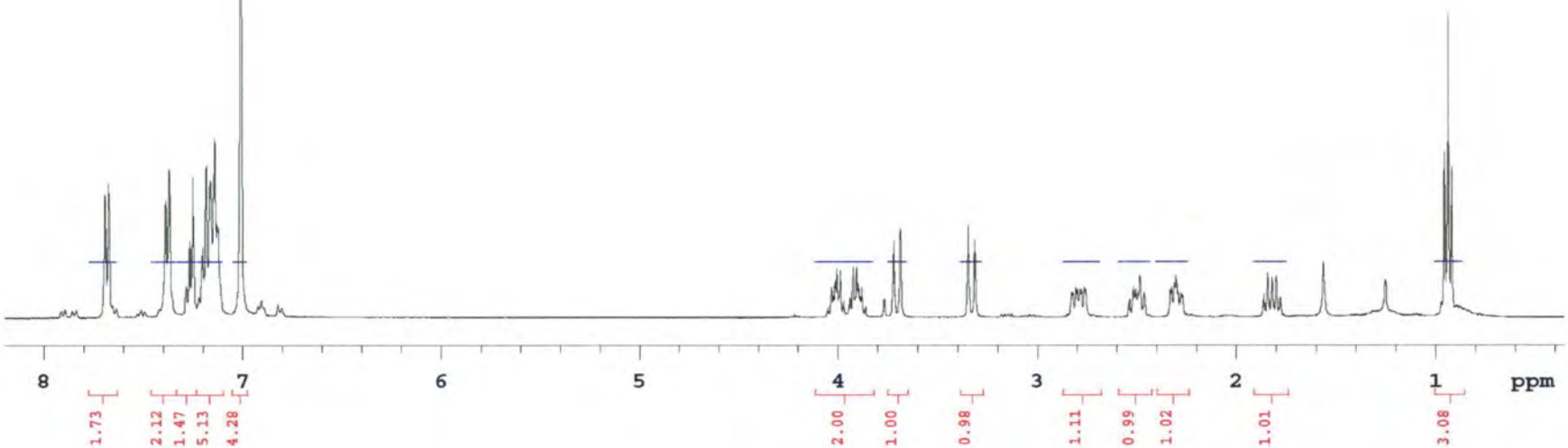
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7535764 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



2-2-2g



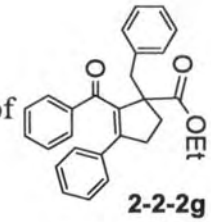
Sample: zj-3-74-1
Sample ID: ZhuangJ_20101026_03
File: ZhuangJ_20101026_03/data/Carbon_01.fid

Pulse Sequence: s2pul

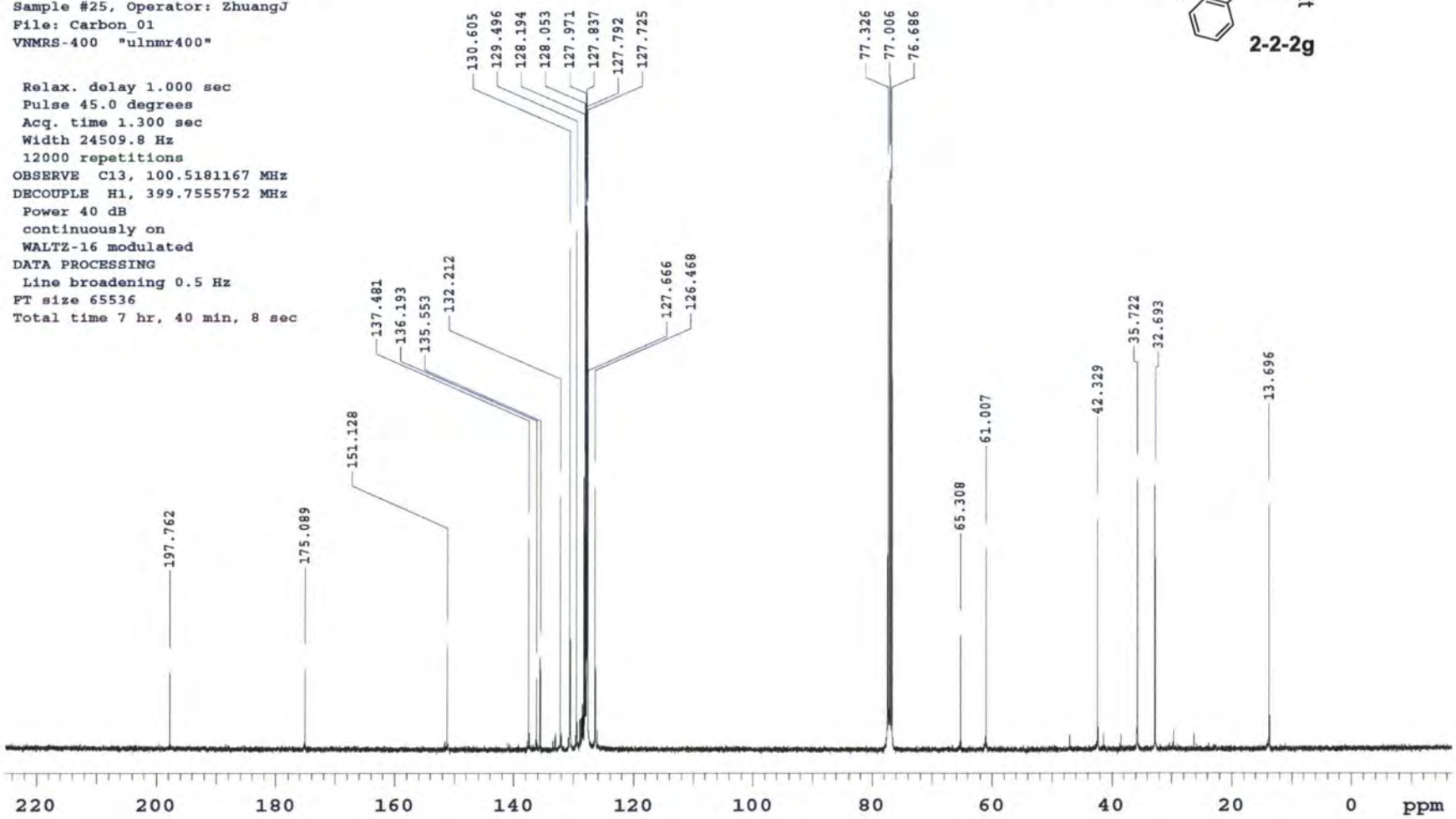
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #25, Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
12000 repetitions
OBSERVE C13, 100.5181167 MHz
DECOUPLE H1, 399.7555752 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 7 hr, 40 min, 8 sec

^{13}C NMR Spectrum of



2-2-2g



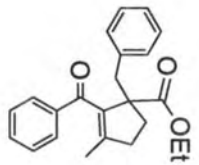
Sample: ZJ-3-73-1-2
Sample ID: ZhuangJ_20101022_03
File: ZhuangJ_20101022_03/data/Proton_01.fid

Pulse Sequence: s2pul

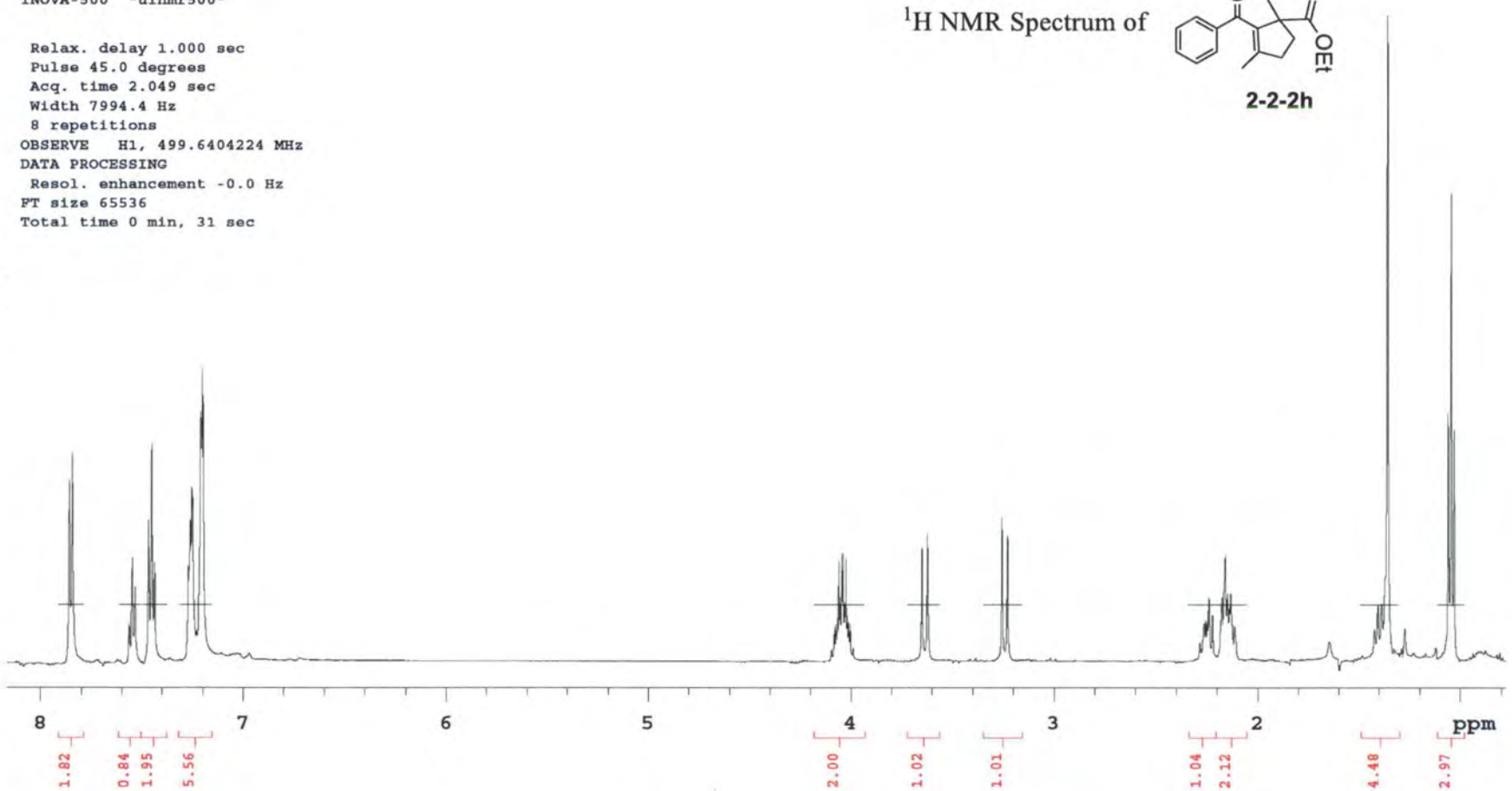
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
INOVA-500 "ulnmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7994.4 Hz
8 repetitions
OBSERVE H1, 499.6404224 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec

^{1}H NMR Spectrum of



2-2-2h

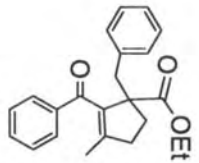


Sample: ZJ-3-73-1-2
Sample ID: ZhuangJ_20101022_04
File: ZhuangJ_20101022_04/data/Carbon_01.fid

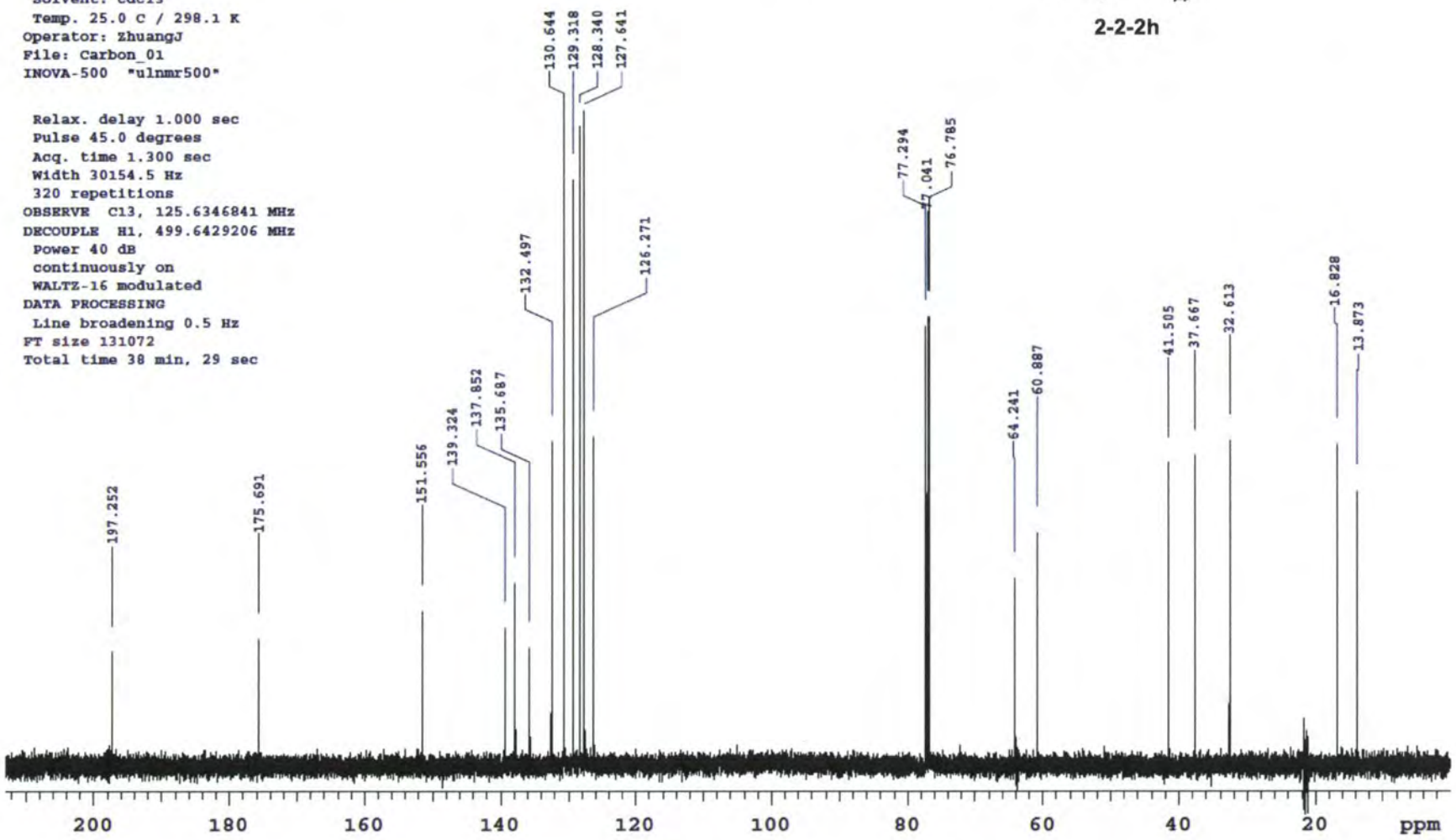
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
INOVA-500 "ulnmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30154.5 Hz
320 repetitions
OBSERVE C13, 125.6346841 MHz
DECOUPLE H1, 499.6429206 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 38 min, 29 sec

^{13}C NMR Spectrum of



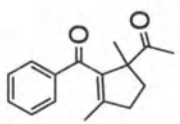
2-2-2h



Sample: ZJ-3-74-2
Sample ID: ZhuangJ_20101023_04
File: ZhuangJ_20101023_04/data/Proton_01.fid

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 6410.3 Hz
 8 repetitions
OBSERVE H1, 399.7535764 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of 

2-2-2i

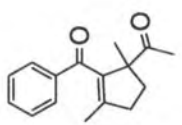
Sample: ZJ-3-74-2
Sample ID: ZhuangJ_20101023_05
File: ZhuangJ_20101023_05/data/Carbon_01.fid

Pulse Sequence: s2pul

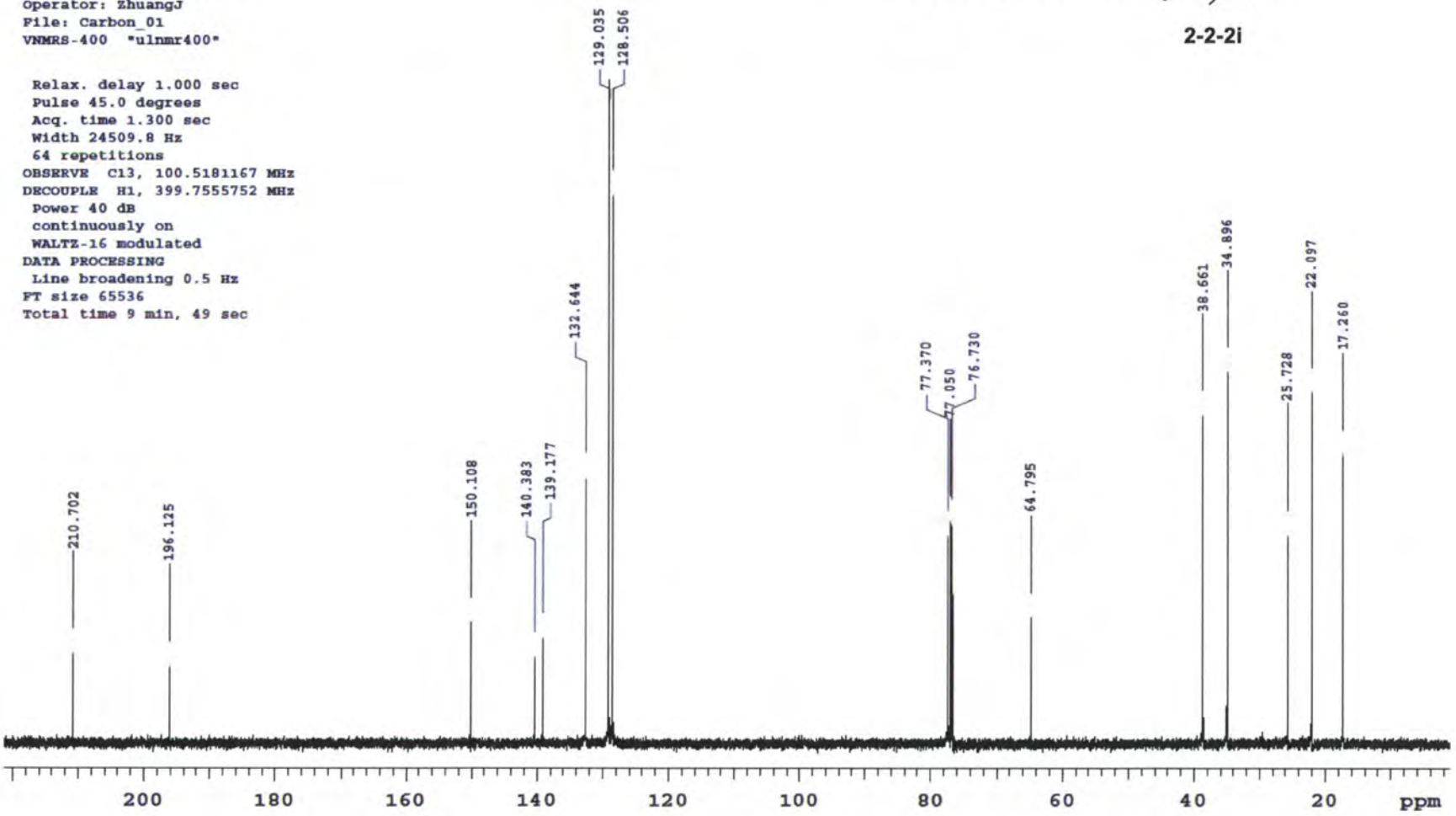
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
64 repetitions
OBSERVE C13, 100.5181167 MHz
DECOUPLE H1, 399.7555752 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min, 49 sec

^{13}C NMR Spectrum of



2-2-2i



zj-3-113-2

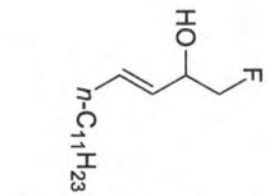
Sample Name:
zj-3-113-2
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
zj-3-113-2_20111022_01
FidFile: PROTON_001

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2011

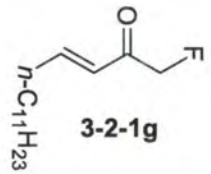
Temp. 25.0 C / 298.1 K
Sample #44, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7275307 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec

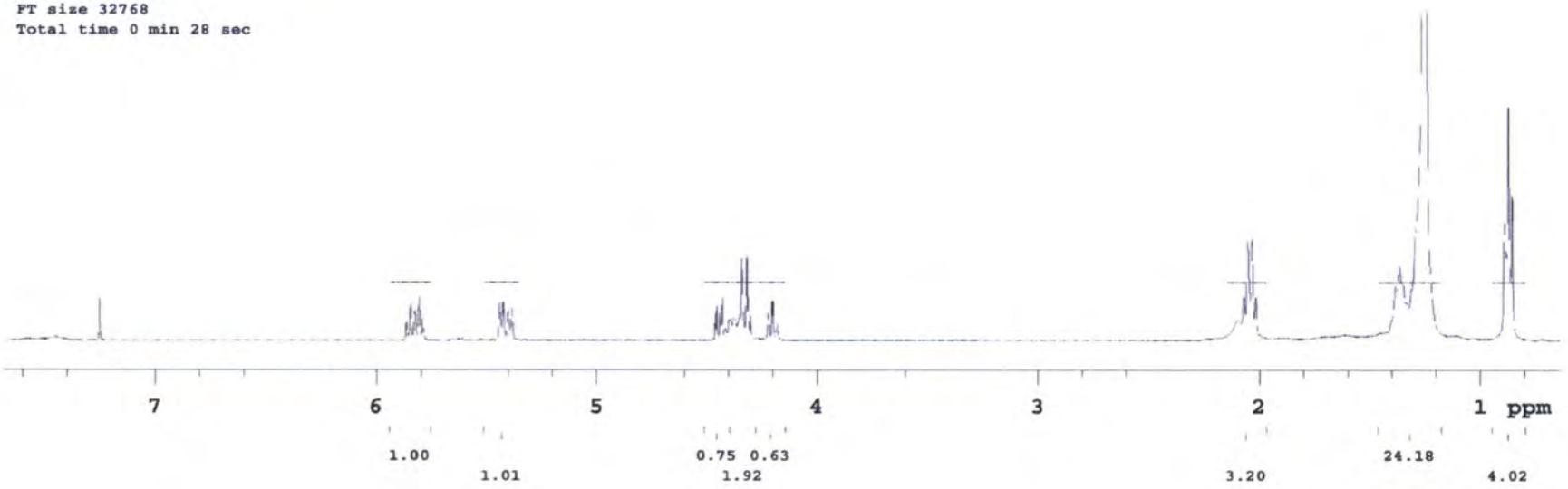
^{1}H NMR Spectrum of



derived from



3-2-1g



zj-3-115-2

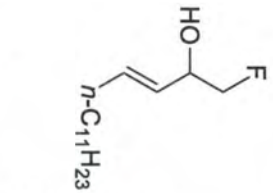
Sample Name:
zj-3-115-2
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
zj-3-115-2_20111108_02
FidFile: CARBON_001

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 8 2011

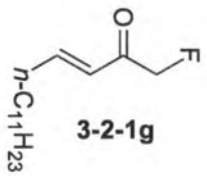
Temp. 25.0 C / 298.1 K
Sample #42, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
20000 repetitions
OBSERVE C13, 100.5094869 MHz
DECOUPLE H1, 399.7212548 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 hr, 41 min

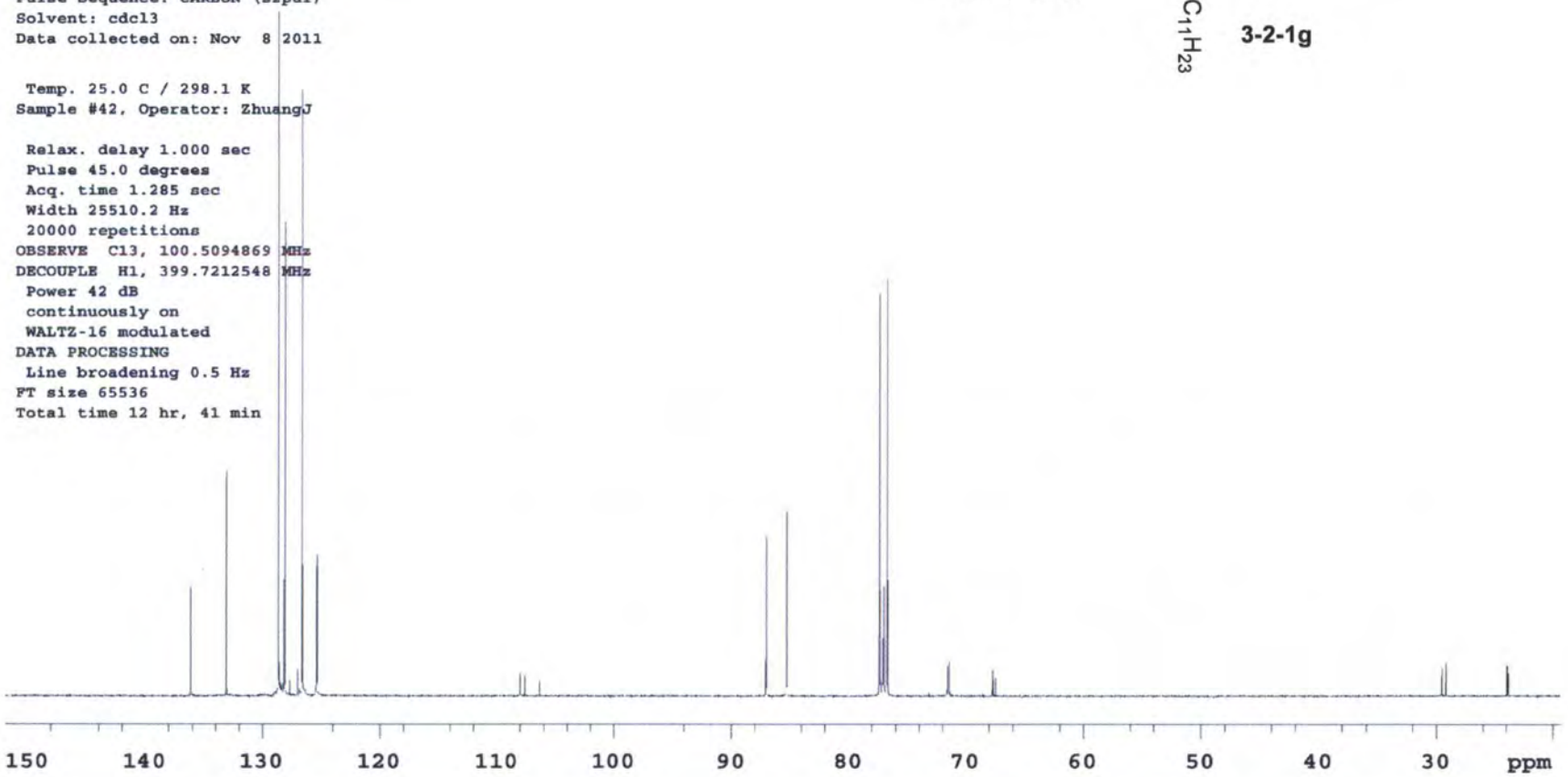
^{13}C NMR Spectrum of



derived from



3-2-1g



zj-3-113-2

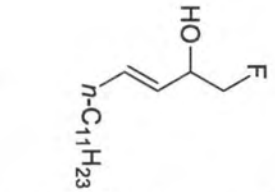
Sample Name:
zj-3-113-2
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
zj-3-113-2_20111022_01
FidFile: FLUORINE_001

Pulse Sequence: FLUORINE (s2pul)
Solvent: cdcl3
Data collected on: Oct 22 2011

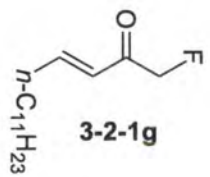
Temp. 25.0 C / 298.1 K
Sample #44, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 35.0 degrees
Acq. time 0.603 sec
Width 108.7 kHz
16 repetitions
OBSERVE F19, 376.1196667 MHz
DATA PROCESSING
FT size 131072
Total time 0 min 26 sec

^{19}F NMR Spectrum of



derived from



3-2-1g

Zj-3-110-2-1

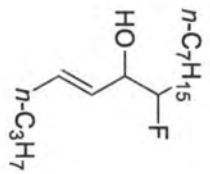
Sample Name:
Zj-3-110-2-1
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
Zj-3-110-2-1_20110707_01
FidFile: PROTON_001

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 7 2011

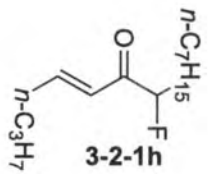
Temp. 25.0 C / 298.1 K
Sample #37, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7353714 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec

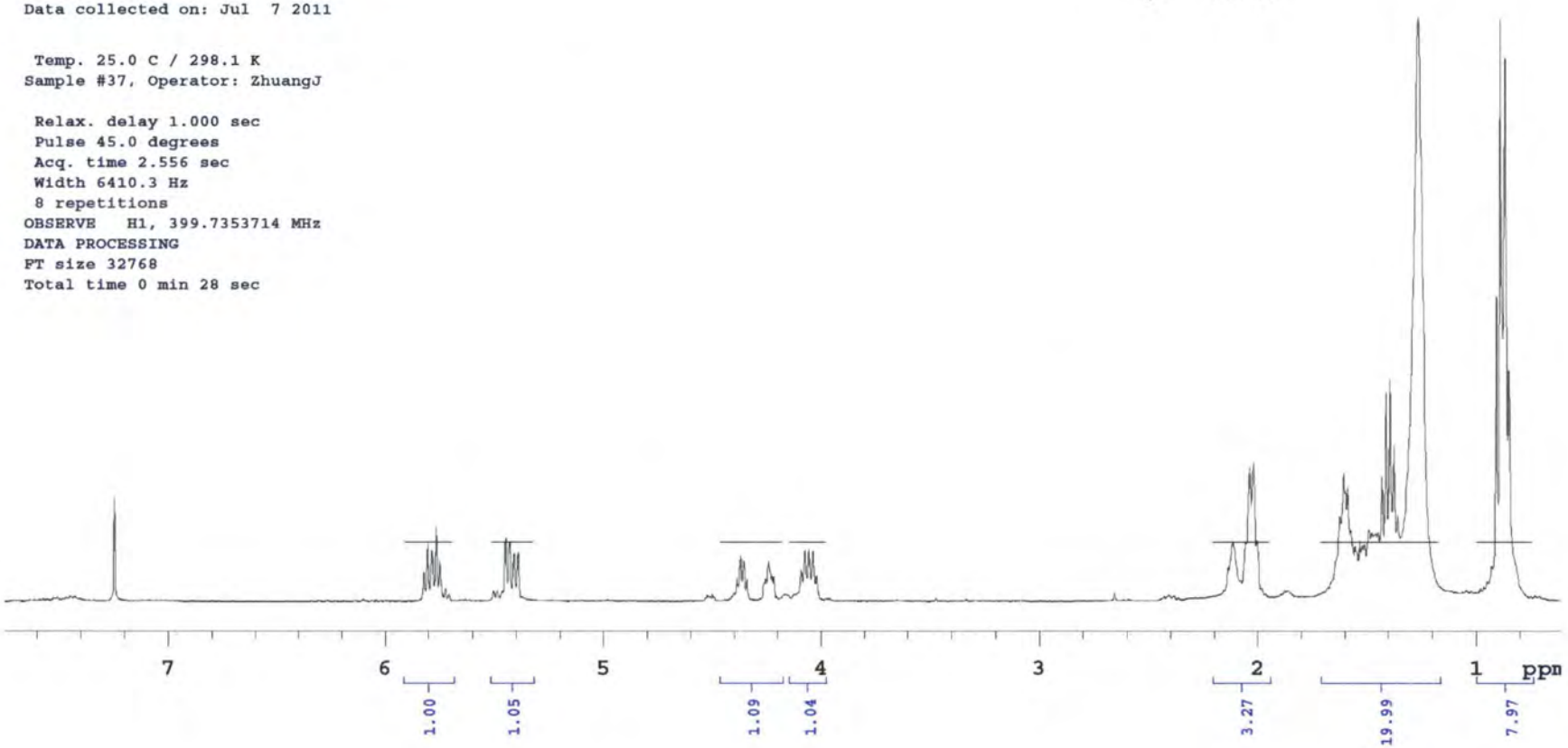
^{1}H NMR Spectrum of



derived from



3-2-1h



ZJ-3-110-2-1

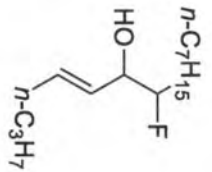
Sample Name:
ZJ-3-110-2-1
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
ZJ-3-110-2-1_20110708_01
FidFile: CARBON_001

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jul 8 2011

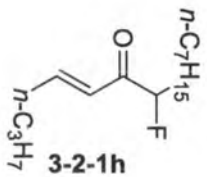
Temp. 25.0 C / 298.1 K
Sample #42, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
20000 repetitions
OBSERVE C13, 100.5135391 MHz
DECOUPLE H1, 399.7373701 MHz
Power 41 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 hr, 41 min

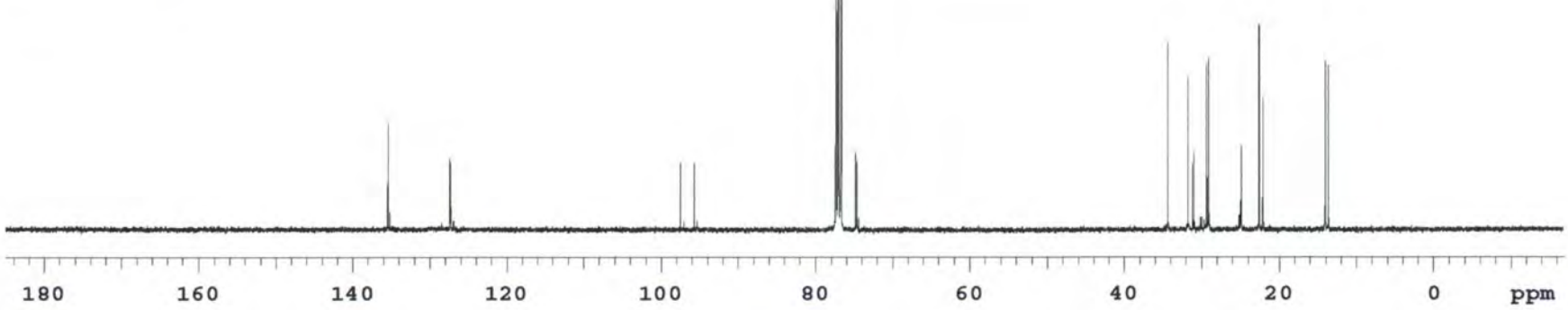
^{13}C NMR Spectrum of



derived from



3-2-1h



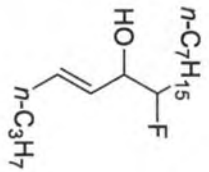
Zj-3-110-2-1

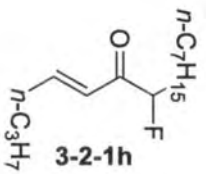
Sample Name:
Zj-3-110-2-1
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
Zj-3-110-2-1_20110707_01
FidFile: FLUORINE_001

Pulse Sequence: FLUORINE (s2pul)
Solvent: cdcl3
Data collected on: Jul 7 2011

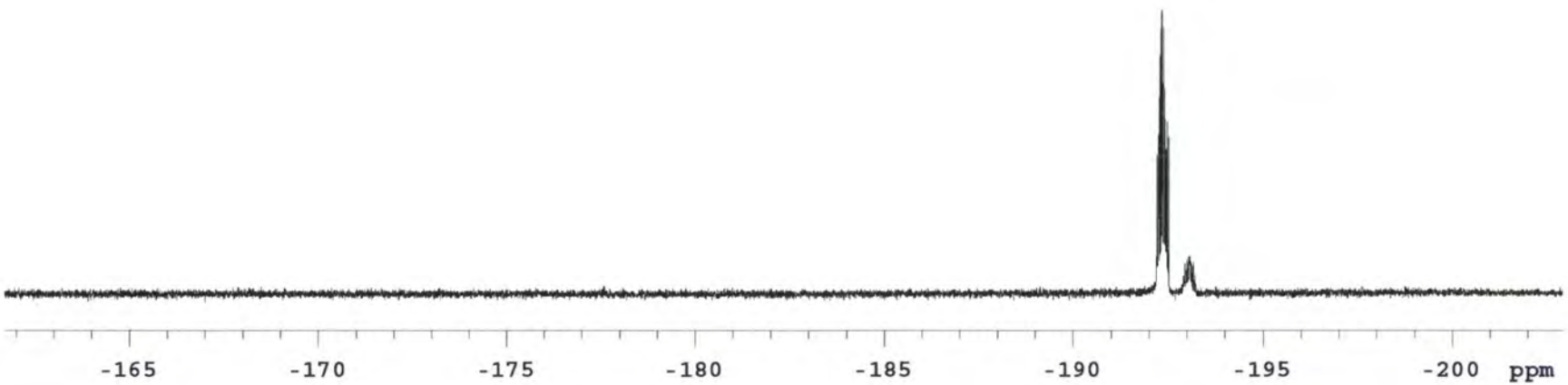
Temp. 25.0 C / 298.1 K
Sample #37, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 35.0 degrees
Acq. time 0.734 sec
Width 89285.7 Hz
16 repetitions
OBSERVE F19, 376.1270443 MHz
DATA PROCESSING
FT size 131072
Total time 0 min 28 sec

^{19}F NMR Spectrum of 

derived from 

3-2-1h



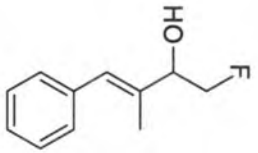
Sample: zj-3-113-1
Sample ID: ZhuangJ_20111017_01
File: ZhuangJ_20111017_01/data/Proton_01.fid

Pulse Sequence: s2pul

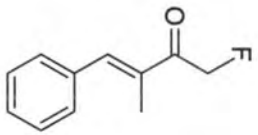
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
INOVA-500 "ulnmr500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 7994.4 Hz
8 repetitions
OBSERVE H1, 499.6404224 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec

^{1}H NMR Spectrum of



derived from



3-2-1i

zj-3-113-1

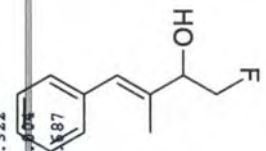
Sample Name:
zj-3-113-1
Data Collected on:
ulnmr400-vnmrs400
Archive directory:
/home/walkup/vnmrsys/data/ZhuangJ
Sample directory:
zj-3-113-1_20111017_01
FidFile: CARBON_001

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Oct 17 2011

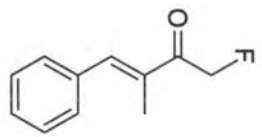
Temp. 25.0 C / 298.1 K
Sample #48, Operator: ZhuangJ

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
20000 repetitions
OBSERVE C13, 100.5115675 MHz
DECOUPLE H1, 399.7295294 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 12 hr, 41 min

^{13}C NMR Spectrum of



derived from



3-2-1i

77.322
77.005
76.687

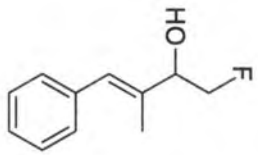
200 180 160 140 120 100 80 60 40 20 ppm

Sample: zj-3-113-1
Sample ID: ZhuangJ_20111017_01
File: ZhuangJ_20111017_01/data/Fluorine_01.fid

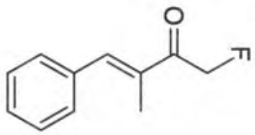
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Fluorine_01
INOVA-500 "ulnmr500"

^{19}F NMR Spectrum of



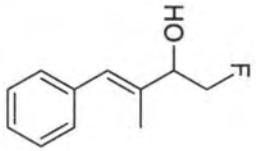
derived from



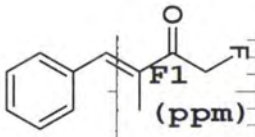
3-2-1i

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.000 sec
Width 103.5 kHz
16 repetitions
OBSERVE F19, 470.1317140 MHz
DATA PROCESSING
Line broadening 0.9 Hz
FT size 262144
Total time 0 min, 36 sec

ROESY Spectrum of



derived from



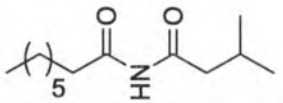
Sample: zj-3-41-2
Sample ID: ZhuangJ_20100610_01
File: /home/walkup/vnmrsys/data/auto_2010.06.08/ZhuangJ_20100610_01/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7698366 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of

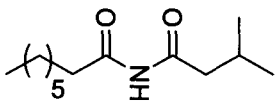


3-3-2-2c

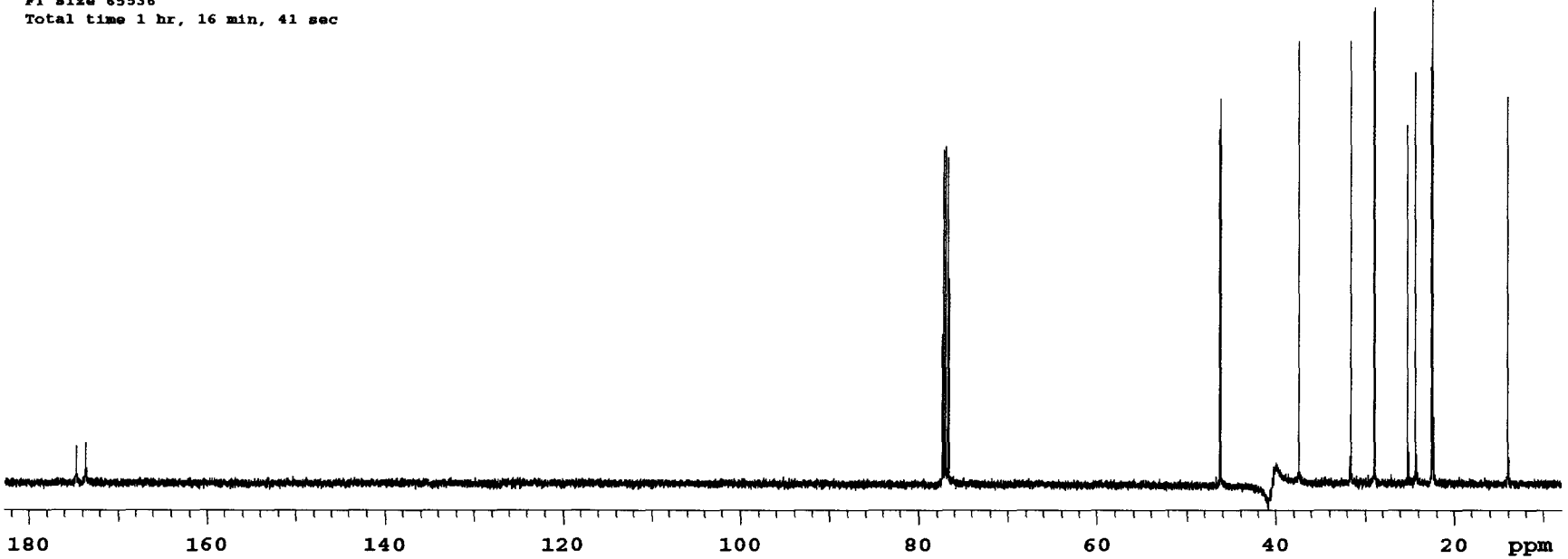
Sample: zj-3-41-2
Sample ID: ZhuangJ_20100610_02
File: /home/walkup/vnmrsys/data/auto_2010.06.08/ZhuangJ_20100610_02/data/Carbon_01.fid

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5222010 MHz
DECOUPLE H1, 399.7718181 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 16 min, 41 sec

^{13}C NMR Spectrum of 

3-3-2-2c



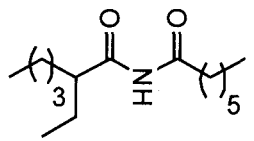
Sample: zj-3-50-1
Sample ID: ZhuangJ_20100730_03
File: /home/walkup/vnmrsys/data/auto_2010.07.19/ZhuangJ_20100730_03/data/Proton_01.fid

Pulse Sequence: s2pul

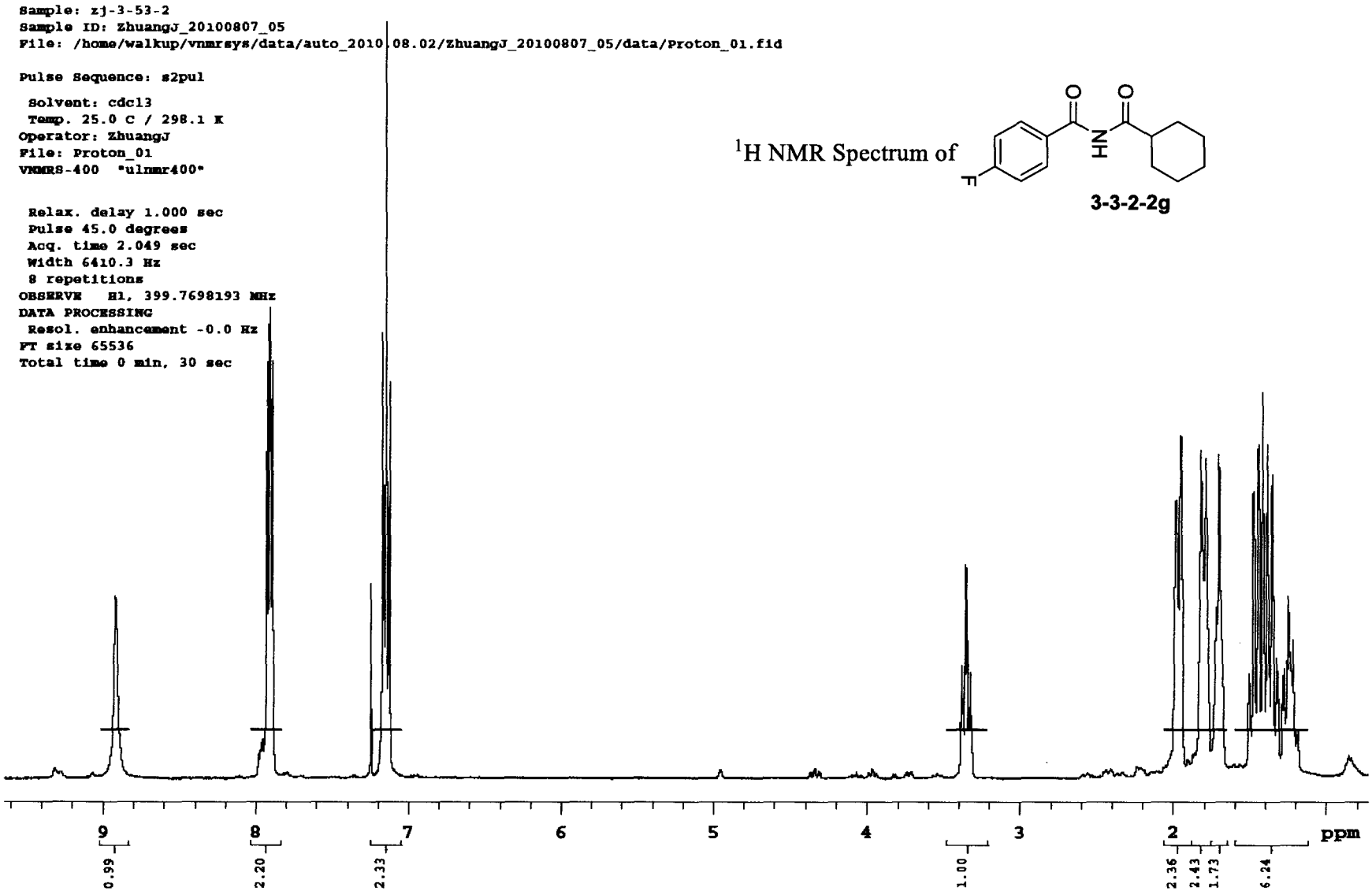
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7698350 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



3-3-2-2f

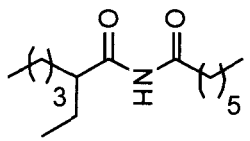

Sample: zj-3-53-2
Sample ID: ZhuangJ_20100807_05
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100807_05/data/Proton_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7698193 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
1H NMR Spectrum of
3-3-2-2g
9
8
7
6
5
4
3
2
ppm
0.99
2.20
2.33
1.00
2.36
2.43
1.73
6.24

Sample: zj-3-50-1
Sample ID: ZhuangJ_20100730_04
File: /home/walkup/vnmrsys/data/auto_2010.07.19/ZhuangJ_20100730_04/data/Carbon_01.fid

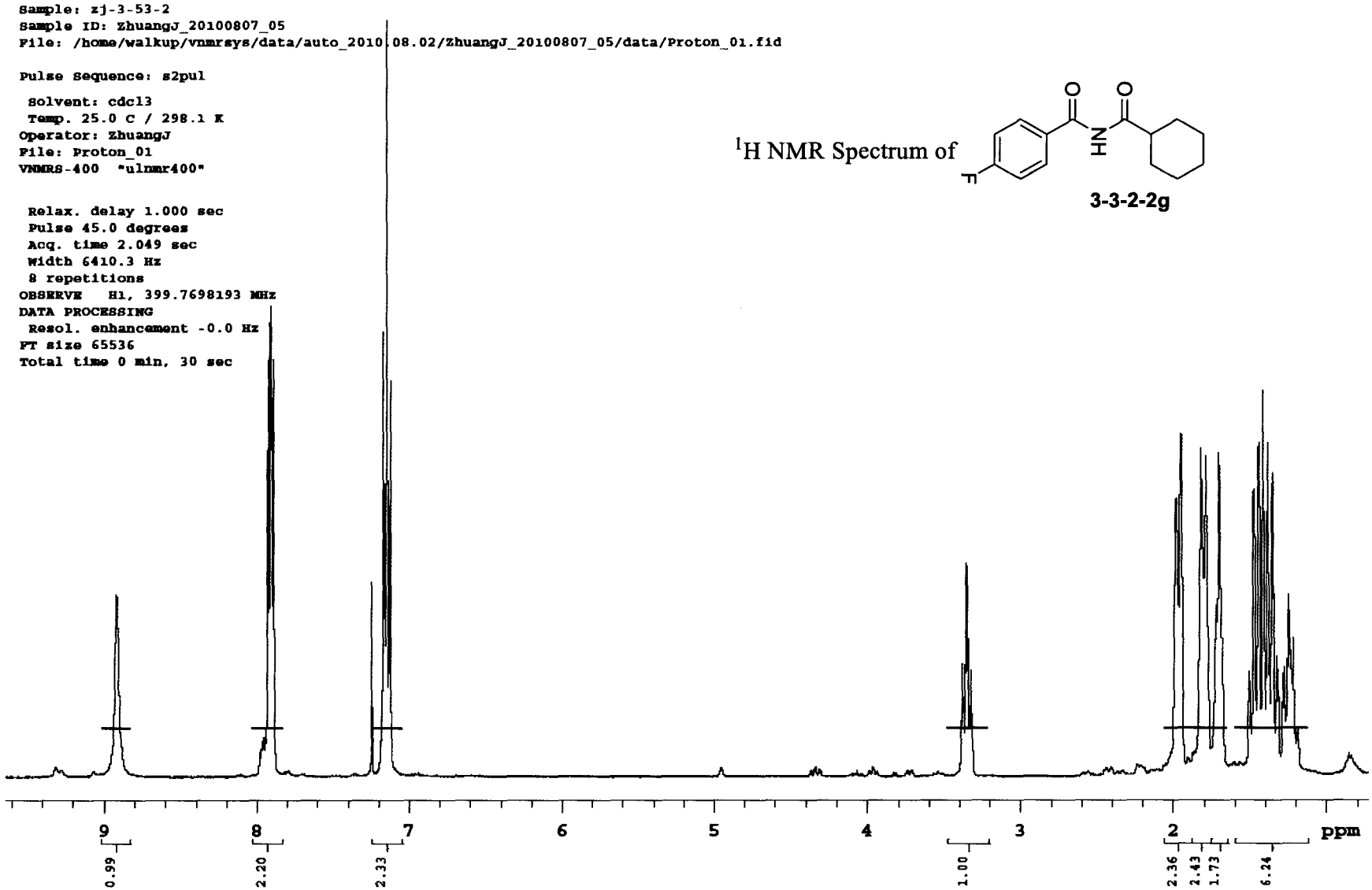
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

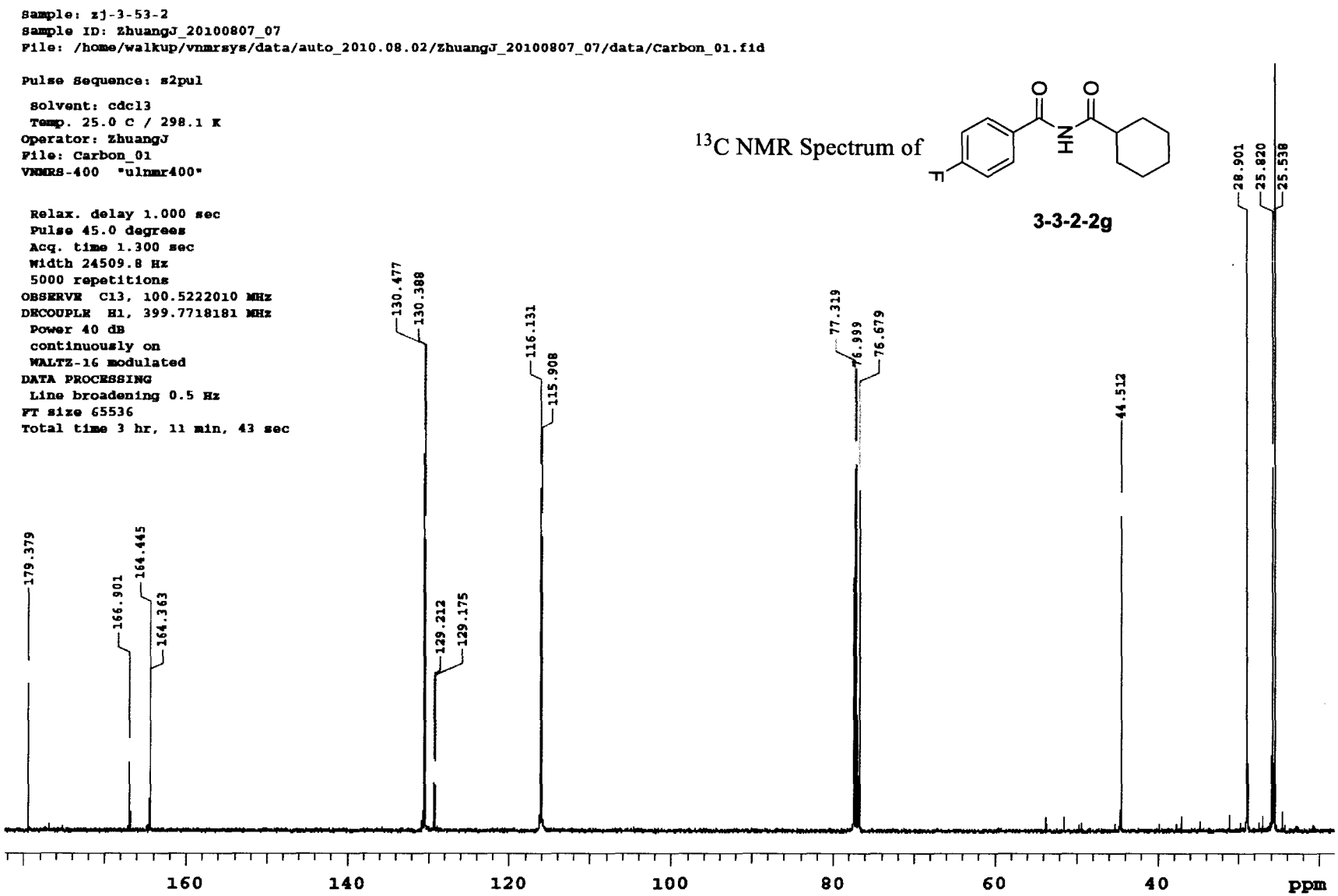
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
 1000 repetitions
OBSERVE C13, 100.5222010 MHz
DECOUPLE H1, 399.7718181 MHz
 Power 40 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 38 min, 21 sec

^{13}C NMR Spectrum of



3-3-2-2f


Sample: zj-3-53-2
Sample ID: ZhuangJ_20100807_05
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100807_05/data/Proton_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7698193 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
1H NMR Spectrum of
3-3-2-2g
9
8
7
6
5
4
3
2
ppm
0.99
2.20
2.33
1.00
2.36
2.43
1.73
6.24

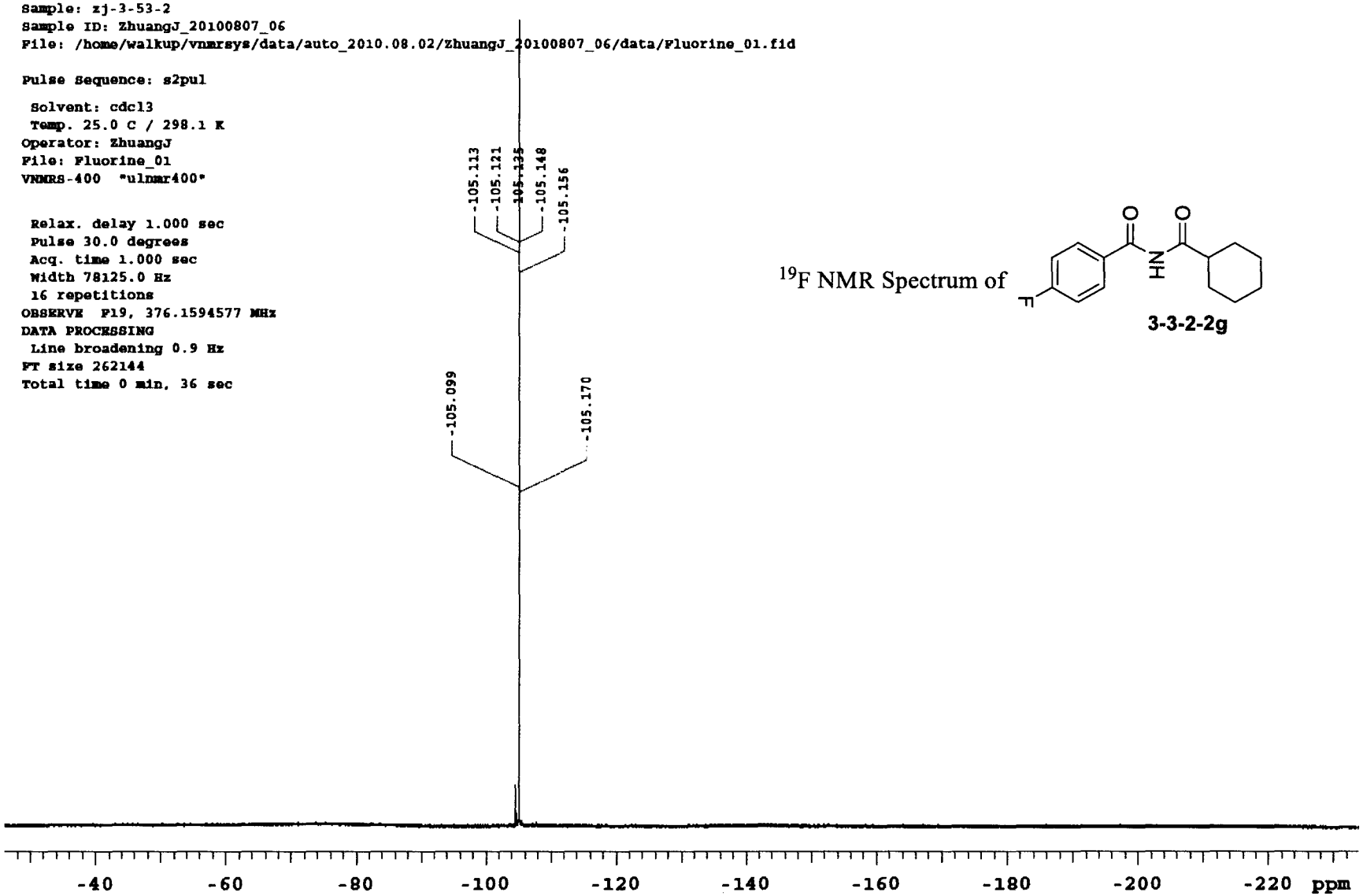

Sample: zj-3-53-2
Sample ID: ZhuangJ_20100807_07
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100807_07/data/Carbon_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5222010 MHz
DECOUPLE H1, 399.7718181 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 11 min, 43 sec
13C NMR Spectrum of
3-3-2-2g
179.379
166.901
164.445
164.363
130.477
130.388
129.212
129.175
116.131
115.908
77.319
76.999
76.679
44.512
28.901
25.820
25.538
160
140
120
100
80
60
40
ppm

Sample: zj-3-53-2
Sample ID: ZhuangJ_20100807_06
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100807_06/data/Fluorine_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Fluorine_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.000 sec
Width 78125.0 Hz
16 repetitions
OBSERVE F19, 376.1594577 MHz
DATA PROCESSING
Line broadening 0.9 Hz
FT size 262144
Total time 0 min, 36 sec



^{19}F NMR Spectrum of

3-3-2-2g

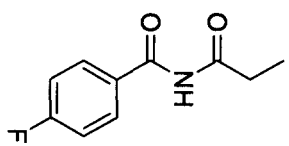
Sample: zj-3-54-2
Sample ID: ZhuangJ_20100810_02
File: /home/walkup/vnmrsys/data/auto_2010.08.09/ZhuangJ_20100810_02/data/Proton_01.fid

Pulse Sequence: s2pul

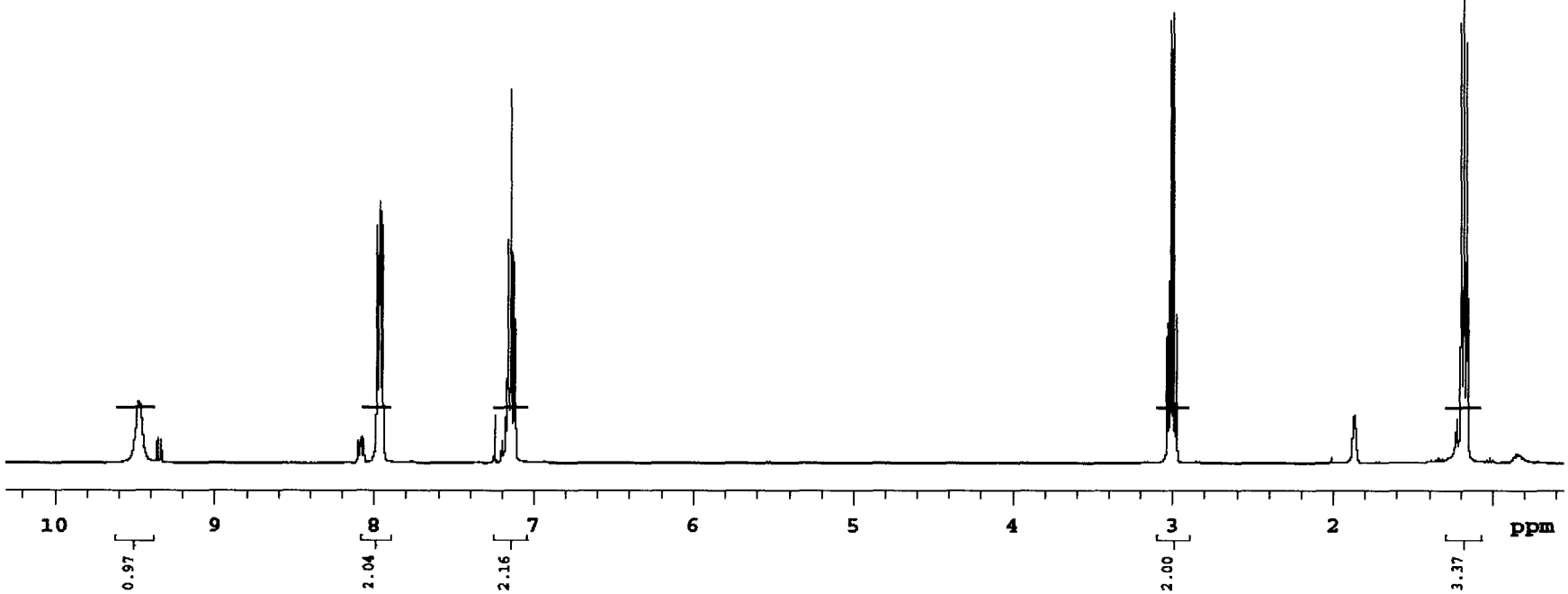
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"

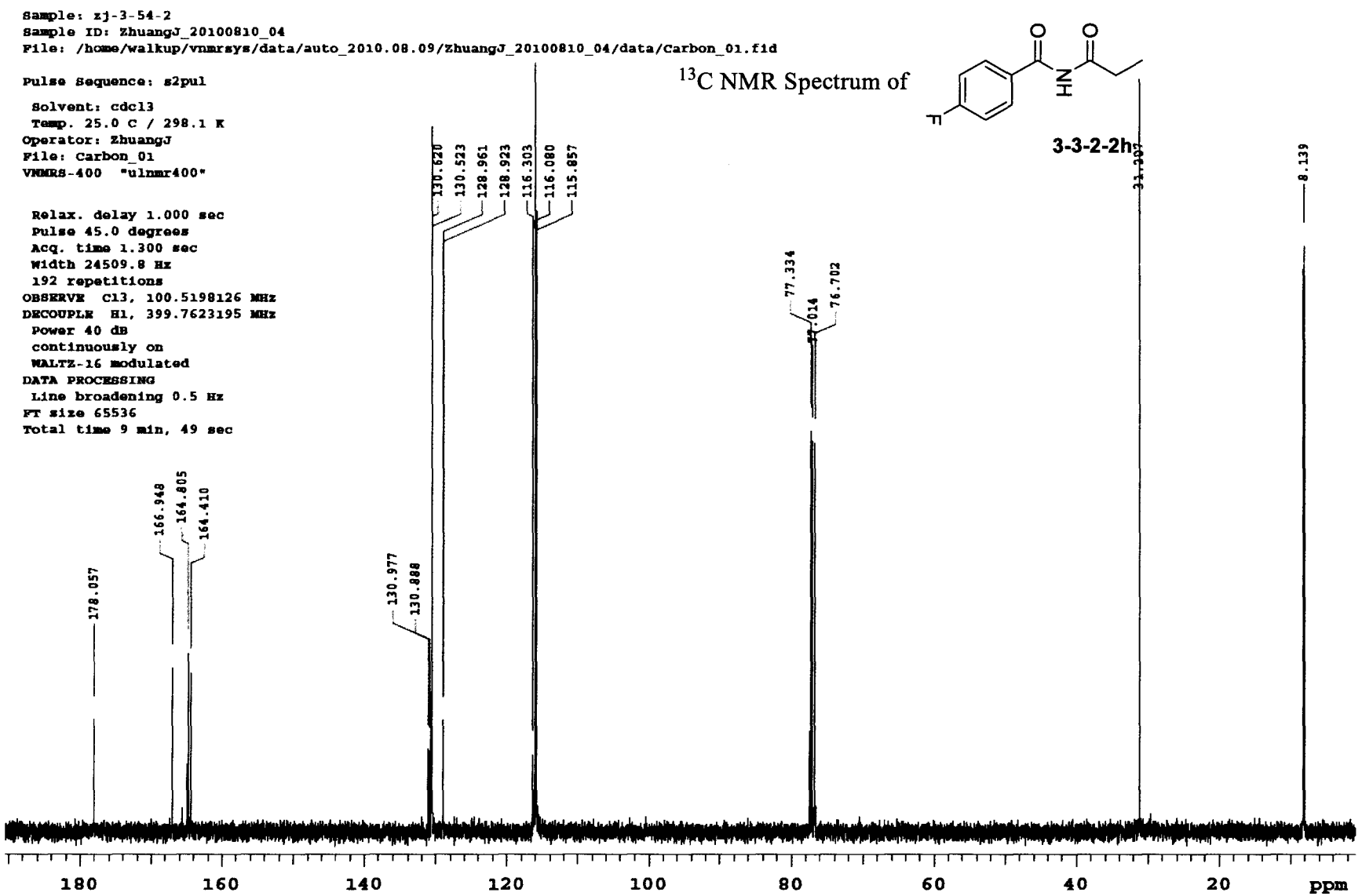
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7603207 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



3-3-2-2h




Sample: zj-3-54-2
Sample ID: ZhuangJ_20100810_04
File: /home/walkup/vnmrsys/data/auto_2010.08.09/ZhuangJ_20100810_04/data/Carbon_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
192 repetitions
OBSERVE C13, 100.5198126 MHz
DECOUPLE H1, 399.7623195 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min, 49 sec
13C NMR Spectrum of
3-3-2-2h
178.057
166.948
164.805
164.410
130.977
130.888
130.620
130.523
128.961
128.923
116.303
116.080
115.857
77.334
77.014
76.702
31.807
8.139
180
160
140
120
100
80
60
40
20
ppm

Sample: zj-3-54-2
Sample ID: ZhuangJ_20100810_03
File: /home/walkup/vnmrsys/data/auto_2010.08.09/ZhuangJ_20100810_03/data/Fluorine_01.fid

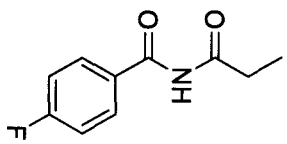
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Fluorine_01
VNMRS-400 "ulnmr400"

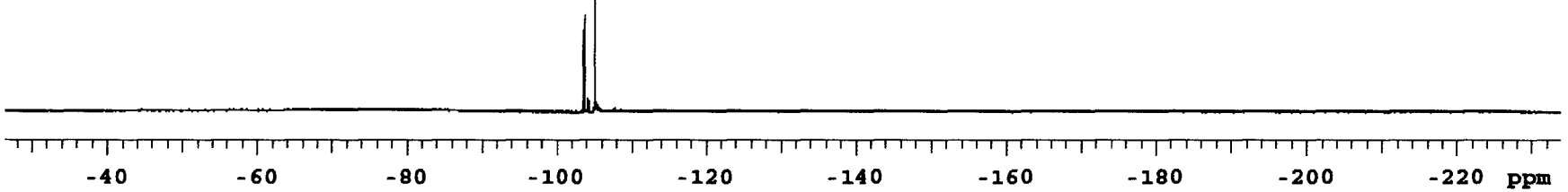
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.000 sec
Width 78125.0 Hz
16 repetitions
OBSERVE F19, 376.1505201 MHz
DATA PROCESSING
Line broadening 0.9 Hz
FT size 262144
Total time 0 min, 36 sec

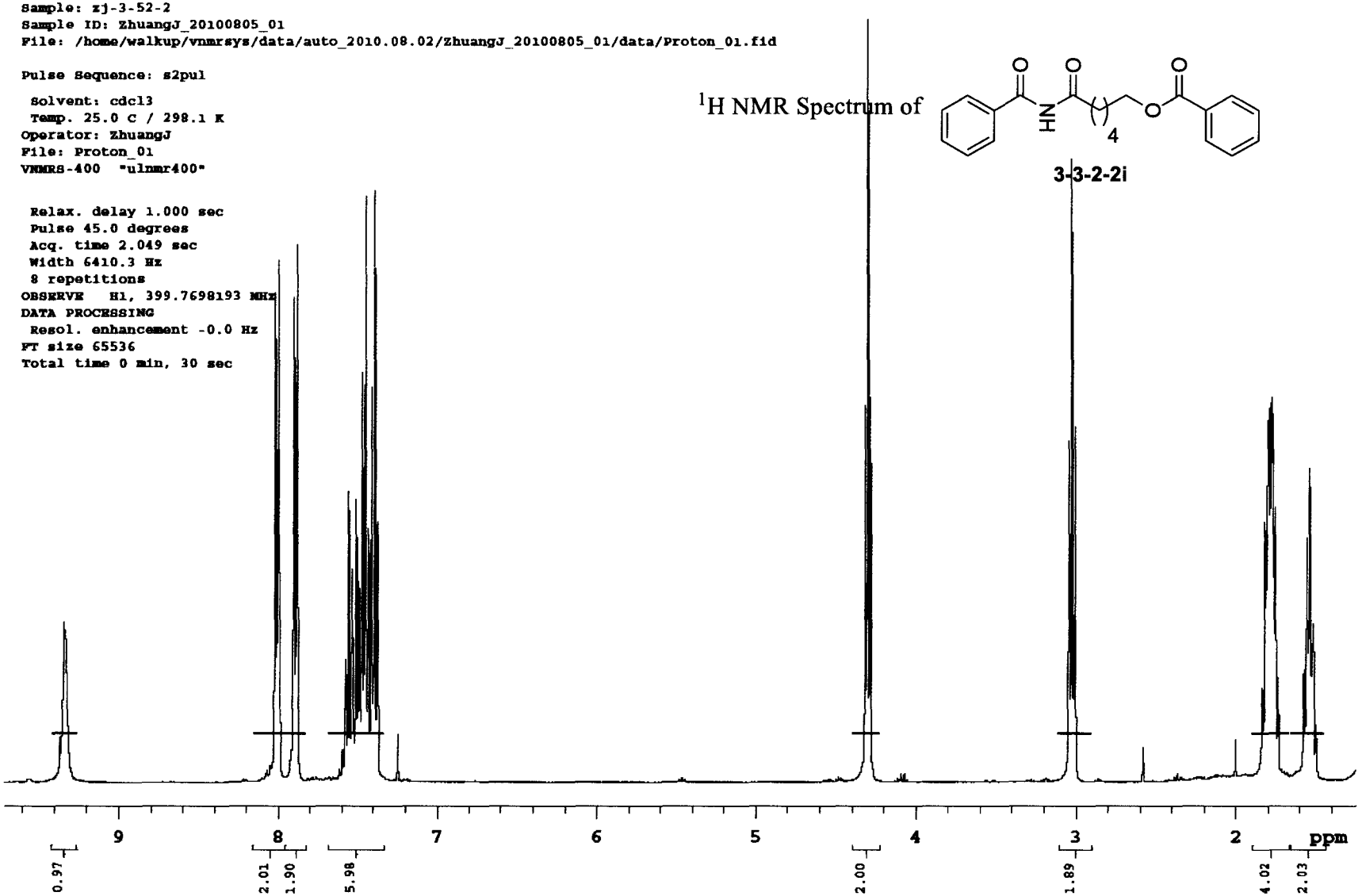
-105.120
-105.128
-105.134
-105.141
-105.155

^{19}F NMR Spectrum of



3-3-2-2h




Sample: zj-3-52-2
Sample ID: ZhuangJ_20100805_01
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100805_01/data/Proton_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Proton_01
VNMRS-400 "ulnmr400"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7698193 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec
1H NMR Spectrum of
HN
4
3-3-2-2i
9
8
7
6
5
4
3
2
ppm
0.97
2.01
1.90
5.98
2.00
1.89
4.02
2.03

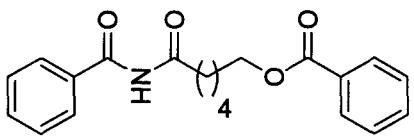
Sample: zj-3-52-2
Sample ID: ZhuangJ_20100805_02
File: /home/walkup/vnmrsys/data/auto_2010.08.02/ZhuangJ_20100805_02/data/Carbon_01.fid

Pulse Sequence: s2pul

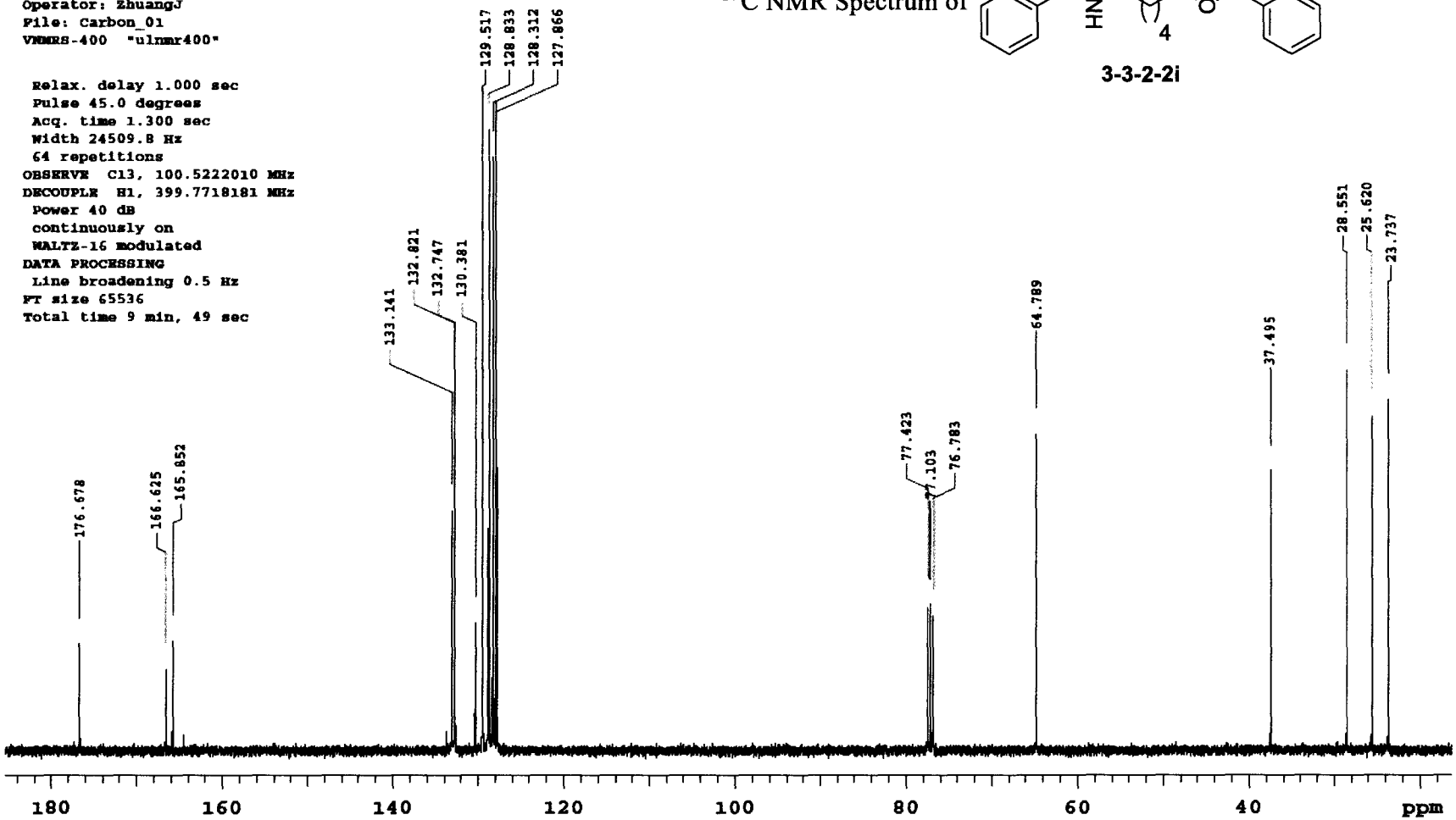
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: ZhuangJ
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
64 repetitions
OBSERVE C13, 100.5222010 MHz
DECOUPLE H1, 399.7718181 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min, 49 sec

^{13}C NMR Spectrum of



3-3-2-2i



SPA14-3-4
Zhuang Jin
15 mg in cdcl3

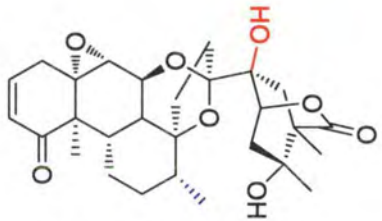
Sample: SPA14-3-4
Sample ID: hammond_SPA14-3-4_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-4_20110613_02/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #2, Operator: hammond
File: Proton_01
VNMRS-400 "ulnmr-ds"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 5605.4 Hz
8 repetitions
OBSERVE H1, 699.8134495 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



Physangulidine A (1)

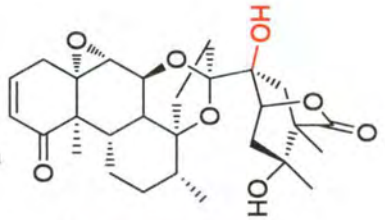
SPA14-3-4
Zhuang Jin
15 mg in cdcl3

Sample: SPA14-3-4
Sample ID: hammond_SPA14-3-4_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-4_20110613_02/data/Carbon_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #2, Operator: hammond
File: Carbon_01
VNMRS-400 "ulnmr-ds"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 43103.4 Hz
2000 repetitions
OBSERVE C13, 175.9682318 MHz
DECOUPLE H1, 699.8169486 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 1 hr, 16 min, 41 sec

^{13}C NMR Spectrum of



Physangulidine A (1)

201.621 176.961 143.748 129.261 109.709 90.027 78.743 77.214 77.031 76.852 75.055 69.496 67.070 63.008 62.596 48.461 47.459 40.499 37.345 36.926 34.112 33.974 32.957 32.064 31.462 28.535 27.044 20.488 14.470 14.228 14.041

200 180 160 140 120 100 80 60 40 20 ppm

SPA14-3-4
Zhuang Jin
15 mg in cdcl3

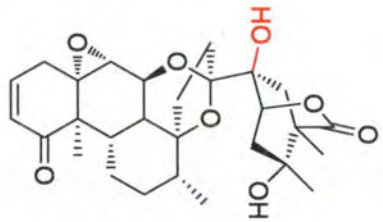
Sample: SPA14-3-4
Sample ID: hammond_SPA14-3-4_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-4_20110613_02/data/Ghsqcad_01.fid

Pulse Sequence: gHSQCAD

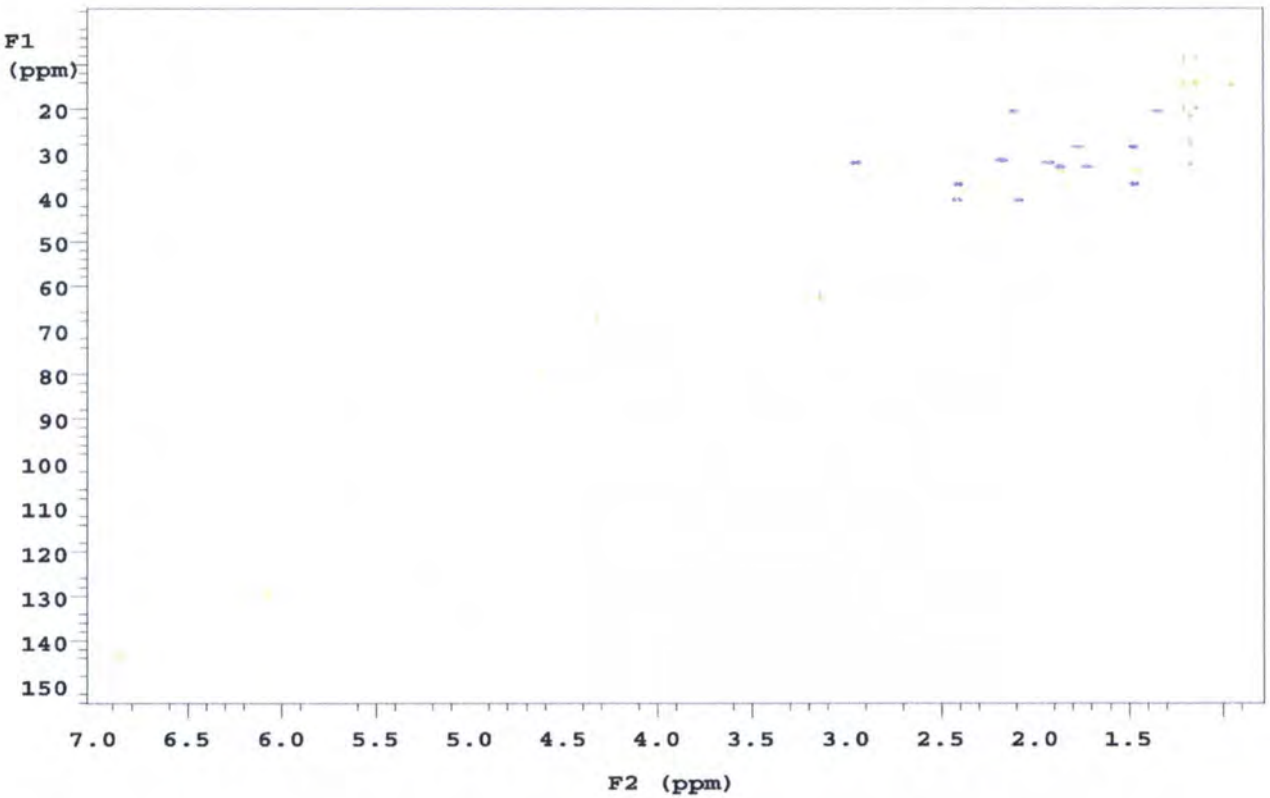
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #2, Operator: hammond
File: Ghsqcad_01
VNMRS-400 "ulnmr-ds"

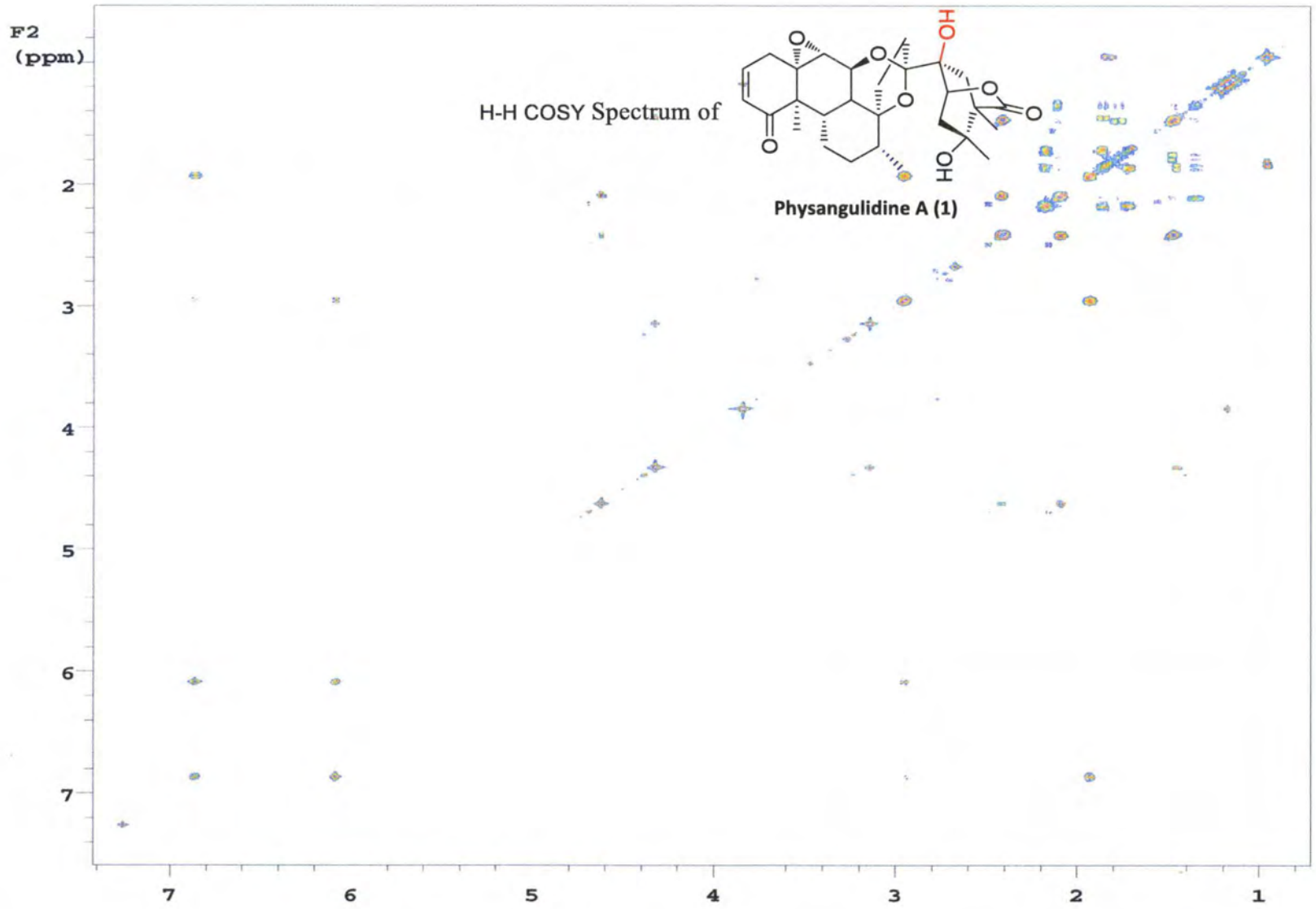
Relax. delay 1.000 sec
Mixing 0.500 sec
Acq. time 0.230 sec
Width 5605.4 Hz
2D Width 29917.7 Hz
2 repetitions
2 x 256 increments
OBSERVE H1, 699.8134488 MHz
DECOUPLE C13, 175.9814294 MHz
Power 43 dB
on during acquisition
off during delay
W40_HCN_CP modulated
DATA PROCESSING
Gauss apodization 0.106 sec
F1 DATA PROCESSING
Gauss apodization 0.008 sec
FT size 4096 x 2048
Total time 22 min, 6 sec

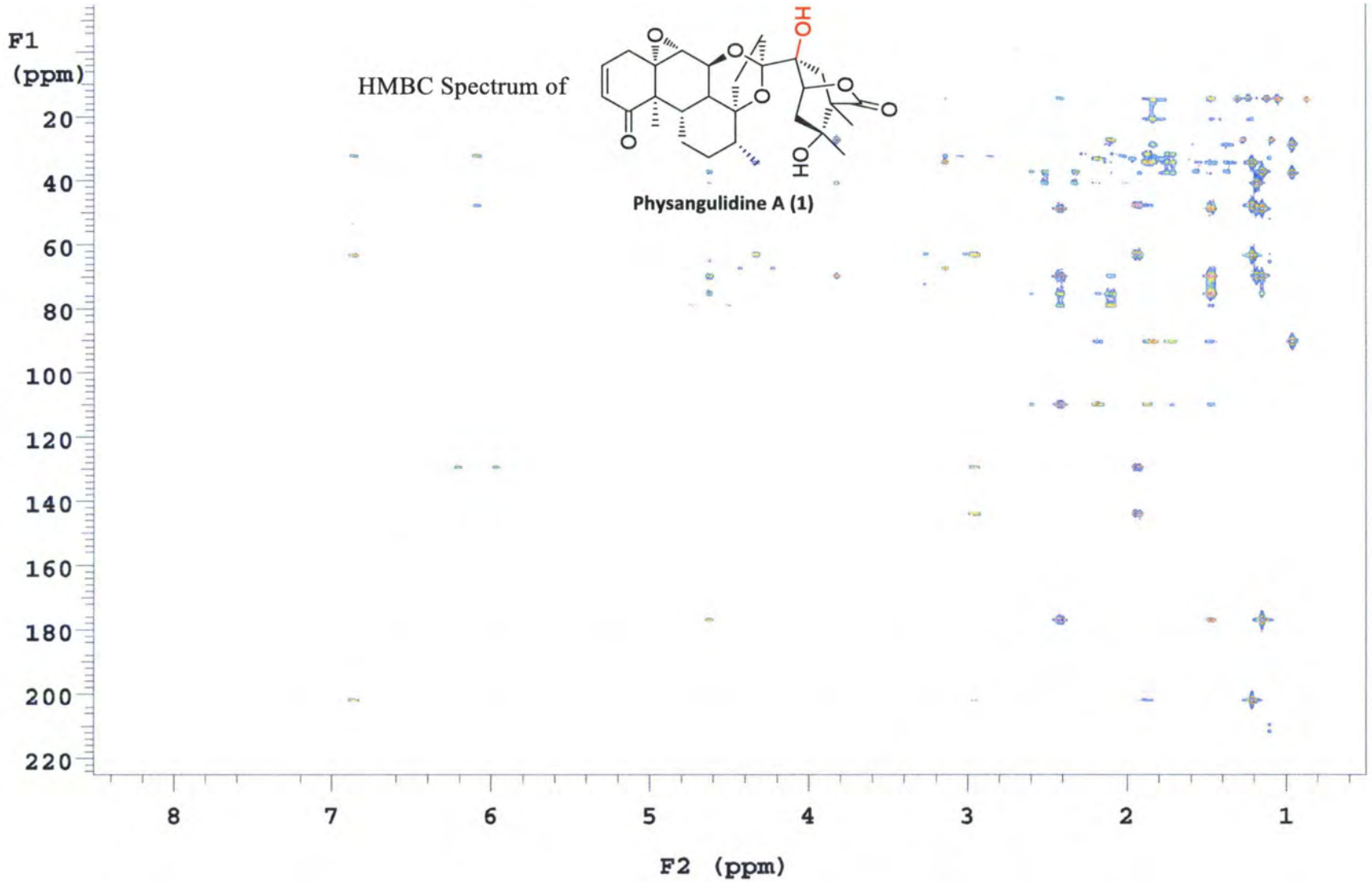
HSQC Spectrum of

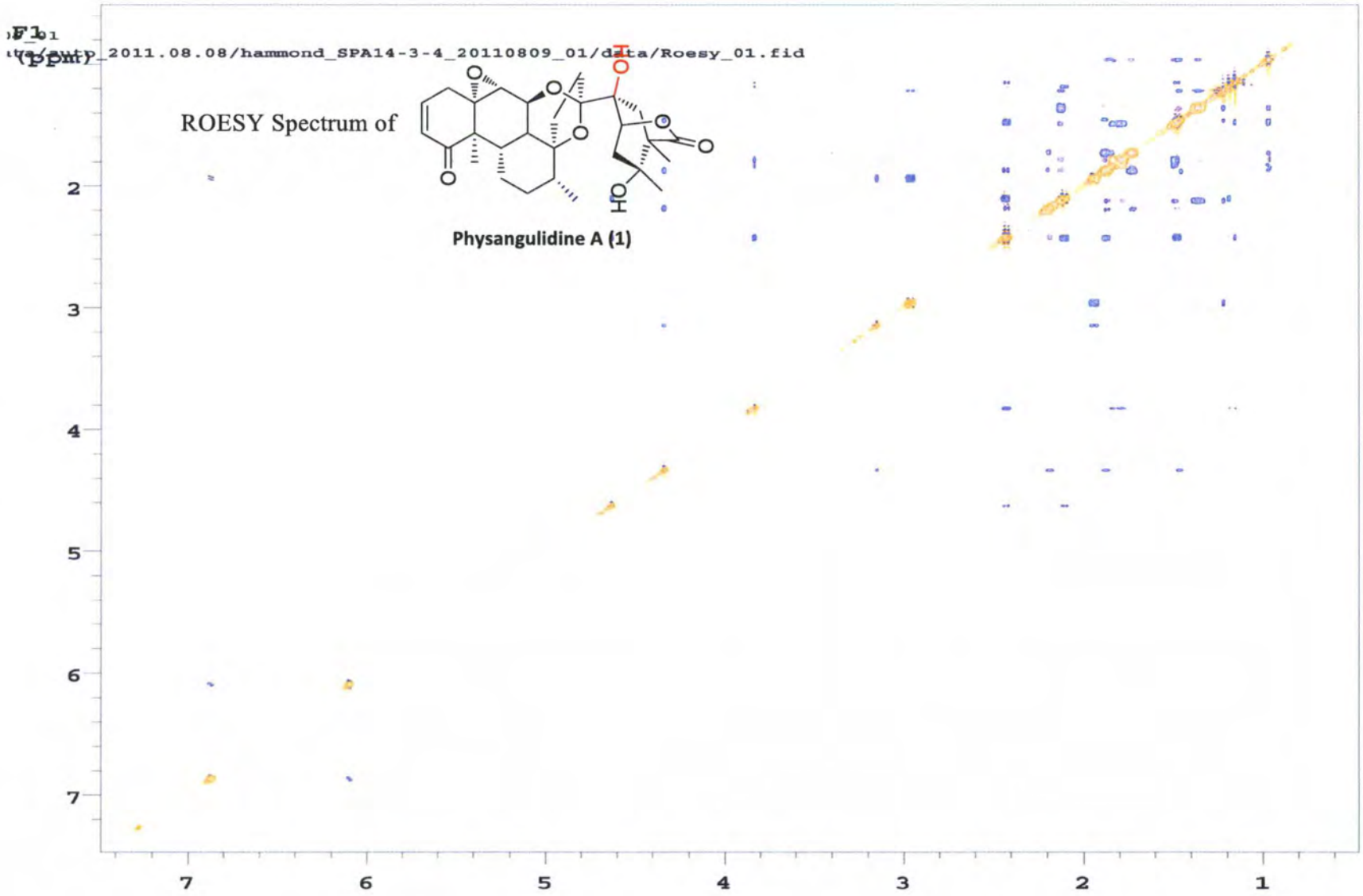


Physangulidine A (1)




H-H COSY Spectrum of
Physangulidine A (1)
F2
(ppm)
2
3
4
5
6
7
7
6
5
4
3
2
1


HMBC Spectrum of
Physangulidine A (1)
F1
(ppm)
20
40
60
80
100
120
140
160
180
200
220
8
7
6
5
4
3
2
1
F2 (ppm)


F1
(ppm)
/data/nutp_2011.08.08/hammond_SPA14-3-4_20110809_01/data/Roesy_01.fid
ROESY Spectrum of
Physangulidine A (1)
1
2
3
4
5
6
7

SPA14-3-2
Zhuang Jin
1.2 mg in cdcl3

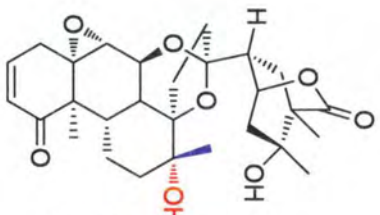
Sample: SPA14-3-2
Sample ID: hammond_SPA14-3-2_20110613_01
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-2_20110613_01/data/Proton_01.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #3, Operator: hammond
File: Proton_01
VNMRS-400 "ulnmr-ds"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 11261.3 Hz
8 repetitions
OBSERVE H1, 699.8134495 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



Physangulidine B (2)

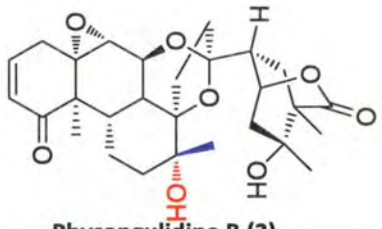
SPA14-3-2
Zhuang Jin
1.2 mg in cdcl3

Sample: SPA14-3-2
Sample ID: hammond_SPA14-3-2_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-2_20110613_02/data/Carbon_01.fid

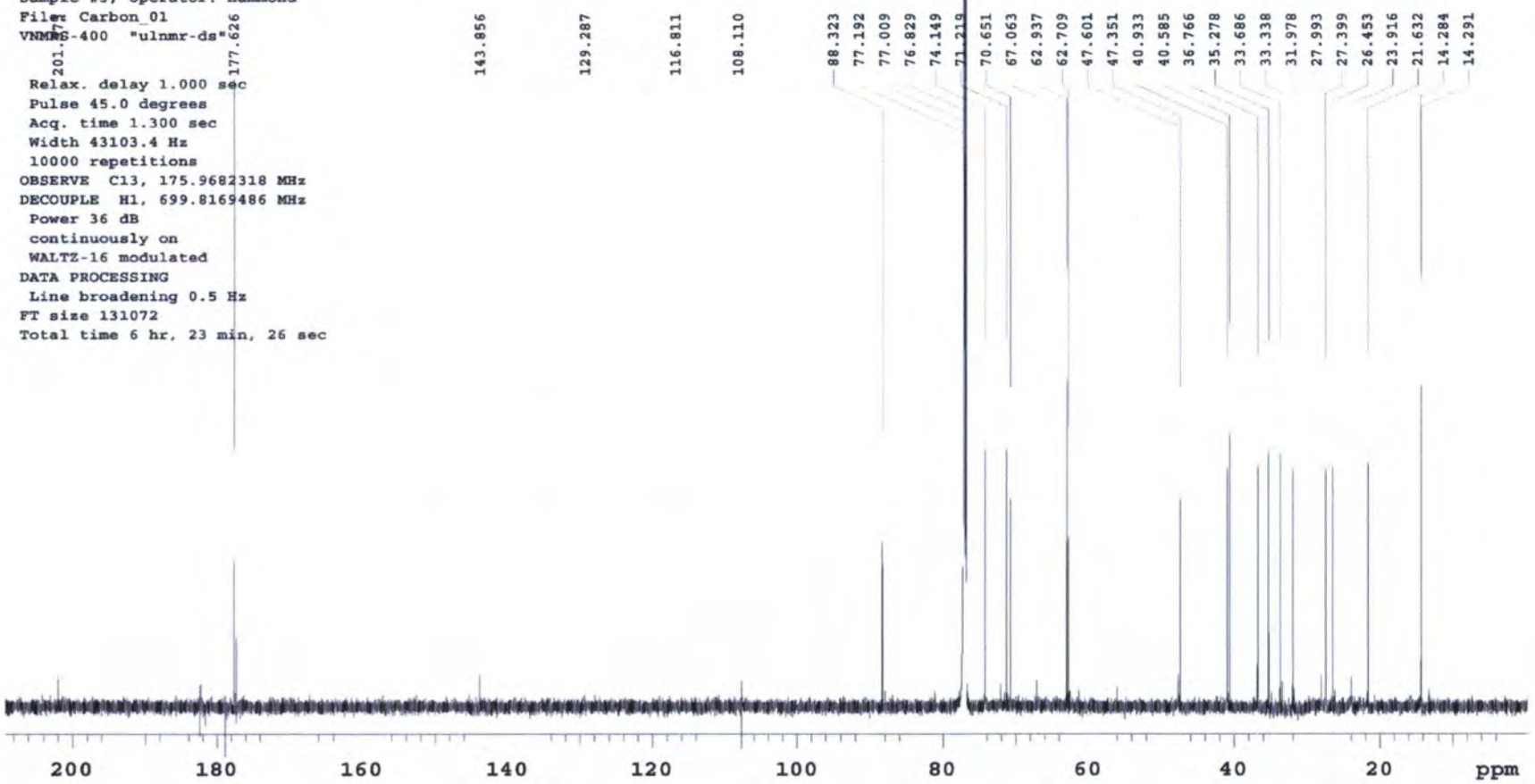
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #3, Operator: hammond
File: Carbon_01
VNMRS-400 "ulnmr-ds"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 43103.4 Hz
10000 repetitions
OBSERVE C13, 175.9682318 MHz
DECOUPLE H1, 699.8169486 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 23 min, 26 sec

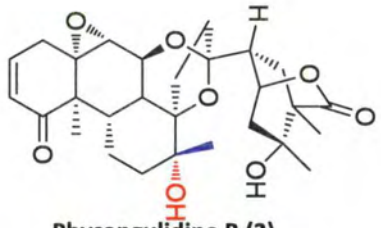
^{13}C NMR Spectrum of



Physangulidine B (2)

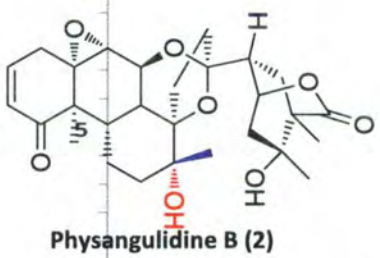


HSQC Spectrum of



Physangulidine B (2)

H-H COSY Spectrum of

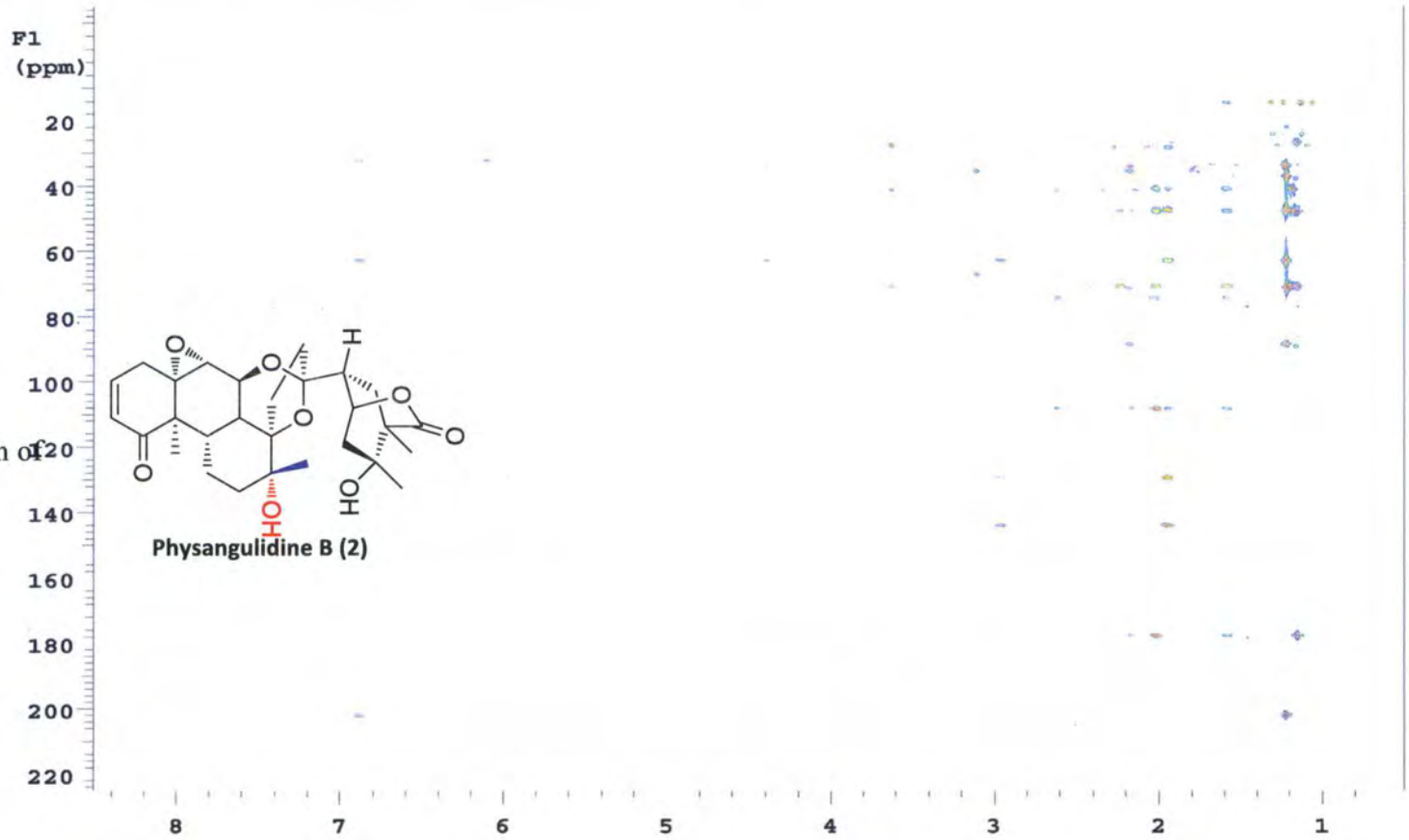


Physangulidine B (2)

SPA14-3-2 (Zhuang Jin)
< 3mg in cdcl3

Sample: SPA14-3-2
Sample ID: hammond_SPA14-3-2_20110808_01
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.08.08/hammond_SPA14-3-2_20110808_01/data/Ghmbc_01.fid

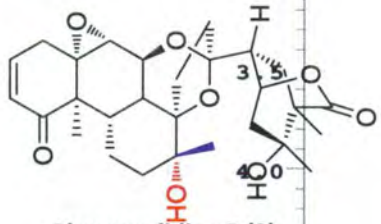
Pulse Sequence: gHMBC



Physangulidine B (2)

HMBC Spectrum of 1

ROESY Spectrum of



Physangulidine B (2)

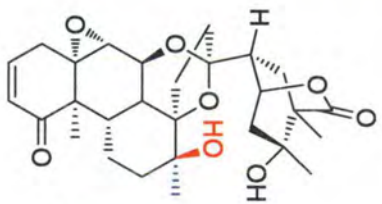
SPA14-3-3
Zhuang Jin
4.1 mg in cdcl3

Sample: SPA14-3-3
Sample ID: hammond_SPA14-3-3_20110613_01
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-3_20110613_01/data/Proton_01.fid

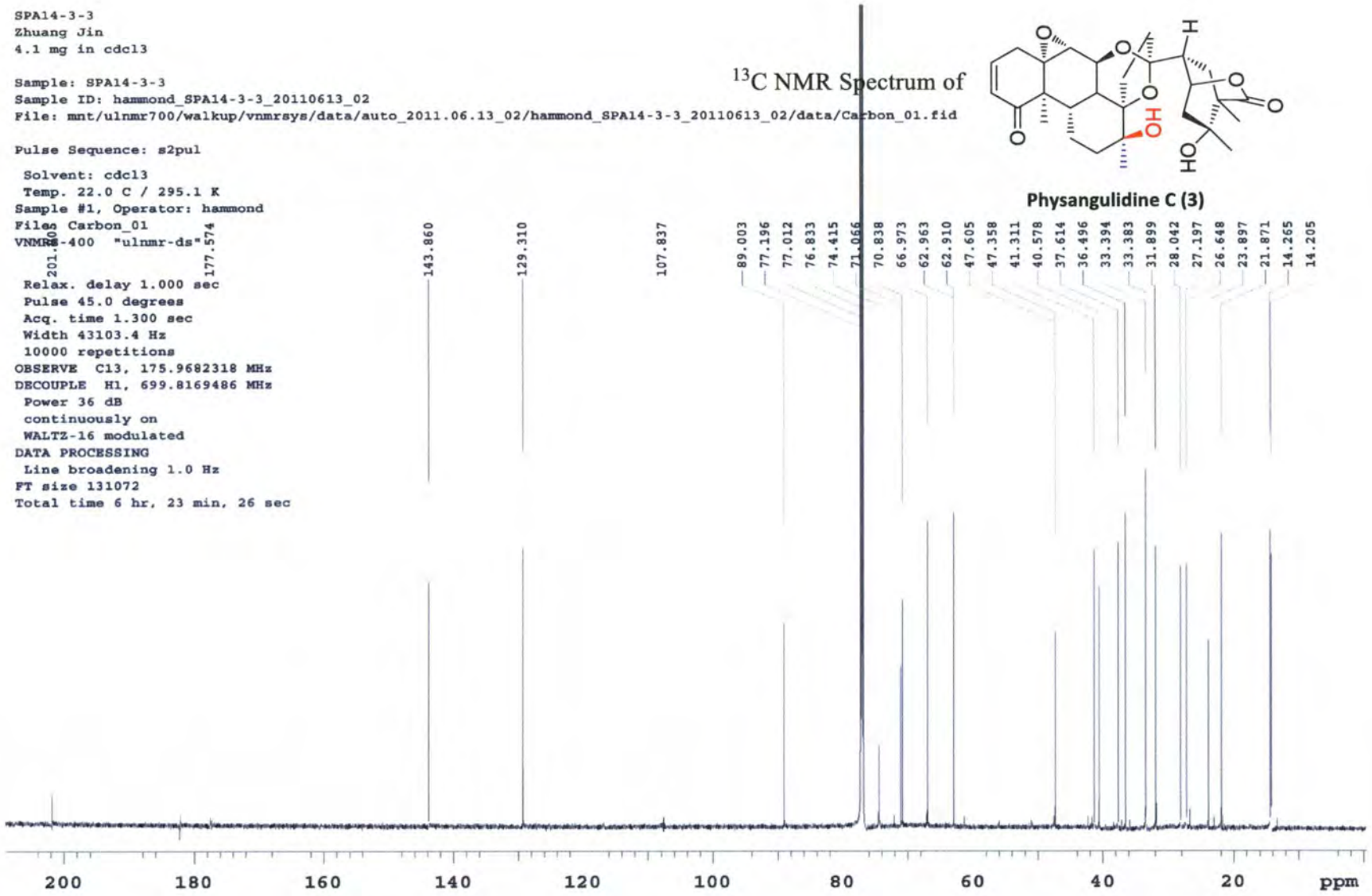
Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 22.0 C / 295.1 K
Sample #1, Operator: hammond
File: Proton_01
VNMRS-400 "ulnmr-ds"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 2.049 sec
 Width 11261.3 Hz
 8 repetitions
OBSERVE H1, 699.8134935 MHz
DATA PROCESSING
 Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 30 sec

^{1}H NMR Spectrum of



Physangulidine C (3)


SPA14-3-3
Zhuang Jin
4.1 mg in cdcl3
Sample: SPA14-3-3
Sample ID: hammond_SPA14-3-3_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-3_20110613_02/data/Carbon_01.fid
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #1, Operator: hammond
File: Carbon_01
VNMRS-400 "ulnmr-ds"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 43103.4 Hz
10000 repetitions
OBSERVE C13, 175.9682318 MHz
DECOUPLE H1, 699.8169486 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 6 hr, 23 min, 26 sec
13C NMR Spectrum of
Physangulidine C (3)
201.400
177.574
143.860
129.310
107.837
89.003
77.196
77.012
76.833
74.415
71.066
70.838
66.973
62.963
62.910
47.605
47.358
41.311
40.578
37.614
36.496
33.394
33.383
31.899
28.042
27.197
26.648
23.897
21.871
14.265
14.205
200
180
160
140
120
100
80
60
40
20
ppm

SPA14-3-3
Zhuang Jin
4.1 mg in cdcl3

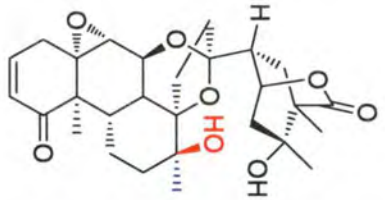
Sample: SPA14-3-3
Sample ID: hammond_SPA14-3-3_20110613_02
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.06.13_02/hammond_SPA14-3-3_20110613_02/data/Ghsqcad_01.fid

Pulse Sequence: gHSQCAD

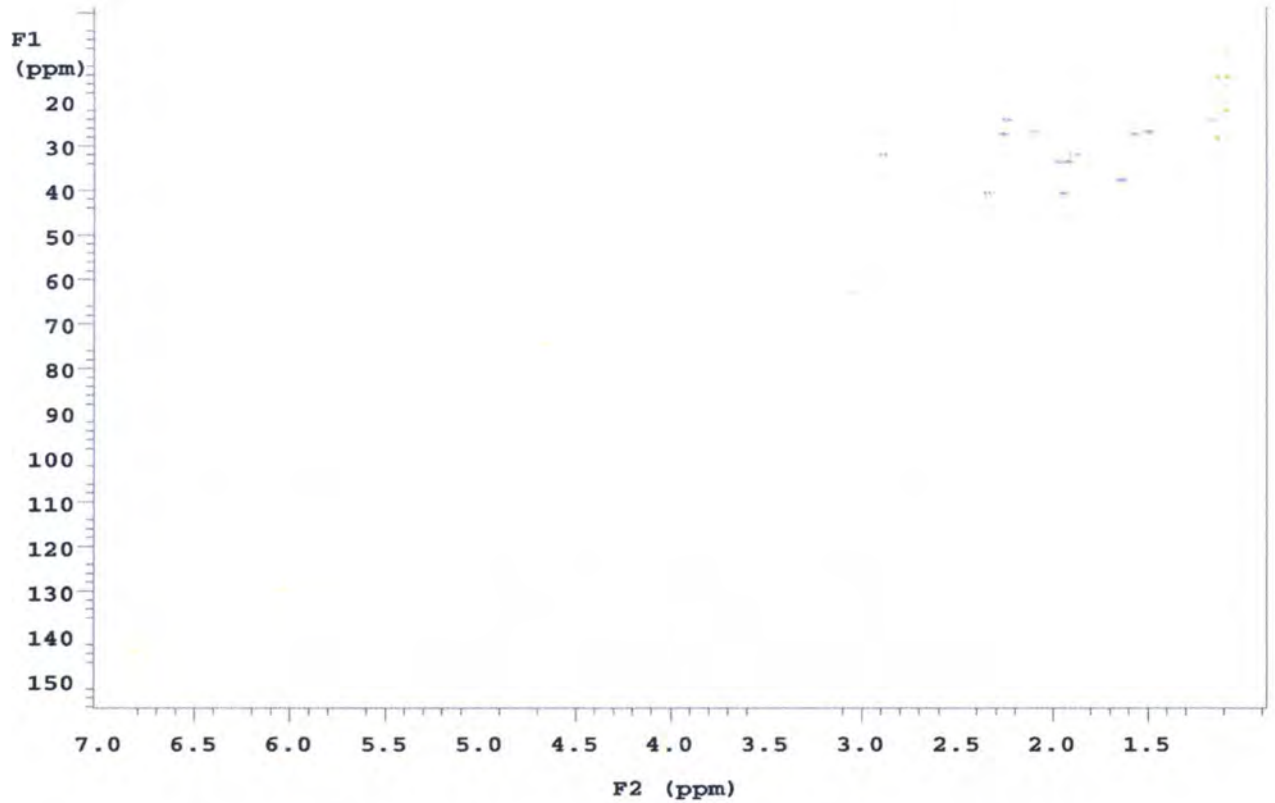
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #1, Operator: hammond
File: Ghsqcad_01
VNMRS-400 "ulnmr-ds"

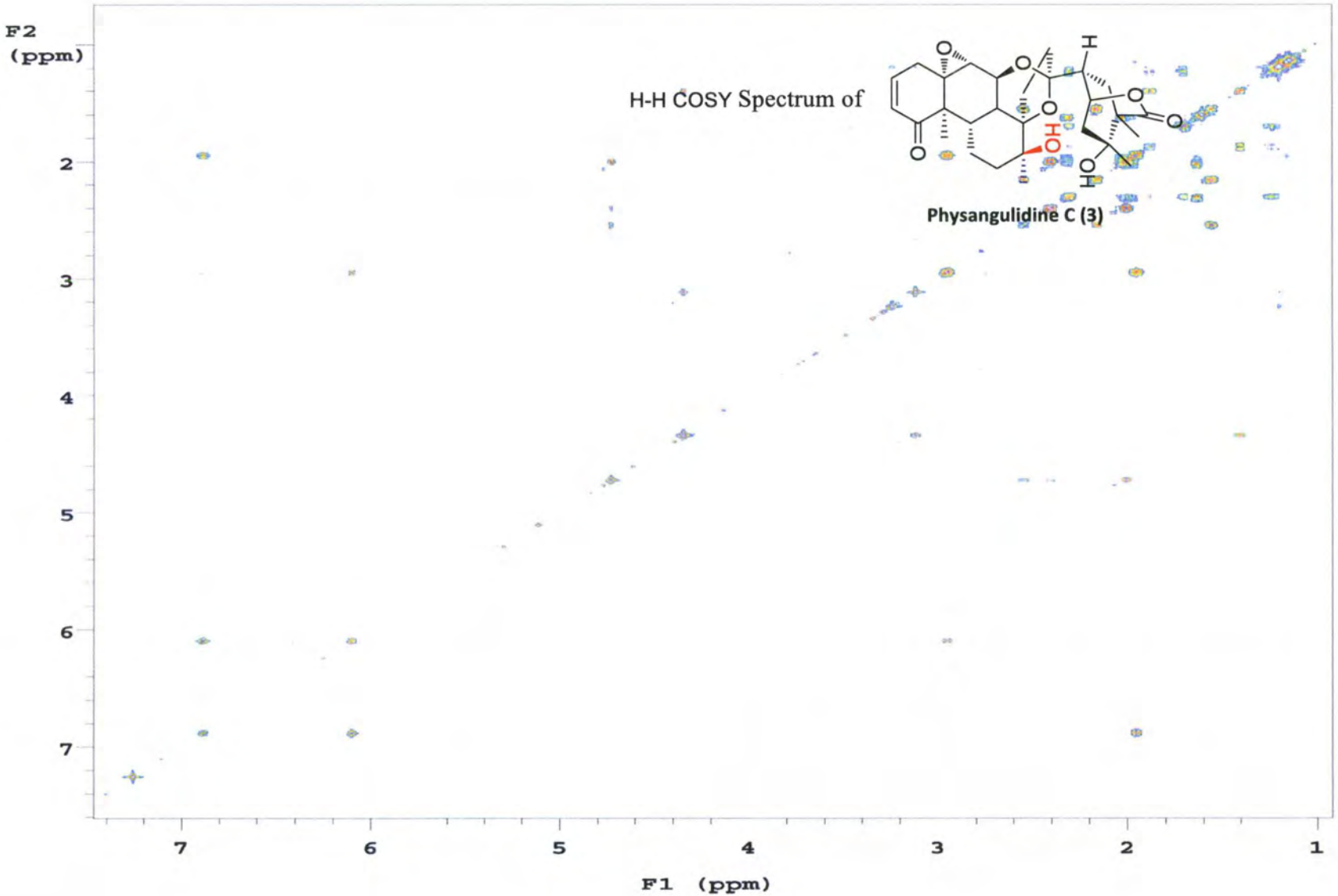
Relax. delay 1.000 sec
Mixing 0.500 sec
Acq. time 0.230 sec
Width 5605.4 Hz
2D Width 29917.7 Hz
2 repetitions
2 x 256 increments
OBSERVE H1, 699.8134922 MHz
DECOUPLE C13, 175.9814294 MHz
Power 43 dB
on during acquisition
off during delay
W40_HCN_CP modulated
DATA PROCESSING
Gauss apodization 0.106 sec
F1 DATA PROCESSING
Gauss apodization 0.008 sec
FT size 4096 x 2048
Total time 22 min, 6 sec

HSQC Spectrum of



Physangulidine C (3)



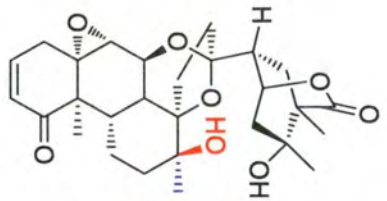

H-H COSY Spectrum of
Physangulidine C (3)
F2 (ppm)
F1 (ppm)
1
2
3
4
5
6
7

SPA14-3-3 (Zhuang Jin)
~ 6m in cdcl3

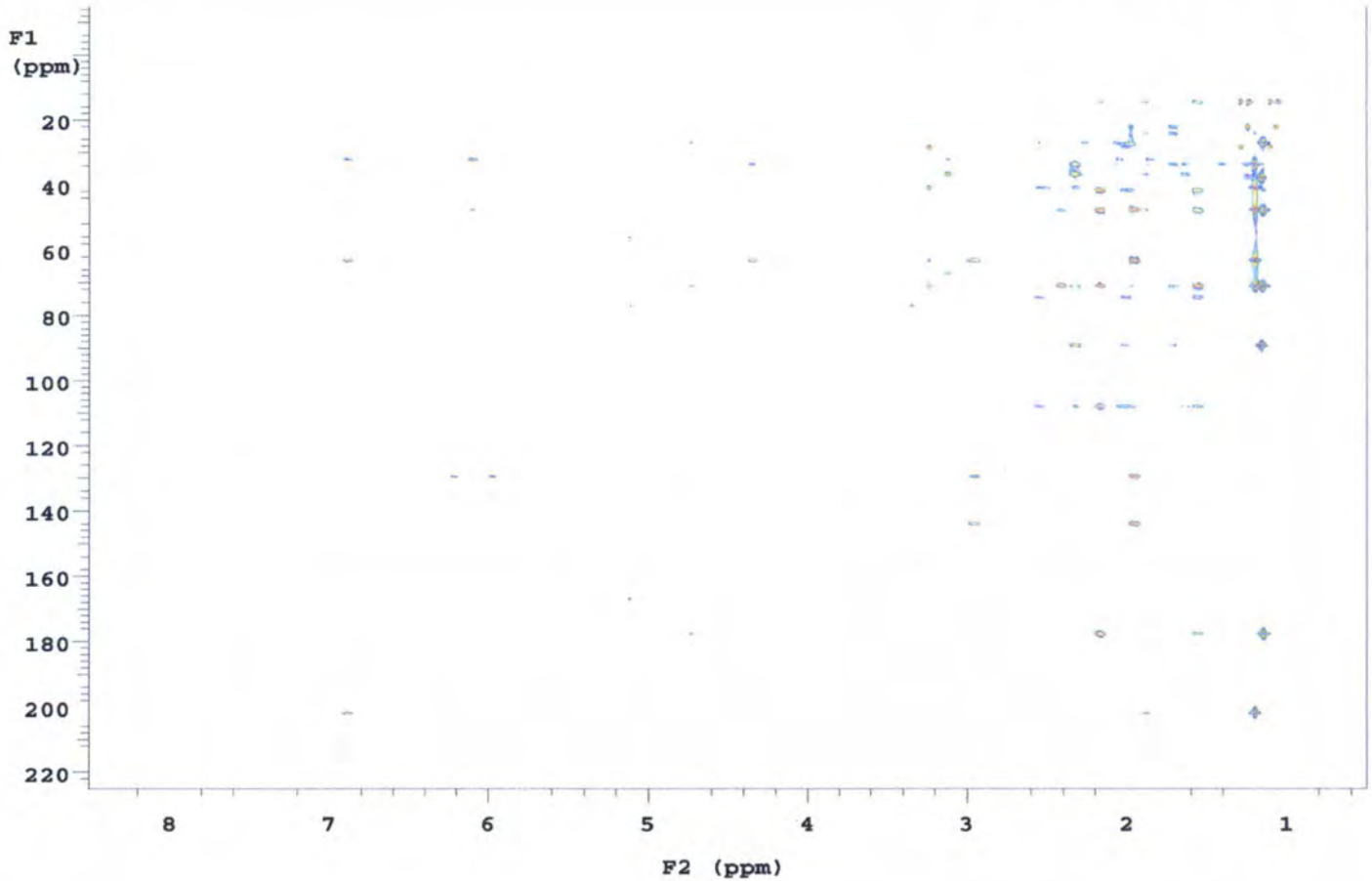
Sample: SPA14-3-3
Sample ID: hammond_SPA14-3-3_20110808_01
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.08.08/hammond_SPA14-3-3_20110808_01/data/Ghmbc_01.fid

Pulse Sequence: gHMBC

HMBC Spectrum of



Physangulidine C (3)



SPA14-3-3 (Zhuang Jin)
6 mg in cdcl3

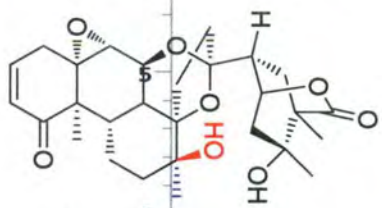
Sample: SPA14-3-3
Sample ID: hammond_SPA14-3-3_20110809_01
File: mnt/ulnmr700/walkup/vnmrsys/data/auto_2011.08.08/hammond_SPA14-3-3_20110809_01/data/Roesy_01.fid

Pulse Sequence: ROESY

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #6, Operator: hammond
File: Roesy_01
VNMRS-400 "ulnmr-ds"

Relax. delay 1.000 sec
Mixing 0.400 sec
Acq. time 0.183 sec
Width 5605.4 Hz
2D Width 5605.4 Hz
16 repetitions
2 x 256 increments
OBSERVE H1, 699.8134459 MHz
DATA PROCESSING
Gauss apodization 0.084 sec
F1 DATA PROCESSING
Gauss apodization 0.084 sec
FT size 4096 x 4096
Total time 3 hr, 40 min, 37 sec

ROESY Spectrum of



Physangulidine C (3)

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Education:

- 1996 – 2000 BS, Inner Mongolia University GPA:3.30
- 2001 – 2004 MS, Inner Mongolia University GPA: 3.70
- 2007 –present University of Louisville, graduate student GPA: 3.69

Professional experience:

- 2004 – 2007: Lecturer, Inner Mongolia Agricultural University.
- 2007-2012: Graduate research assistant, Graduate teaching assistant of general chemistry (Chem 103 and 201), organic chemistry (Chem 341 and 342) and organic chemistry lab (Chem 343 and 344), University of Louisville.

Honors and awards:

- **Awards Received in the United States:**
- 2010 IMD3 Student Travel Award, University of Louisville
- 2010 David Carew Student Travel Award, from The American Society of Pharmacognosy

- 2008 Graduate Students Lab Safety Awards, University of Louisville
- **Awards Received in China:**
- 2004 Excellent Master Thesis, Inner Mongolia University
- 2002 Guanghua Fellowship, Inner Mongolia University
- 1999 Excellent Students Awards, Inner Mongolia University
- 1998 Guanghua Fellowship, Inner Mongolia University
- 1997 Excellent Students Awards, Inner Mongolia University

Manuscript in Preparation or Submitted

(2) "Replacement of BF_4^- by PF_6^-, Makes Selectfluor Greener" (in preparation).

(1) "Stereoselective Synthesisof Fluoroalkyl (*E*)-α,β-Unsaturated Ketones Using a Combination of Gold and Selectfluor" (submitted).

Publications:

(7) "Physangulidines A, B and C, Three New Antiproliferative Withanolides from *Physalis angulata* L." **Z. Jin**, M. S. Mashuta, N. J. Stolowich, A. J. Vaisberg, N. Stivers, P. J. Bates, W. H. Lewis, G. B.Hammond. *Org. Lett.* **2012**, *14*, 1230-1233.

(6) "Gold-Catalyzed Intramolecular Oxygen-Transfer Reaction of 2-Alkynyl-1,5-Diketones or 2- Alkynyl-5-ketoesters. Scope, Expansion and Mechanistic Investigation on A Novel [4+2] Cycloaddition" L.-P. Liu, D. Molhotra, **Z. Jin**, R. S. Paton, K. N. Houk, and G. B. Hammond. *Chem. Eur. J.* **2011**, *17*, 10690-10699.

(5) "Cytotoxic and Antiinfective Phenolic Compounds Isolated from *Mikania decora* (Compositae) and *Cremastosperma microcarpum* (Annonaceae)" J. C. Aponte, **Z. Jin**, A. J. Vaisberg, D. Castillo, E. Málaga, W. H. Lewis, C. Sarasara, M. Sauvain, R. H. Gilman, and G. B. Hammond. *Planta Medica*. **2011**, *77*, 1597-1599.

(4) "Copper Mediated Oxidation of Amides into Imides by Selectfluor" **Z. Jin**, B. Xu, and G. B. Hammond *Tetrahedron Lett*. **2011**, *52*, 1956-1959.

(3) "Synthetic Evolutions in the Nucleophilic Addition to Alkynes" B. Xu, W. Wang, L. Liu, J. Han, **Z. Jin** and G. B. Hammond *J. Organomet. Chem.* **2011,** *696*, 269-276.

(2) "Green Synthesis of Vicinal Dithioethers and Alkenyl Thioethers from the Reaction of Alkynes and Thiols in Water" **Z. Jin**, B. Xu and G. B. Hammond, *Eur. J. Org. Chem.* **2010**,168-173.

(1) "Antihyperlipidemic Compounds from the Fruit of *Piper Longum L.*" **Z. Jin**, G. Borjihan, R. Zhao, Z. Sun, G. B. Hammond and T. Uryu, *Phytother. Res.* **2009**, *23*, 1194-1196.

Patents:

(2) "Physangulidines A, B and C: Three New Antiproliferative Withanolides from *Physalis angulata* L." patent application is currently underway.

(1) "Preparation of piperamides and their uses in medicines and health food for reducing blood fat" G. Borjihan, S. Na, **Z. Jin**, R. Zhao, J. Gao, and L. Song, (**2005**), CN 1634029 A 20050706.

Presentations in National and Regional Meetings:

(5) "Isolation of bioactive metabolites from targeted peruvian amazonian plants" G. B. Hammond, P. J. Bates, **Z. Jin**, J. C. Aponte, N. S. Stivers, and A. J. Vaisberg. Poster presented at 13th Annual Symposium of the Institute for Molecular Diversity & Drug Design (IMD3), University of Louisville. Mar 8, 2011.

(4) "Isolation of bioactive metabolites from targeted peruvian amazonian plants" G. B. Hammond, P. J. Bates, **Z. Jin**, J. C. Aponte, N. S. Stivers, and A. J. Vaisberg. Poster presented at the Conference on Innovative Minds in Prostate Cancer Today (IMPaCT), Hilton Orlando, Florida, March 9-12, 2011. **Poster**: P4-5.

(3) "Antileishmanial, trypanocidal, antituberculosis and cytotoxic activities of targeted plant species from the Peruvian rain forest" **Z. Jin**, J. C. Aponte, M. Sauvain, R. H. Gilman, and G. B. Hammond. Oral presentation at the 240th ACS National Meeting, Boston, MA, August 22 – 26, 2010. **Abstract**: AGFD 202.

(2) "Hydroxyl group directed copper/Selectfluor-activated C-H bond amination" **Z. Jin**, J. C. Aponte, B. Xu, and G. B. Hammond. Oral presentation at the 240th ACS National Meeting, Boston, MA, August 22 – 26, 2010. **Abstract**: ORGN 1.

(1) "Antileishmanial, trypanocidal, antituberculosis and cytotoxic activities of targeted plant species from the Peruvian rain forest" **Z. Jin**, J. C Aponte, A. J. Vaisberg, R. H. Gilman, and G. B. Hammond. Oral presentation at the 2010 Joint Annual Meeting of the American Society of Pharmacognosy and the Phytochemical Society of North America, St. Petersburg Beach, Florida, July 10-14, 2010. **Abstract**: O-33.

Membership in Professional Organizations:

1. American Chemical Society, Student Member since 2010.