SYNTHESIS OF A SMALL LIBRARY OF NONNATURAL ANALOGUES BASED ON SCHULZEINE STRUCTURE AND SCREENING FOR ALPHA-GLUCOSIDASE INHIBITORS

By

Nuanpan Piboonsrinakra

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree

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การสังเคราะห์ไลบรารีขนาดเล็กตามแบบโครงสร้างของสารผลิตภัณฑ์ธรรมชาติชุดเซอีน และการทดสอบฤทธิ์ยับยั้งเอนไซม์อัลฟากลูโคซิเดส

โดย

นางสาวนวลพรรณ ไพบูลย์ศรีนครา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

สาขาวิชาเคมีอินทรีย์

ภาควิชาเคมี

บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร

ปีการศึกษา 2551

The Graduate School, Silpakorn University has approved and accredited the Thesis title of "Synthesis of a Small Library of Nonnatural Analogues Based on Schulzeine Structure and Screening for Alpha-Glucosidase Inhibitors" submitted by Miss. Nuanpan Piboonsrinakra as a partial fulfillment of the requirements for the degree of Master of Science in Organic Chemistry.

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(Associate Professor Surachai Nimgirawath, Ph.D.)

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(Punlop Kuntiyong, Ph.D.)

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Schulzeines, a group of marine natural products isolated from Japanese sponge, *Penares schulzei*, inhibit the enzyme alpha-glucosidase with IC_{50} values in the nanomalar range. Thus it has the potential for development into diabetes medication. The structure of schulzeines, markedly different from commercial α-glucosidase inhibiting type II diabetes drugs, consists of tricyclic benzoquinolizidinone core and C28 fatty acid side chain with three sterocenters bearing polar sulfate groups. In this thesis, we describe the syntheses of a small library of designed molecules based on the structure of schulzeines. The key reaction in the syntheses of the heterocyclic core was cyclization *of N*-acyliminium ion with three different π-nucleophiles which were benzene ring, indole and terminal alkene. These nucleophiles gave three different heterocyclic core for the non-natural analogs of schulzeines, namely, benzoquinolizidinone, indoloquinolizidinone, and quinolizidinone systems, respectively. For the fatty acid side chain of the analogs, a 21-carbon fatty acid was synthesized. This less complex side chain still retains the polar functionality in the form of 1, 2-diol. The non-natural analogues of schulzeines were used for Structure- Activity Relationship (SAR) studies for better understanding of the mode of reactivity of schulzeines, as well as, screening for new active compounds.

Department of Chemistry Graduate School, Silpakorn University Academic Year 2008
Student's signature .....
Thesis Advisor's signature .....

9028 สาขาวิชาเคมีอินทรีย์
คำสำคัญ : สารอนุพันธ์ของชุลเซอีน/ การปิดวงของ *N*-acyliminium ion/ สารออกแบบ

นวลพรรณ ไพบูลย์ศรีนครา : การสังเคราะห์ไลบรารีขนาดเล็กตามแบบโครงสร้างของสารผลิตภัณฑ์ธรรมชาติชุลเซอีนและการทดสอบฤทธิ์ยับยั้งเอนไซม์อัลฟากลูโคซิเดส. อาจารย์ที่ปรึกษาวิทยานิพนธ์ : อ. ดร. พัลลภ คันธิยงค์.114 หน้า.

สารผลิตภัณฑ์ธรรมชาติชุลเซอีนสกัดได้จากฟองน้ำทะเล *Penares schulzei* มีฤทธิ์ยับยั้งการทำงานของเอนไซม์อัลฟากลูโคซิเดส โดยมีค่า IC_{50} อยู่ในช่วง nanomolar จึงอาจนำไปพัฒนาเป็นยารักษาโรคเบาหวานได้ โครงสร้างของชุลเซอีนนั้นแตกต่างกับยารักษาโรคเบาหวานประเภท 2 ที่ยับยั้งการทำงานของเอนไซม์อัลฟากลูโคซิเดส โครงสร้างของชุลเซอีนประกอบด้วยโครงหลักสามวงที่เป็น benzoquinolizidinone และส่วนที่เป็นสายโซ่กรดไขมัน 28 คาร์บอน ที่มีหมู่ฟังก์ชันเกลือซัลเฟตแทนที่อยู่ ในวิทยานิพนธ์ นี้เราจะบรรยายการสังเคราะห์ไลบรารีขนาดเล็กตามแบบโครงสร้างของ ชุลเซอีนโดยใช้ปฏิกิริยาการปิดวงของ *N*-acyliminium ion กับ π-นิวคลีโอไฟล์สามชนิดได้แก่ ระบบวงเบนซีน วงอินโดล และ อัลคีน ทำให้ได้ heterocyclic core ของอนุพันธ์ของชุลเซอีนที่เป็นระบบต่างๆกัน ได้แก่ benzoquinolizidinone indoloquinolizidinone และ quinolizidinone ในส่วนของสายโซ่กรดไขมันของโมเลกุล เราได้สังเคราะห์สายโซ่กรดไขมันที่มีโครงสร้างซับซ้อนน้อยกว่าในสารผลิตภัณฑ์ธรรมชาติชุลเซอีน แต่ยังมีหมู่ฟังก์ชันที่มีขั้วในรูปของไดออล สารที่ออกแบบ และสังเคราะห์ขึ้นนี้ถูกนำไปทดสอบฤทธิ์การยับยั้งเอนไซม์อัลฟากลูโคซิเดสเพื่อให้เข้าใจในกลไกการทำงานของสารผลิตภัณฑ์ธรรมชาติชุลเซอีนและค้นหาสารที่อาจมีฤทธิ์ดีกว่าหรือเทียบเท่ากับชุลเซอีนแต่สังเคราะห์ได้ง่ายกว่า

ภาควิชาเคมี บัณฑิตวิทยาลัย มหาวิทยาลัยศิลปากร ปีการศึกษา 2551

ลายมือชื่อนักศึกษา.....

ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์ .....

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Finally, none of this would have been possible without love and encouragement of my family and friends.

CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

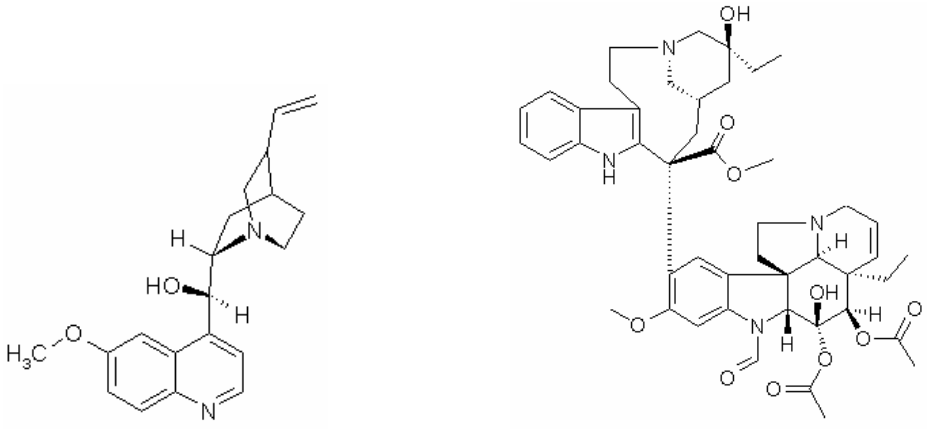
ABBREVIATIONS

AD-mix	asymmetric dihydroxylation catalyst mixture
DCC	dicyclohexyl carbodiimide
DIBALH	diisobutyl aluminum hydride
DMAP	dimethylamino pyridine
Dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
IC_{50}	inhibitory concentration at 50%
IR	infrared
LAH	lithium aluminium hydride
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
rt	room temperature
SAR	structure-activity-relationship
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	ultraviolet

CHAPTER 1

INTRODUCTION

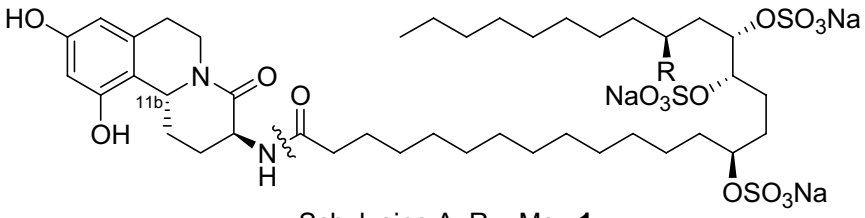
Plants and animals have been used for medicinal purposes since time immemorial. The early medicines were easily prepared without knowledge of active ingredients from the natural sources. In the 19th century, when the methods of organic chemistry became a major tool for medicinal research and development, scientists began extracting and purifying the active ingredients from living organisms. The structures of these compounds were elucidated and activity screening was carried out. This process collected information of natural products, some of which were developed into medicine. For example cinchona bark is the source of malaria-fighting quinine[1], and vincristine[2], used to treat certain types of cancers, comes from periwinkle.



Quinine Vincristine

Figure 1.1 Structure of Quinine and Vincristine

In 2004 Fusetani isolated schulzeines from Japanese sponge, *Penares schulzei*[3]. This group of natural products exhibit potent inhibitory effect against α-glucosidase with the IC_{50} in the nanomolar ranges. α-Glucosidases are enzymes that play a major role in cells. Thus these natural products have great potential for development into new leads in drug discovery for diseases such as diabetes, cancers, and viral infections.



Schulzeine A, R = Me **1**
Schulzeine B, 11b(S), R =H **2**
Schulzeine C, R = H **3**

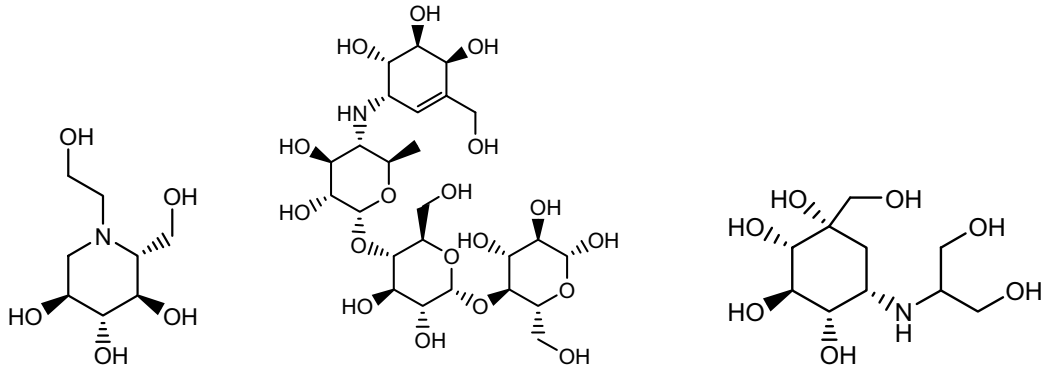
Figure 1.2 Structure of Schulzeines

α-Glucosidases (EC 3.2.1.20, α-D-glucoside glucohydrolase) catalyze the final step in the digestive process of carbohydrates by facilitating the liberation of α-D-glucose from the non-reducing end of oligo- and poly-saccharides. Several glucosidases are specific for the cleavage of glycosidic bonds depending on the number, position, or configuration of the hydroxyl groups in the sugar molecule. These enzymes are widespread in mammals, plants, and microorganisms.

α-Glucosidase has drawn a special interest of the pharmaceutical research community because it was shown in earlier studies that the inhibition of its catalytic activity resulted in the retardation of glucose absorption and the decrease in postprandial blood glucose level. Therefore, effective α-glucosidase inhibitors may serve as chemotherapeutic agents for clinical use in the treatment of diabetes and obesity. Due to the catalytic role in digesting carbohydrate substrates, α-glucosidase has also been well appreciated as a therapeutic target for the other carbohydrate mediated diseases including cancers and viral infections.

Commercially available α-glucosidase inhibitors such as Acrobose® , Voglibose and Miglitol® are saccharides that act as competitive inhibitors of enzymes needed to digest

carbohydrates specifically α-glucosidase enzymes in the brush border of the small intestine. The membrane-bound intestinal α-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. Structures of commercial drugs for type 2 diabetes are shown in Figure 1.3.



Miglitol Acarbose Voglibose

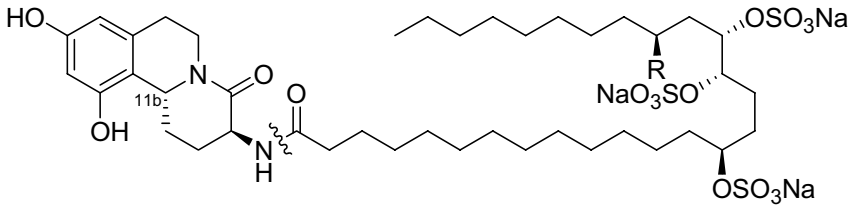
Figure 1.3 Structures of commercial α-glucosidase inhibiting drugs.

Diabetes results from insulin deficiency which may result from inadequate insulin production or resistance to its action. Insulin is a naturally occurring hormone secreted by the beta cells of the islands of Langerhans in the pancreas in response to increased levels of glucose in the blood. Insulin lowers blood glucose levels and promotes transport and entry of glucose into the muscle cells and other tissues. Insulin deficiency causes the amount of glucose in the blood to reach abnormally high level (hyperglycemia) and if this level exceeds the renal threshold, glucose passes into the urine. This in turn increases the amount of urine which has to be produced. At the same time the effective lack of glucose as an energy substrate at the cellular level means that the body has to use its stores of fat and if necessary, muscle tissue as an alternative energy source. The combination produces the classic symptoms of diabetes which are excessive urine production, thirst and unexplained weight loss. There are two major types of diabetes; type 1 and type 2 diabetes. In addition, diabetes in the pregnant women usually develops during the third

trimester of pregnancy. Type 1 diabetes is caused by gradual destruction of beta cells in pancreas leading to a deficiency of insulin. Patients become dependent on administered insulin for survival. Type 2 diabetes is the most common form of diabetes. It is resulted from insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion. The pancreas usually produces insulin, but the body does not use the insulin effectively.

Oral anti-hyperglycemic drugs are available to help patients with type 2 diabetes control their blood sugar levels. Besides α-glucosidase inhibitors, oral type 2 diabetes drugs include biguanides (metformin), sulfonylureas (glyburide, glipizide, glimepiride, repaglinide), DPP-4 inhibitors (sitagliptin), metformin , meglitinides (repaglinide, nateglinide) and, thiazolidinediones (pioglitazone and rosiglitazone). Moreover insulin replacement may be required when natural insulin reserves are depleted.

Schulzeines



Schulzeine A, R = Me **1**
Schulzeine B, 11b(S), R =H **2**
Schulzeine C, R = H **3**

Figure 1.4 *Penares schulzei*

The structure of schulzeines, marine natural products isolated from Japanese sponge, *Penares schulzei*, shown in Figure 1.4, can be divided into two major subunits, namely, tetrahydroisoquinoline tricyclic core and C28 fatty acid side chain. The structure differs greatly from known commercial α-glucosidase inhibiting drugs, which are structural mimics of carbohydrates. It is likely that the mode of activity of schulzeines is different from those of commercial drugs. More often than not, the structures of the natural products as obtained from their natural sources do not provide the best possible results when the natural products are used as medicines. Many such natural products exhibit serious undesired side effects which prevent them from being used for their intended purpose. Derivatives or analogues of these natural products are synthesized and tested for optimized efficiency and minimized undesired side effects. It could also help medicinal chemists to gain an insight understanding as to how these molecules function at the molecular level (mode of action). This process is called Structure-Activity Relationship studies (SAR). An early example of such studies led to the emergence of Aspirin®, one of the most successful medications in history. Crude extracts of myrtle bark, and willow tree had been used for the relief of pain and fever by Egyptian and Greek physicians in ancient time as well as in other parts of the world. These extracts contained salicin, the active ingredient, which was identified in 1828. Salicin was later hydrolyzed to give saligenin and oxidation of this compound gave salicylic acid. The latter was used for pain relieving and anti-inflammation in the last quarter of the 19th century. However it has several undesired side effects. Beside its foul taste, it also caused irritation to the mucosal membranes of the digestive tract leading to vomiting and ulceration. Early medicinal chemists made a number of derivatives of salicylic acid in hope to eliminate undesired side effect. Eventually, in 1897 acetylsalicylic acid (Aspirin®) was synthesized by Felix Hoffman. This medicine has become a standard item in every household medicine cabinet and researchers have reported an increasing number of conditions treated by this wonder drug.

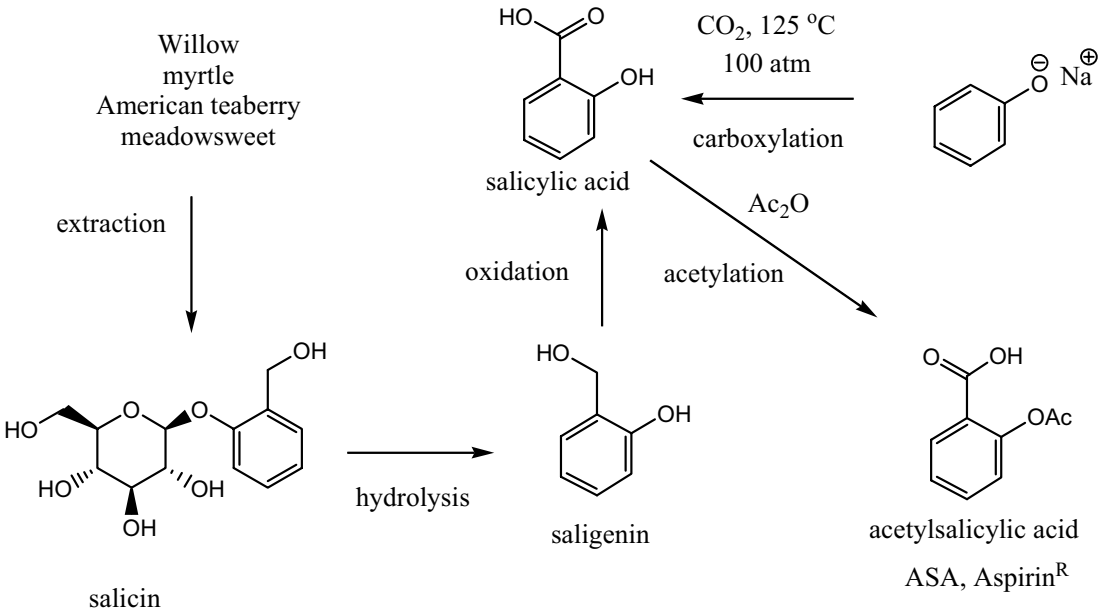
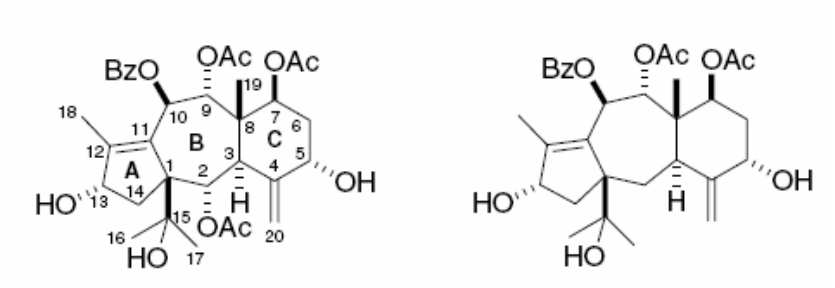


Figure 1.5 Structure-Activity Relationship studies of aspirin

A more recent example of SAR studies was reported by Zhao *et al*[4]. in 2008. They synthesized a number of derivatives of the natural products taxchinnin (A), a cytotoxic natural product against human lung cancer (A549) cell line, and brevifoliol (B). They found that several of these derivatives exhibit significantly more potent cytotoxicity than the parent compounds.

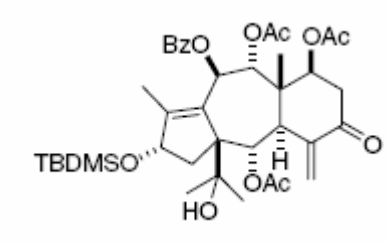


A

IC_{50} 60.50 IM

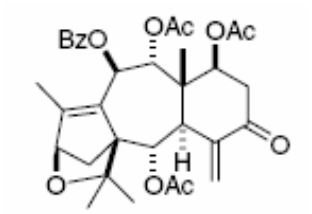
B

Not active



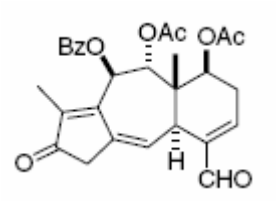
K

IC_{50} 0.48 IM



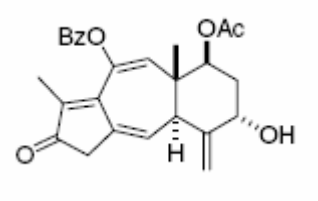
O

IC_{50} 0.75 IM



W

IC_{50} 11.27 IM



U

IC_{50} 80.72 IM

Figure 1.6 Derivatives of the natural products taxchinnin and brevifoliol

These results indicated that exocyclic unsaturated ketone at ring C is the key structural element for the activity, and all derivatives containing this unit presented potent activity, while the α,β-unsaturated ketone positioned at ring A has no effect for the activity. Moreover, introduction of more double bonds in the molecule gave no remarkable advantage for the activity, and certain derivatives possessing the unsaturated aldehyde group at ring C showed weak activity. In this thesis, we describe total synthesis of non-natural analogues of schulzeines with structural variations both in the tricyclic core and fatty acid side chain. *N*-acyliminium ion cyclization is the key reaction for these cyclic core syntheses. Cross olefin metathesis, and Sharpless asymmetric

dihydroxylation are key reactions for fatty acid side chain synthesis. The structures of these analogues are shown in Figure 1.7. These synthetic analogues will be used in the structure-activity relationship studies for better understanding of the mode of reactivity of this group of marine natural products.

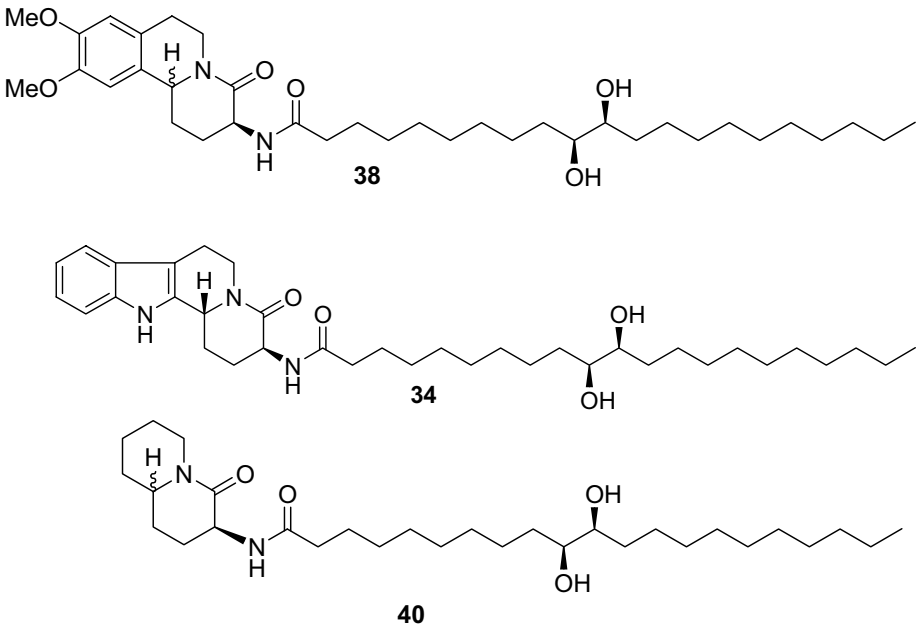


Figure 1.7 Non-natural analogues of schulzeine

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2. Boger, D. L; Jolla, L. *Org. Lett.* **2005**, *7*, 4539**.**

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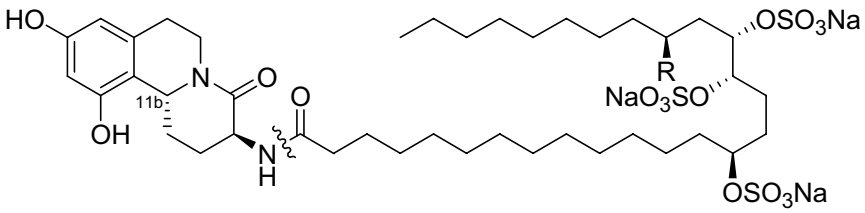
4. Yu, Z.; Na, G.; Li-Guang, L.; Yu-Wen, C.; Li-Yan, P.; Qin-Shi, Z. *Bioorganic & Medicinal Chemistry*, **2008***, 16,* 4860.

CHAPTER 2

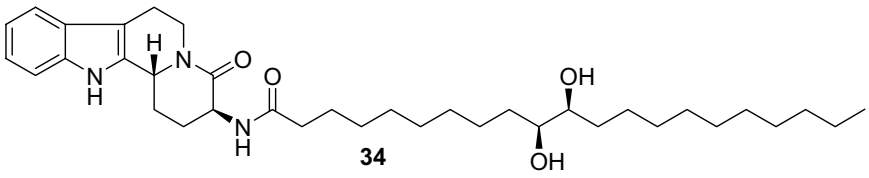
TOTAL SYNTHESIS OF SCHULZEINE ANALOGUES

ANALOGUE DESIGN

a)



Schulzeine A, R = Me **1**
Schulzeine B, 11b(S), R =H **2**
Schulzeine C, R = H **3**



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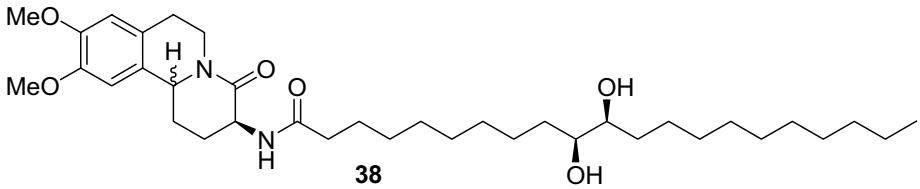
b)



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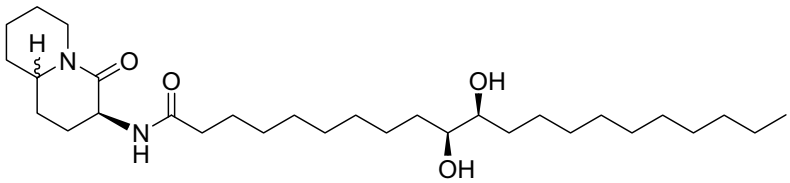
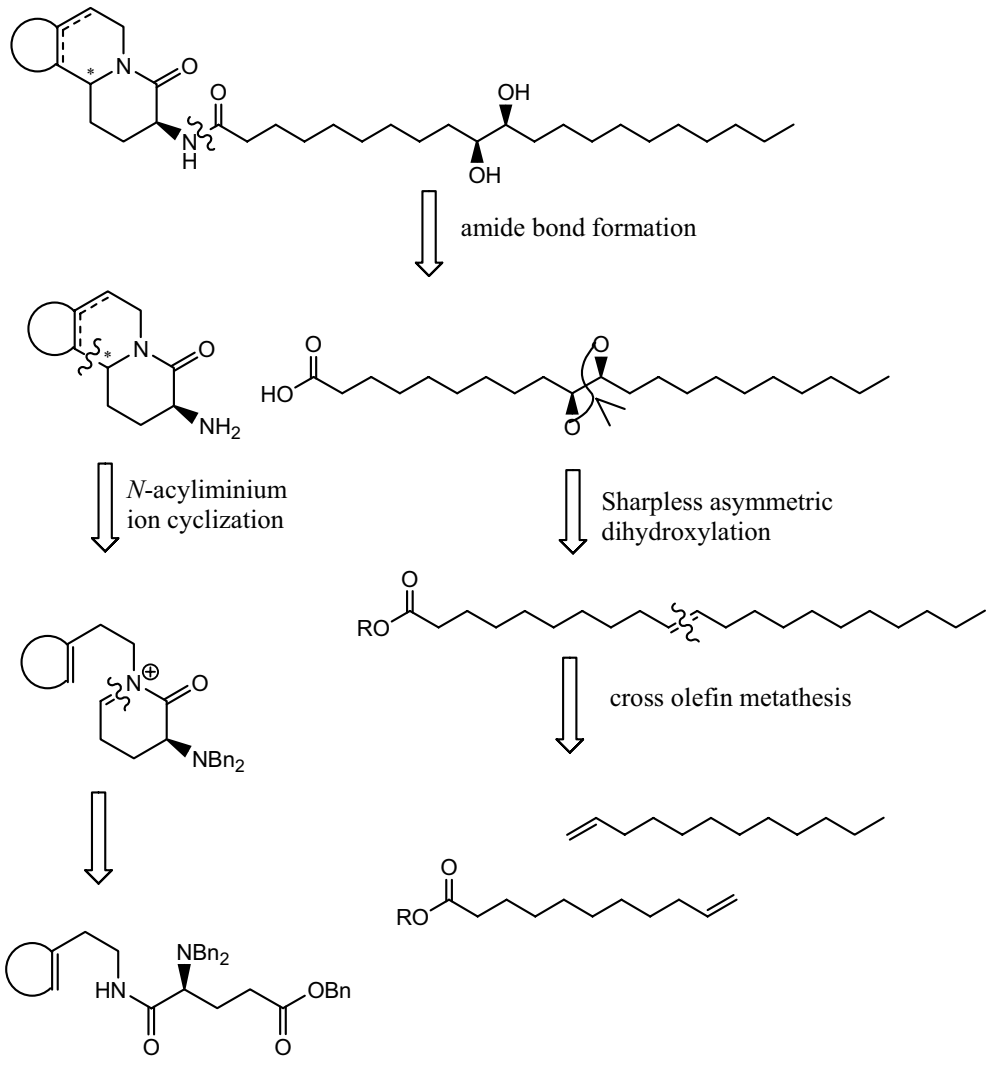


40

Figure 2.1 Analogue design

In this chapter we describe total synthesis of non-natural analogues of schulzeines (Figure 2.1a) with structural variations both in the tricyclic core and fatty acid side chain. We designed three hetereocyclic systems as structural variations for the tetrahydroisoquinoline part of the natural products. These are (1) indoloquinolizidinone, (2) 3,4-dimethoxybenzoquinolizidinone, and (3) quinolizidinone systems (Figure 2.1b). The shorter fatty acid side chain (21 carbons) still retains the polar functionality in the form of 1,2-diol. This can later be converted into sulfate salts if it is deemed necessary for anti-α-glucosidase activity.

Retrosynthetic Analysis

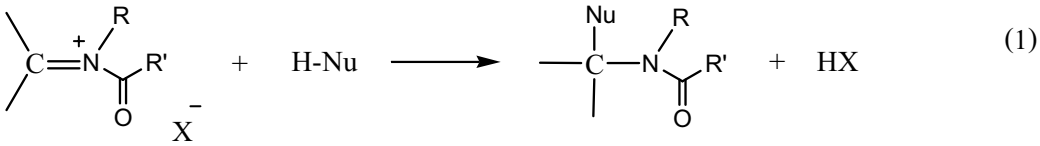


Scheme 2.1 Retrosynthetic Analysis

The retrosynthetic analysis for the target analogues is summarized in Schemes 2.2. The key step for construction of the heterocyclic core involves intramolecular cyclization of *N*-acyliminium ion, synthesized from the corresponding amine and L-glutamic acid derivative via hydroxylactam and amide. The new stereogenic center could theoretically be formed with some level of diastereoselectivity by the influence of the chiral center in the *N*-acyliminium ion. In the case of the side chain, Sharpless asymmetric dihydroxylation and cross olefin metathesis were used as the key reactions.

Cyclizations of *N*-Acyliminium Ions

Iminium ions are important, reactive species in organic synthesis for the construction of carbon-carbon and carbon-heteroatom bonds. Recently, there has been considerable interest in the development of cyclizations that proceed via *N*-acyliminium species, in contrast to cyclizations involving iminium cations, such as the Mannich reaction and the Pictet-Spengler reaction. Both reactions have been employed in organic chemistry for nearly 100 years. The *N*-acyl iminium carbon is more electron-deficient due to the electron attracting properties of the carbonyl group on nitrogen, which causes *N*-acyliminium ions to be more reactive as electrophile than simple *N*-akyliminium ions. This versatile electrophile is very useful in the α-amidoalkylation with various nucleophiles, as expressed in eq. 1[1-5]



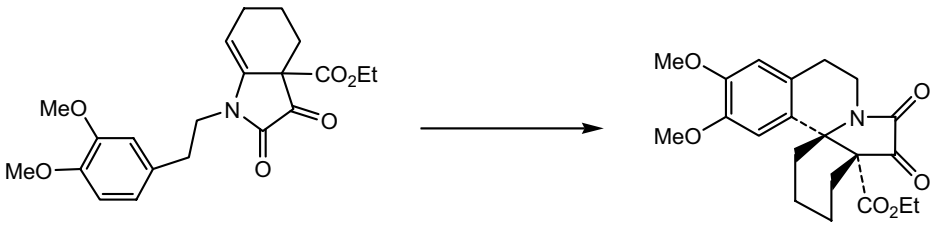
(1)

N-Acyliminium ions can be generated as discrete salts[5, 6-8], paired with non- nucleophilic anions, although this is a relatively rare undertaking restricted to physicochemical studies. In synthetic transformations, the reactive species are almost exclusively produced in situ during the course of the desired reaction by a variety of useful techniques, such as reaction of amide with aldehyde or ketone, addition of nucleophile to imide, and acylation of *N*-substituted imine.

Various nucleophiles could react with *N*-Acyliminium ions. However, in the synthesis of schulzeiene analogues, we employed intramolecular reaction of *N*-Acyliminium ion with π-electron-nucleophiles. Some examples of these reactions are discussed below.

1. Reactions of Benzenoid Nucleophiles

N-Acyliminium cyclizations have been widely applied to aromatic nucleophiles. Unactivated benzene rings, as well as benzene rings substituted with moderate deactivating groups (e.g., fluoro), can participate effectively.



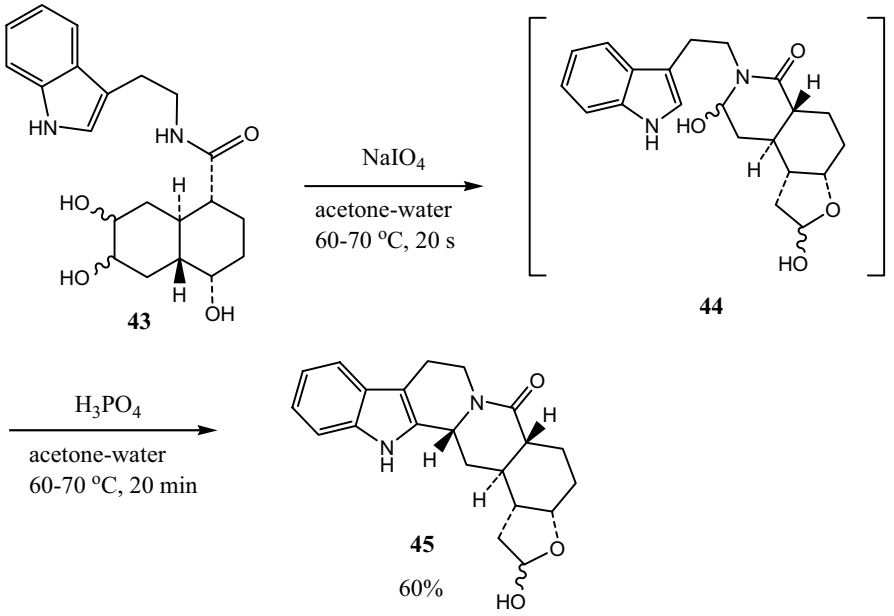
41 **42** (2)

Reagent	Temp. (^{o}C)	Time (h)
Polyphosphoric ester (PPE)	90	1.5
Boron trifluoride etherate	23	3
$AgClO_4$ / benzene	80	0.5

For example, in the synthesis of erythrinanes (eq.2)[9-11, 12], the conversion of enamide **41** to tetracyclic product **42** was quantitative in three different conditions; polyphosphoric ester (PPE) at 90 °C in 1.5 h, boron trifluoride etherate at 23 °C in 3 h, or $AgClO_4$ in benzene at 80 °C for 0.5 h. In these conditions, enamide **41** was converted to *N*-acyliminium ion which cyclized to give the desired product **42** with cis-fused perhydroindole configurations.

2. Reactions of Heterocyclic Nucleophiles

π-Electron rich heterocycles like furan, pyrrole, and indole are at the higher end of the reactivity spectrum, comparable to a phenyl bearing one or two methoxy substituents. The reactivities of π-electron-deficient heterocycles, such as pyridine, are significantly attenuated. There have been numerous examples of syntheses of natural products which featured *N*-Acyliminium ion cyclizations of heterocyclic and benzenoid nucleophiles. An early example of an unambiguous *N*-acyliminium ion cyclization of indole is exhibited in a total synthesis of yohimbine (eq. 3)[13-14]. Oxidative cleavage of diol **43** gave hydroxylactam **44**, which was converted to *N*-acyliminium ion by treatment with phosphoric acid. Polycyclic lactam **45** was obtained in 60% as a single diastereomer.

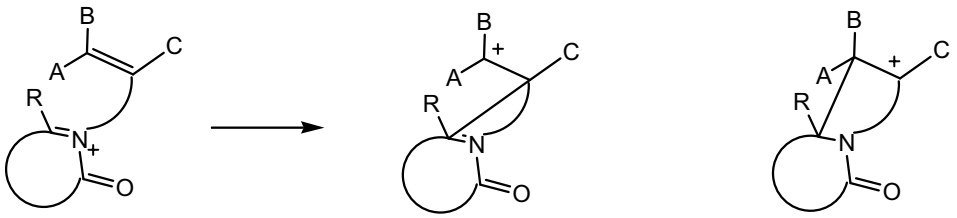


(3)

3. Reactions of Alkenes

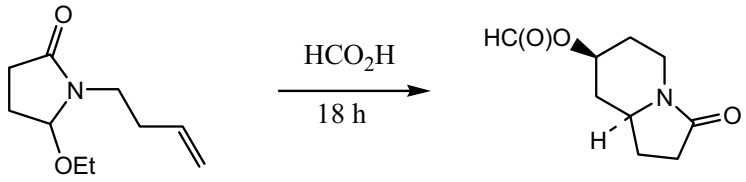
Cationic π-cyclizations involving alkene nucleophiles and *N*-acyliminium ions have broad utility in the synthesis of cyclic systems. Cyclization of a nitrogen-tethered, proximal

alkene can occur by two different modes of attack to furnish products with two different ring sizes, via exocyclic [n-exo-trig ring closure] or endocyclic [(n + 1)-endo-trig ring closure] carbocation intermediates (eq 4)[15]. Subsequently, these carbocations could undergo standard transformations, such as solvent capture, addition of nucleophiles, elimination, or rearrangement, to yield the final reaction products.



(4)

The cyclization of ethoxylactam **46** to bicyclic lactam **47** (eq 5)[16], a prototype reaction in this area, proceeds at room temperature in nearly quantitative yield with a high degree of stereochemical control (>90%).

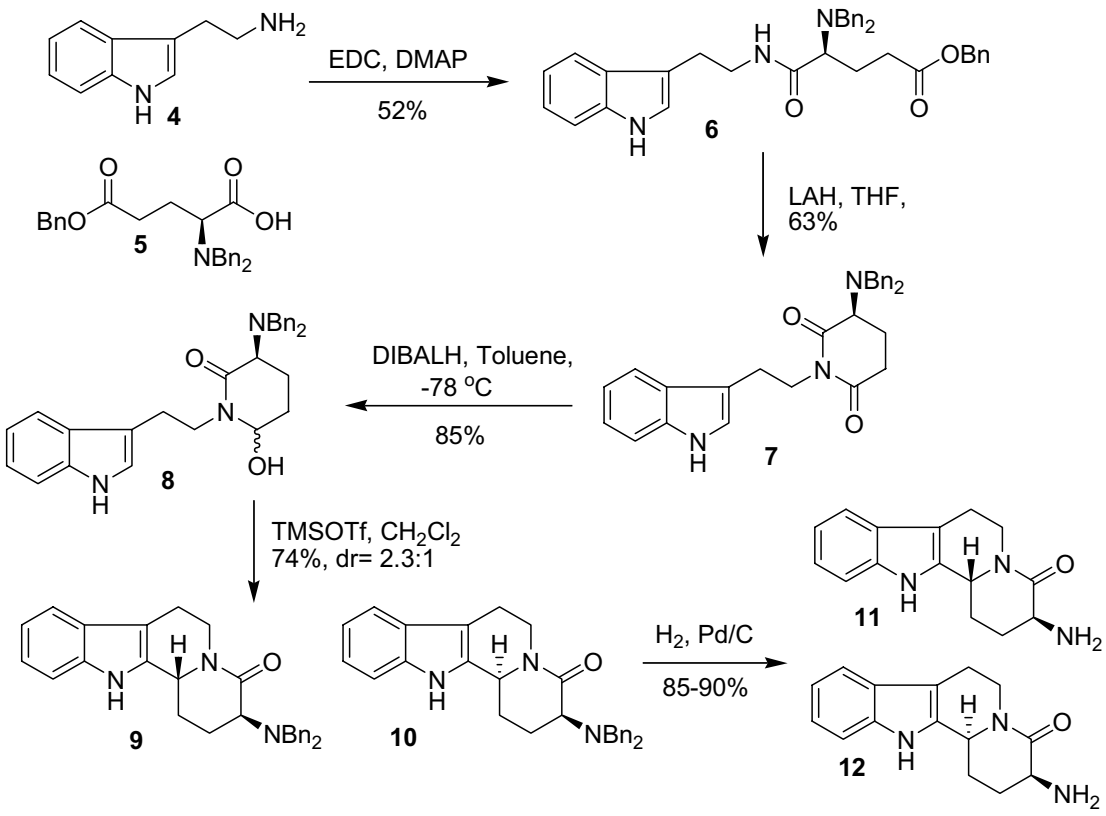


(5)

46 **47**

The *N*-acyliminium ion cyclization has proven to be a potential tool for the construction of complex polycyclic heterocycles. The utilization of chiral lactams in the *N*-acyliminium cyclization can result in a stereoselective synthesis of various alkaloids.

SYNTHESIS OF INDOLOQUINOLIZIDINONE SYSTEMS

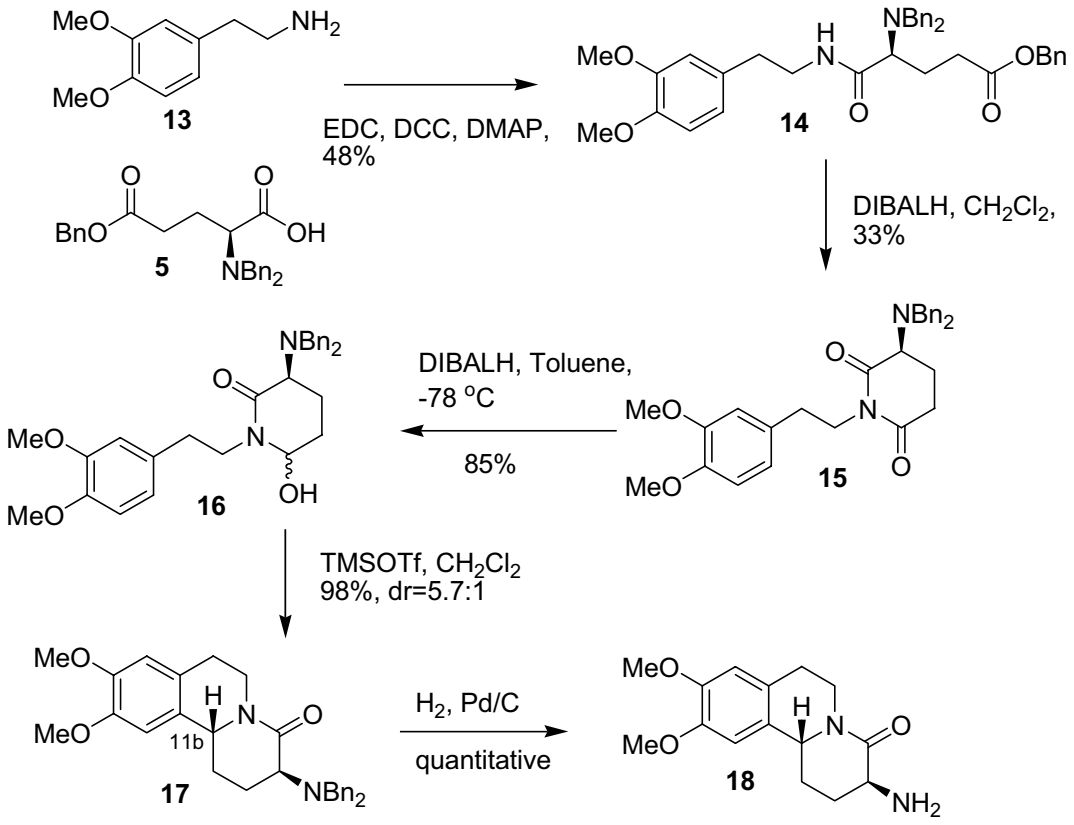


Scheme 2.2 Synthesis of indoloquinolizidinone systems

The synthesis of the indoloquinolizidinone systems began with amide formation of tryptamine **4** and benzylated glutamic acid **5** to give amide **6** in moderate yield. This amide was converted to imide **7** by treatment with LAH. DIBALH reduction of the imide carbonyl was completely regioselective at the less hindered carbonyl group when toluene was used as solvent and the temperature was controlled at -78 ^{o}C. This gave hydroxylactam **8** in good yield as a single product. Hydroxylactam **8** underwent *N*-acyliminium ion cyclization upon treatment with TMSOTf in dichloromethane. The products were obtained as a mixture of two diastereomers **9** and **10** at the newly generated stereocenter (*R* and *S* respectively). The mixture was readily separable by flash chromatography to give **9** as the major product with the diastereomeric ratio of 2.3:1. The separated diastereomers were converted to the free amines **11** and **12** by debenzylation

(scheme 2.2). The configuration of the newly generated stereocenter was deduced from NOESY experiments.

SYNTHESIS OF 3,4-DIMETHOXYBENZOQUINOLIZIDINONE SYSTEMS

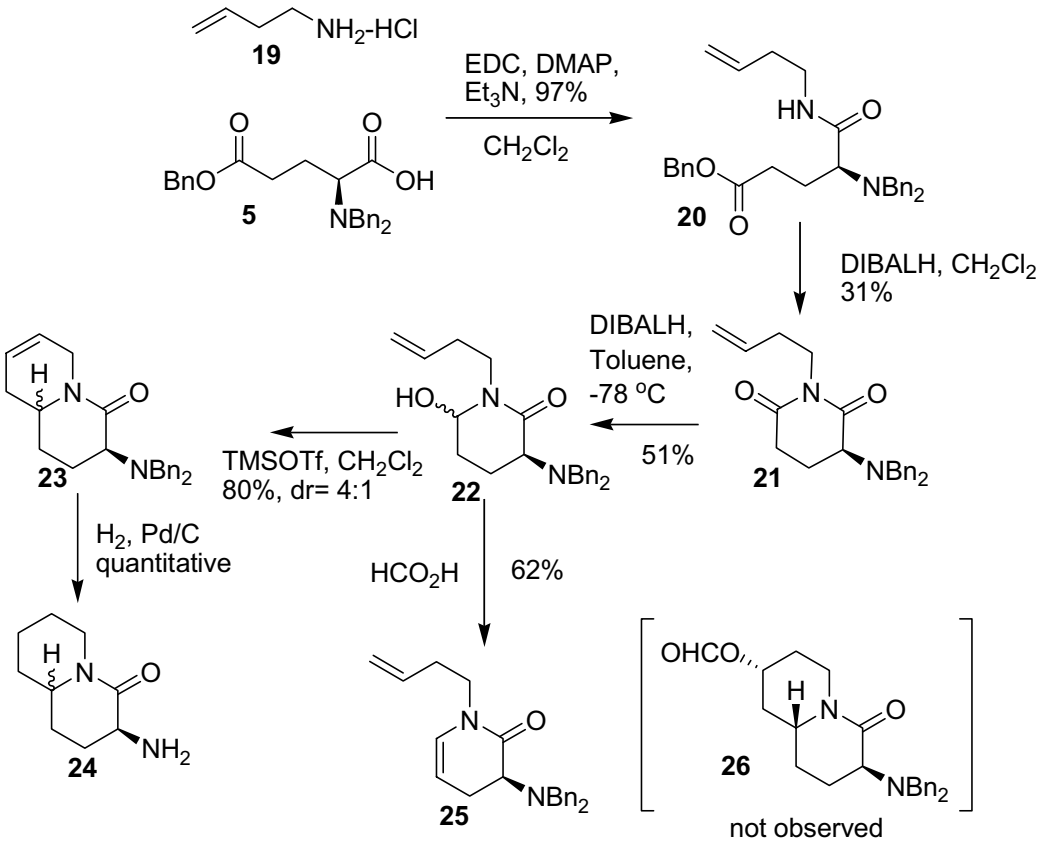


Scheme 2.3 Synthesis of 3,4-dimethoxybenzoquinolizidinone systems

The synthesis of the 3,4-dimethoxybenzoquinolizidinone systems employed the similar reaction sequence used in the synthesis of indoloquinolizidinone systems. The starting material in this case is (3,4-dimethoxyphenyl)2-ethylamine **13** which coupled with glutamic acid derivative **5** to give amide **14** in moderate yield. Amide **14** in turn was converted to imide **15** by treatment with DIBALH in CH_2Cl_2 and subsequent DIBALH reduction of the less hindered carbonyl gave hydroxylactam **16** without incident. *N*-acyliminium ion cyclization of **16** was achieved in a surprisingly high diastereoselectivity of 5.7:1 to give **17** as the major product along with its C11b

epimer (not shown). We consider this diastereoselectivity synthetically useful. This is significant considering the two diastereomers are inseparable by flash chromatography. Debenzylation was achieved using hydrogen gas and Pd/C to give amine **18** (Scheme 2.3).

SYNTHESIS OF QUINOLIZIDINONE SYSTEMS



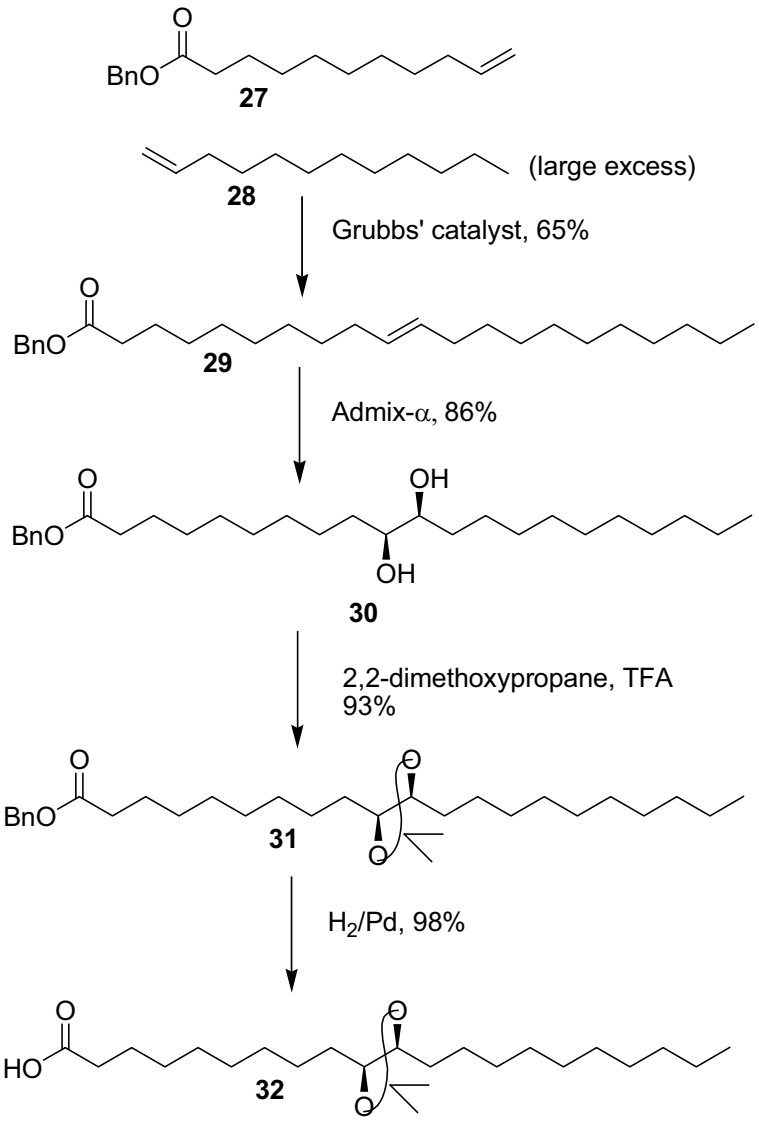
Scheme 2.4 Synthesis of quinolizinone systems

In the same vain, the quinolizidinone **24** was synthesized in 5 steps starting from 3-butenylamine hydrochloride salt **19**, the synthesis went smoothly via amide **20**, imide **21** and hydroxylactam **22**. The nucleophile in the *N*-acyliminium ion cyclization in this case is the π system of the terminal olefin **22**, unlike the nucleophilic aromatic rings in the previous systems. Treatment of **22** with TMSOTf gave a mixture of two diastereomers at newly generated

stereocenter C6 (dr = 4:1). Compound **23** shown in Scheme 2.4 was the major product assigned by correlations observed in NOESY experiments. Debenzylation of **23** gave amine **24** in quantitive yield. Attempt at *N*-acyliminium ion cyclization under a different condition, namely stirring in formic acid, gave a dehydration product **25**. The expected cyclization product formate **26** was not observed. The diene **25** could conceivably be synthetically useful for construction of other quinolizidine natural products.

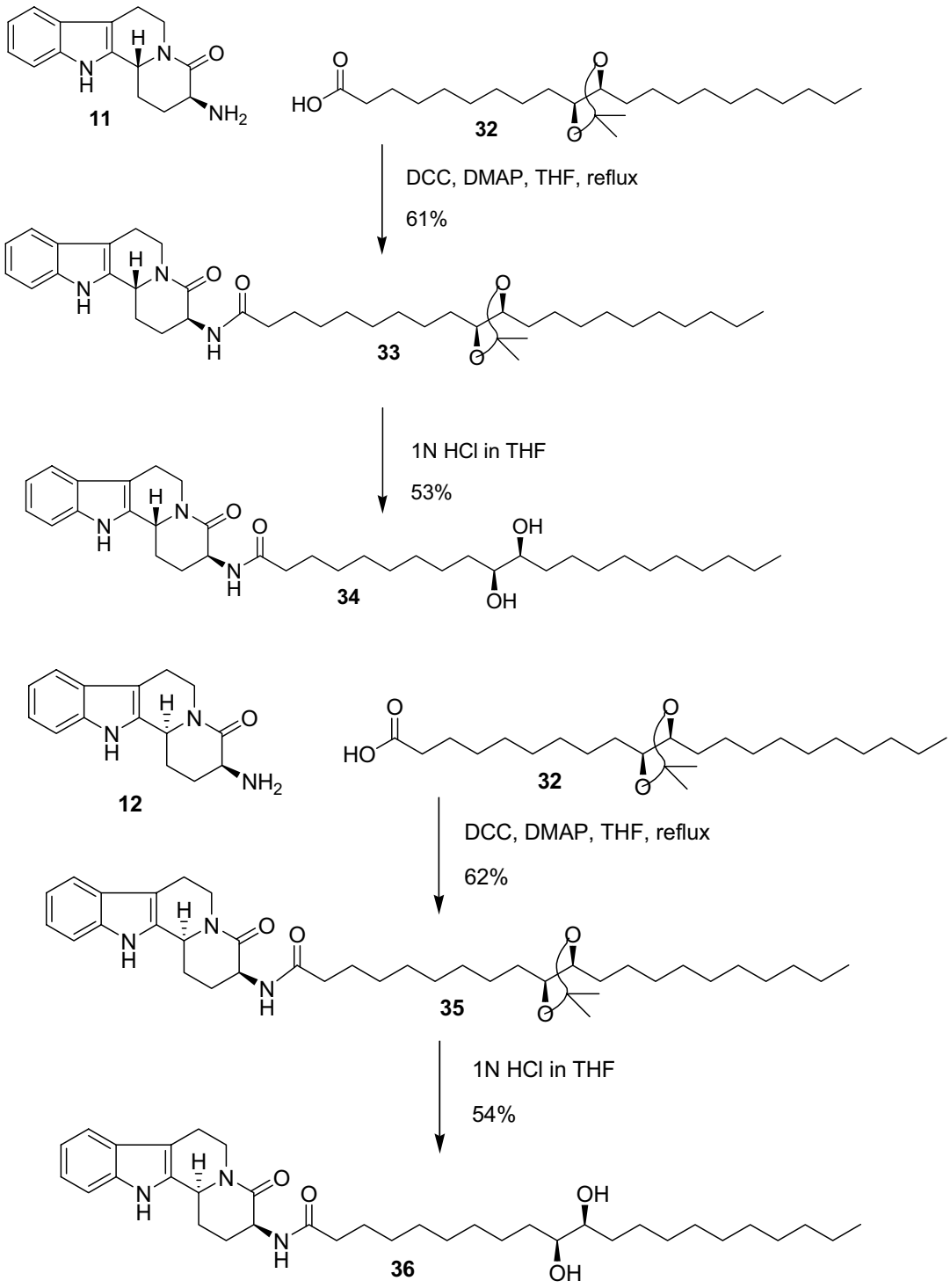
SYNTHESIS OF C21 FATTY ACID SIDE CHAIN

We designed a synthesis of a non-natural fatty acid side chain based on availability of chemicals in our laboratory, while trying to maintain the key features observed in the natural products. In this manner the C21 fatty acid which contains long alkyl chain with polar diol functionality was synthesized (Scheme 2.5). Cross olefin metathesis of benzyl-10-undecanoate **27** and 1-dodecene **28** (large excess) using Grubbs' first generation catalyst gave predominantly *E*-olefin **29**. Sharpless asymmetric dihydroxylation of **29** using AD-mix-α followed by protection of the resulting diol as isopropylidene ketal and debenzylation gave protected fatty acid **32**.



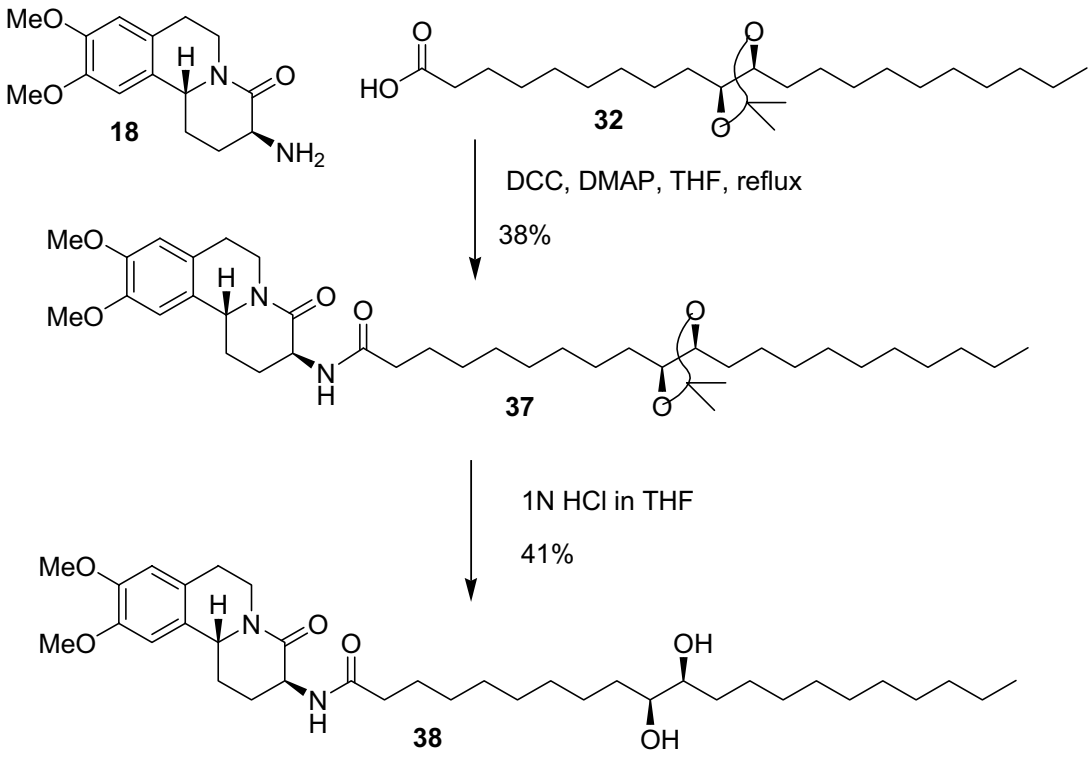
Scheme 2.5 Synthesis of C21 fatty acid side chain

COUPLING OF HETEROCYCLIC CORE AND C21 FATTY ACID SIDE CHAIN



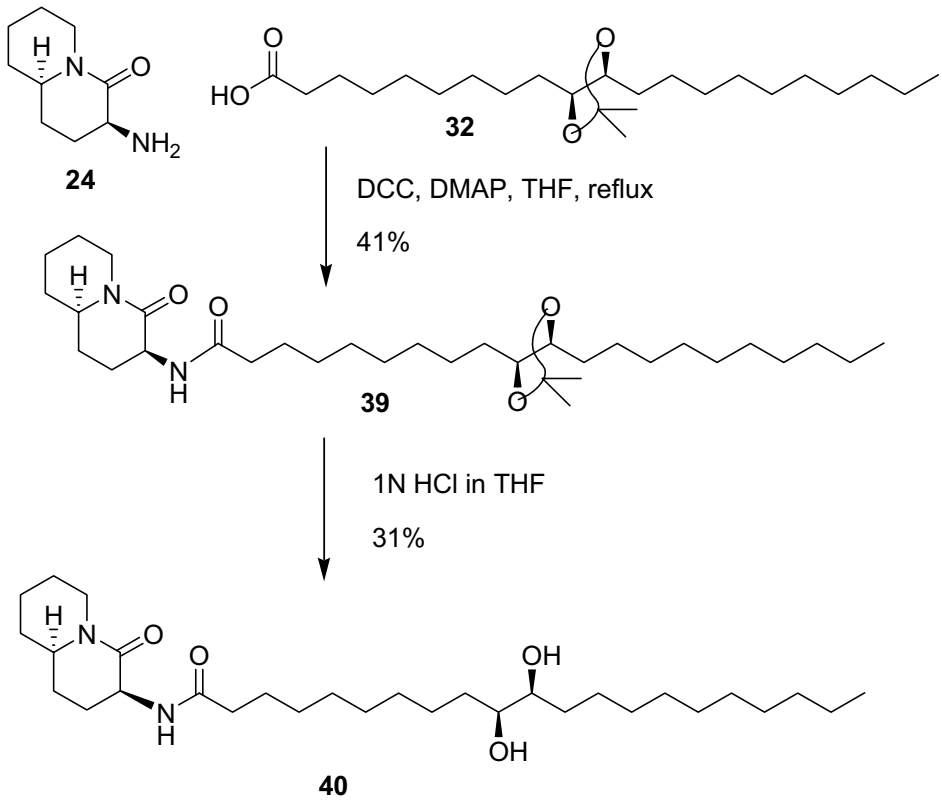
Scheme 2.6 Coupling of indoloquinolizidinone core and C21 fatty acid side chain

Indoloquinolizidinones **11**, **12** were coupled with the C21 fatty acid via amide bond formation in the presence of DCC and DMAP to give amides **33** and **34,** respectively, in moderate yields. The removal of the isopropylidene protecting group was achieved in acidic condition (1N HCl in THF) to give non-natural analogues **34** and **36** of schulzeines (scheme 2.6).



Scheme 2.7 Coupling of 3,4-dimethoxybenzoquinolizidinone core and C21 fatty acid side chain

In the same fashion, non-natural analogues containing the 3,4-dimethoxybenzoquinolizidinone and quinolizidinone systems were synthesized from the corresponding heterocyclic core and C21 fatty acid side chain (Schemes 2.7 and 2.8, respectively).



Scheme 2.8 Coupling of quinolizinone core and C21 fatty acid side chain

STRUCTURE ACTIVITY RELATIONSHIP STUDIES

α-Glucosidase inhibition assay

The enzyme inhibition assay is based on the breakdown of substrate to produce a colored product (Figure 2.2), followed by measuring the absorbance over a period of time. In brief, α-glucosidase (Sigma, type V, from yeast) was dissolved in buffer A (0.1 mol/L potassium phosphate, 3.2 mmol/L-$MgCl_2$, pH6.8) (1 units/ml), *p*-Nitrophenyl-α-D-glucopyranoside dissolved in buffer A at 0.05 mg/mL was used as substrates. 120 μL Sample solution (0.6 mg/ml in methanol), 600 μL enzyme solution and 600 μL substrate were mixed. This mixture was incubated in water-bath at 37 ^{o}C for 30 min. Enzymatic activity was quantified by measuring the absorbance at 410 nm. The preliminary results are shown in Table 2.1. The synthetic analogues in the form of diol were not compatible with this method due to insolubility of these compounds in aqueous media used in the studies. The diols were, therefore, converted into the corresponding bis-sodium sufate salts by reaction with sulfur trioxide-pyridine complex and sodium hydrogen carbonate. The preliminary results from the structure activity relationship studies indicated that these analogues exhibit some inhibitory effect against α-glucosidase in the range of 25-63 μM.

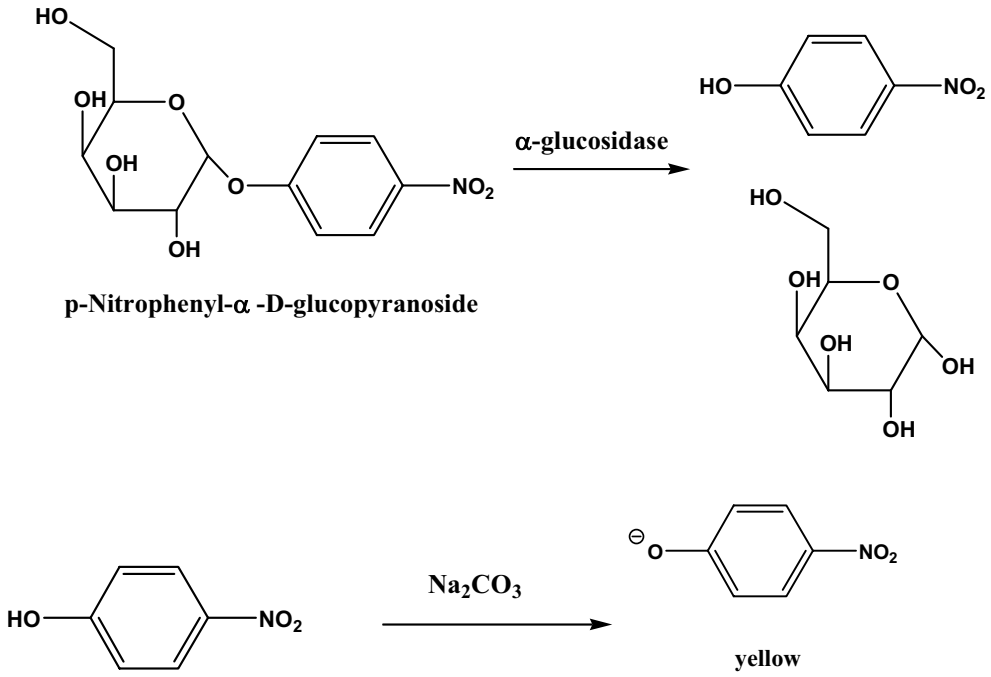


Figure 2.2 α-Glucosidase inhibition assay

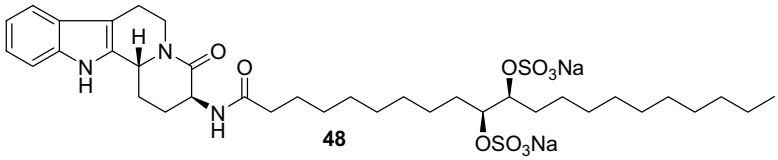
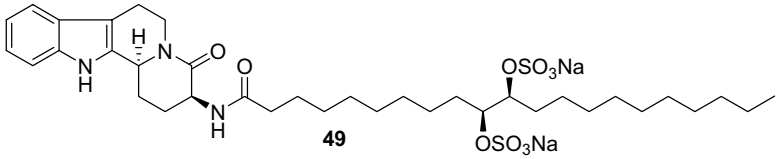
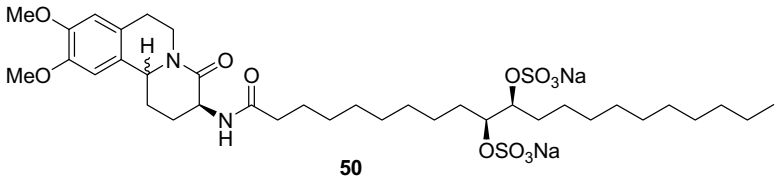
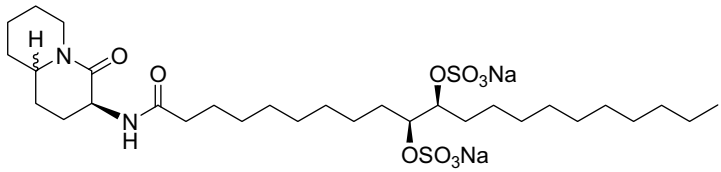
No	Sample	Conc. μM	Abs (410 nm) (AU)
1	Control (α-glucosidase, *p*-Nitrophenyl-α-D-glucopyranoside)	-	1.6289
2	 **48**	25.00	1.2366
3	 **49**	31.82	1.0938
4	 **50**	63.76	1.2155
5	 **51**	37.64	1.2644

Table 2.1 α-Glucosidase inhibition assay

References

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CHAPTER 3

GENERAL CONCLUSIONS

In summary we have synthesized a number of non-natural analogues of schulzeines. These analogues have structural variations both in the heterocyclic core and the fatty acid side chain parts of the natural products. Three different heterocyclic cores were synthesized using *N*-acyliminium ion cyclization. These were 1) indoloquinolizidinone, 2) 3,4-dimethoxybenzoquinolizidinone, and 3) quinolizidinone systems. The fatty acid side chain was designed to retain the shortened alkyl chain of 21 carbon and polar functionalities in the form of 1,2-diol and sodium sulfate salts. The key reactions for the synthesis of the side chain were cross olefin metathesis and Sharpless asymmetric dihydroxylation. The preliminary results of the Structure Activity Relationship studies of the non-natural analogues containing the sodium sulfate groups showed that these synthetic compounds possess some anti-α-glucosidase activity when tested at the concentration of 25-64 μM.

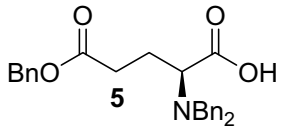
CHAPTER 4

EXPERIMENTAL PROCEDURES

General methods

All commercially available reagents were used without purification. Moisture and air-sensitive compounds were used under an argon atmosphere with oven-dried glasswares. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ or MeOD on a 300 MHz Bruker spectrometer. Chemical shifts are in δ (ppm) with tetramethylsilane as an internal standard. Coupling constants are reported in hertz (Hz). Absorption spectra were collected on a Hewlett Packard 8453 spectrometer. Infrared spectra (IR) were recorded by Perkin Elmer spectrum GX FT-IR system. Major bands (ν_{max}) were recorded in wave number (cm^{-1}). Optical rotations were measured in methanol solution with sodium D line (590 nm) on JASCO P-1010 Polarimeter. Thin layer chromatography (TLC) was performed on Fluka aluminum backed silica gel plates with 0.2 mm thickness. Ultraviolet (UV) active compounds were visualized with a UV light at 254 nm and vanillin stain. Column chromatography was performed using silica gel 60, 230-400 mesh.

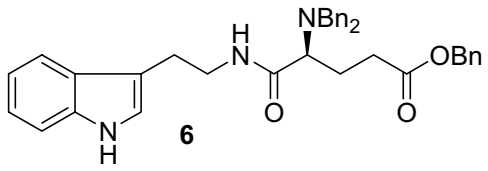
SYNTHESIS OF HETEROCYCLIC CORES



(S)-4-((benzyloxy)carbonyl)-2-(dibenzylamino)butanoic acid

L-glutamic acid (5 g, 0.03 mol) was dissolved in 100 mL of 1:1 MeOH:H_2O. To this solution were added benzyl chloride (15.64 mL, 0.13 mol), K_2CO_3 (10.56 g, 0.07 mol) , and NaOH (3.06 g, 0.07 mol) . The reaction was heated to reflux overnight. 1M HCl (50 mL) and H_2O were added and then the mixture was extracted with $CHCl_3$ (3 x 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude material as a yellow oil. The crude product was purified by column chromatography to give the product as a yellow oil (7.64 g, 53%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.12 (m, 15H); 5.20 (AB system, 2H, *J*=12.2 Hz, *J*=37.4 Hz); 3.90 (d, 2H, *J*=13.6 Hz); 3.48 (d, 2H, *J*=13.6 Hz); 3.38 (t, 1H, *J*=6.9 Hz); 2.37 (m, 2H,); 2.09 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.9; 172.1; 138.9, 128.9, 128.7, 128.6, 128.4, 128.3, 127.1, 66.3, 59.8, 54.4, 30.7, 23.9; $[\alpha]_D^{25.0}$-74.7° (*c* = 1.50, $CHCl_3$); IR (film) 3066, 2959, 1951, 1714, 1603, 1496, 1456, 1420, 1373, 1217, 1162 cm^{-1}.

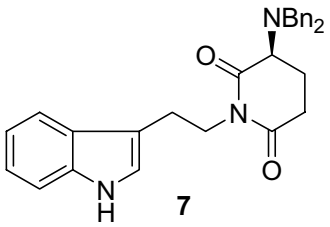


6

(S)-benzyl 4-(2-(1H-indol-3-yl)ethylcarbamoyl)-4-(dibenzylamino)butanoate

To a solution of acid **5** (2.03 g, 4.90 mmol) in dry CH_2Cl_2 (60 mL) under an argon atmosphere at room temperature were added DMAP (0.11 g, 9.80 mmol), tryptamine **4** (1.56 g, 9.70 mmol), and EDC (1.30 mL, 7.40 mmol). The mixture was stirred vigorously. Upon completion adjudged by TLC (1 h), saturated $NaHCO_3$ solution (30 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (1.42 g, 52%).

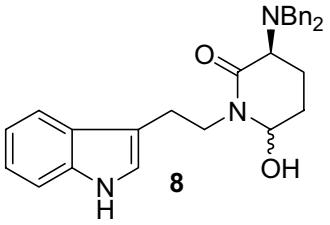
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H); 7.47-6.97 (m, 19H); 6.77-6.77 (d, 1H, *J*=8.1 Hz); 5.14 (d, 2H, *J*=13.7 Hz); 5.01 (d, 2H, *J*=13.7 Hz); 3.39-3.30 (m, 1H); 3.26-3.15 (m, 2H); 2.75-2.70 (m, 2H); 2.10-2.04 (m, 2H); 1.95-1.84 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2; 172.2; 128.9; 128.7, 128.6, 128.4, 128.3, 127.3, 127.1, 122.1, 122.0, 119.4, 118.7, 113.0; 111.2; 66.1; 60.3; 54.5; 39.6; 33.1; 25.3; 25.2; $[\alpha]_D^{25.3}$-54.31° (*c* = 1.40, CH_2Cl_2); IR (film) 3419, 3298, 3060, 3031, 2938, 2850, 1726, 1655, 1523, 1494, 1455, 1212 cm^{-1}.



7

(S)-1-(2-(1H-indol-3-yl)ethyl)-3-(dibenzylamino)piperidine-2,6-dione

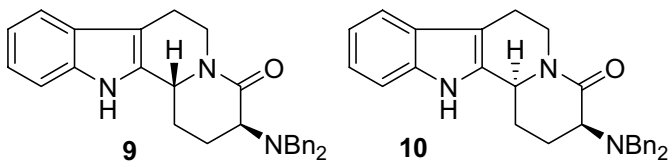
Amide **6** (255 mg, 4.60 mmol) was dissolved in dry THF (8 mL) under an argon atmosphere at 0°C. To this solution was added $LiAlH_4$ (0.05 g., 1.40 mmol). The mixture was stirred vigorously. Upon completion adjudged by TLC (1 h), the reaction was quenched with saturated $NaHCO_3$ solution. Water was added and the mixture was extracted with diethyl ether. The combined organic layers were dried over anh. sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (137 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H); 7.64-6.94 (m, 19H); 6.91-6.90 (d, 1H, *J*=7.1 Hz); 4.08-3.99 (m, 1H); 3.94-3.85 (m, 1H); 3.77 (d, 1H, *J*=14.0 Hz); 3.47 (d, 1H, *J*=14.0 Hz); 3.32-3.26 (dd, 1H, *J*=12.1 Hz, *J*=5.5 Hz); 2.99-2.82 (m, 2H); 2.63-2.56 (td, 1H, *J*=2.7 Hz, *J*=17.2 Hz); 2.27-2.15 (m, 1H); 1.86-1.66 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.1; 170.9; 138.6; 127.8; 127.7; 127.5; 127.4 (3); 127.3; 127.1; 127.0; 126.7; 126.5; 126.3; 126.1; 121.3; 120.8; 118.3; 117.9; 111.6; 110.0; 58.2; 53.7; 39.5; 31.1; 22.5; 21.3; $[\alpha]_D^{25.1}$ -45.68° (*c* = 1.13, CH_2Cl_2); IR (film) 3058, 3029, 2925, 2854, 1723, 1671, 1494, 1455 cm^{-1}.



8

(S)-1-(2-(1H-indol-3-yl)ethyl)-3-(dibenzylamino)-6-hydroxypiperidin-2-one

Imide **7** (72 mg, 0.16 mmol) was dissolved in dry toluene (4 mL) under an argon atmosphere at - 78 ^{o}C. To this solution was added DIBALH (1.60 mL, 1.60 mmol). The reaction was allowed to warm to -20^{o}C and stirred vigorously. This procedure was repeated twice with 1.6 mL and 1.6 mL of DIBALH (1M in toluene), respectively. Upon completion adjudged by TLC (2 h), the reaction was quenched with methanol (16 mL). The resulting mixture was allowed to warm to room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography (1:1 hexane : ethyl acetate) to give a light yellow oil (61.56 mg, 85%). This compound is immediately used for the next step.



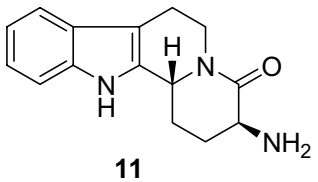
9 **10**

(9) (3S,12bR)-3-(dibenzylamino)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one

(10) (3S,12bS)-3-(dibenzylamino)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one

Hydroxylactam **8** (141.80 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (21 mL) under an argon atmosphere at 0 ^{o}C. To this solution was added TMSOTf (0.10 mL., 0.63 mmol). The

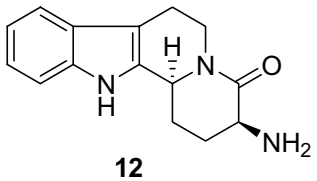
mixture was extracted with $CHCl_3$. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give 2 diastereomers of the indoloquinolizidinone product 9 and 10 (99.70 mg, 2.3:1, 74% combined yield). ^{1}H NMR (300 MHz, $CDCl_3$) **(9)** δ 7.83 (s, 1H); 7.39-6.94 (m, 14H); 4.91-4.89 (m, 1H); 4.64 (s, 1H); 3.97 (d, 2H, *J*=12.6 Hz); 3.58 (d, 2H, *J* =12.6 Hz); 3.34-3.29 (m, 1H); 2.89-2.74 (m, 2H); 2.64-2.60 (m, 1H); 2.08-2.07 (m, 1H); 1.95-1.58 (m, 3H).
^{1}H NMR (300 MHz, $CDCl_3$) **(10)** δ 7.84 (s, 1H); 7.51-7.09 (m, 14H); 5.25-5.16 (m, 1H); 4.72-4.66 (m, 1H); 4.15 (d, 2H, *J*=14.0 Hz); 3.85 (d, 2H, *J*=14.0 Hz); 2.92-2.72 (m, 3H); 2.43-2.37 (m, 1H); 2.09-1.89 (m, 3H).



11

(3S,12bR)-3-amino-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one

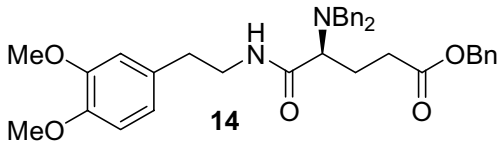
To a solution of benzylated amine **9** (25 mg, 0.05 mmol) in MeOH:CH_2Cl_2 (3 mL, 1:2) was added 10% Pd/C (2.5 mg) and the resulting mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered and the filtrate was concentrated to give **11** (13.60 mg, 93%). ^{1}H NMR (300 MHz, MeOD) δ 7.43-7.33 (dd, 2H, *J*=7.6 Hz, *J*=22.9 Hz); 7.13-6.99 (td, 2H, *J*=7.1 Hz, *J*=27.1 Hz); 5.09 (s, 1H); 4.88-4.78 (m, 1H); 4.05-4.02 (m, 1H); 3.21-2.95 (m, 2H); 2.79-2.71 (m, 1H,); 2.52-2.20 (m, 2H); ^{13}C NMR (300 MHz, MeOD) δ 166.5; 136.6; 132.4; 121.7; 118.7; 117.8; 111.0; 109.0; 54.5; 48.4; 42.7; 23.1; 22.6; 20.1.



12

(3S,12bS)-3-amino-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one

To a solution of benzylated amine **10** (24 mg, 0.05 mmol) in MeOH:CH_2Cl_2 (3 mL, 1:2) was added 10% Pd/C (2.40 mg) and the resulting mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered and the filtrate was concentrated to give **12** (12.80 mg, 91%). ^{1}H NMR (300 MHz, MeOD) δ 7.32-7.21 (dd, 2H, *J*=7.5, *J*=24.9); 7.01-6.87 (td, 2H, *J*=7.1 Hz, *J*=27.2 Hz); 4.92-4.79 (m, 2H,); 3.83-3.77 (dd, 1H, *J*=5.8 Hz, *J*=12.2 Hz); 2.91-2.81 (m, 1H); 2.68-2.66 (m, 2H); 2.29-2.25 (m, 2H); 2.01-1.64 (m, 2H); ^{13}C NMR (300 MHz, MeOD) δ 165.1; 136.8; 132.5; 126.4; 121.3; 118.7; 117.5; 110.7;107.2; 54.6; 50.2; 40.3; 26.3; 23.8; 20.5.

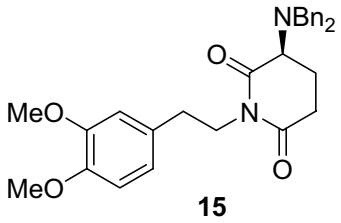


14

(S)-benzyl 4-(3,4-dimethoxyphenethylcarbamoyl)-4-(dibenzylamino)butanoate

Acid **5** (1.29 g, 3.00 mmol) was dissolved in dry CH_2Cl_2 (36 mL) under an argon atmosphere at room temperature. To this solution were added DMAP (0.07 g, 0.60 mmol), EDC (0.8 mL, 4.50 mmol), and 3,4-dimethoxy phenylethylamine **13** (1.02 mL, 6.00 mmol.) The mixture was stirred vigorously. Upon completion adjudged by TLC (1 h), saturated $NaHCO_3$ solution (30mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (836.20 mg, 48%).

^{1}H NMR (300 MHz, MeOD) δ 7.31-7.06 (m, 16H); 6.67-6.54 (m, 2H); 5.16-5.021 (d, 1H, *J*=29.6 Hz); 5.06 (d, 1H, *J*=29.6 Hz); 5.033 (m, 1H); 3.73 (s, 6H); 3.77 (d, 2H, *J*=13.7 Hz); 3.42 (d, 2H, *J*=13.7 Hz); 3.28-3.17 (m, 1H); 3.15-3.06 (m, 1H); 2.53-2.48 (t, 2H, *J*=1.7 Hz); 2.13-2.06 (m, 2H); 1.97-1.86 (m, 2H); ^{13}C NMR (300 MHz, MeOD) δ 172.1; 149.0; 147.6; 139.3; 135.9; 131.4; 129.0; 128.6; 128.3; 127.1; 120.6; 119.3; 111.9; 111.3; 111.0; 110.4; 66.2; 60.3; 55.9; 54.5; 40.7; 35.2; 33.1; 25.3; $[\alpha]_D^{24.4}$-56.63° (*c* = 1.08, CH_2Cl_2); IR (film) 3418, 3057, 3031, 2937, 2837, 1727, 1663, 1591, 1515, 1455, 1419, 1371, 1237, 1156 cm^{-1}.

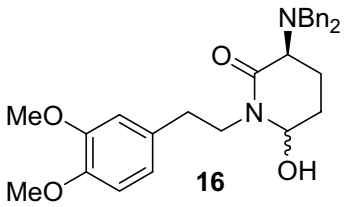


15

(S)-1-(3,4-dimethoxyphenethyl)-3-(dibenzylamino)piperidine-2,6-dione

To a solution of amide **14** (0.09 g, 0.16 mmol) in CH_2Cl_2 (1 mL) was added dropwise DIBALH (0.6 mL, 1 M in toluene) via syringe under an argon atmosphere at -78 °C. The mixture was slowly warmed to room temperature and stirred for additional 2 h. After cooling to 0 °C the reaction mixture was quenched by slow addition of MeOH (1 mL) and 1N HCl (1mL) and extracted with CH_2Cl_2. The combined organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography to give imide **15** (25.10 mg, 33%) as an oil and recovered amide **14** (62.70 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.13 (m, 16H); 6.69-6.62 (m, 2H); 4.01-3.84 (m, 2H); 3.87 (d, 2H, *J*=13.9 Hz); 3.54 (d, 2H, *J*=13.9 Hz); 3.68 (s, 6H); 3.40-3.32 (m, 1H); 2.72-2.63 (m, 3H); 2.38-2.26 (m, 1H); 1.97-1.79 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.2; 171.7; 148.8; 147.6; 139.5; 130.8; 130.3; 130.0; 129.4; 127.4; 127.1; 126.9; 126.6; 121.0; 120.6; 112.5; 111.4; 110.9; 59.3; 55.8; 55.7; 55.0; 40.8; 33.5; 32.2; 22.6; $[\alpha]_D^{24.5}$-46.18° (*c* = 1.17,

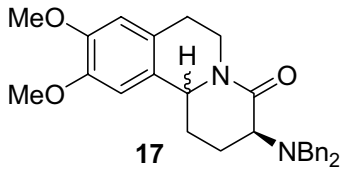
CH_2Cl_2); IR (film) 3060, 3028, 2957, 2935, 2836, 1725, 1674, 1591, 1515, 1494, 1454, 1344, 1319, 1237 cm^{-1}.



16

(S)-1-(3,4-dimethoxyphenethyl)-3-(dibenzylamino)-6-hydroxypiperidin-2-one

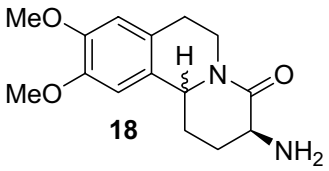
Imide **15** (22.00 mg, 0.05 mmol) was dissolved in dry toluene (1.25 mL) under an argon atmosphere at - 78 °C. To this solution was added DIBALH (0.25 mL, 0.25 mmol). The reaction was allowed to warm to -20 ^{o}C and stirred vigorously. Upon completion adjudged by TLC (2 h), the reaction was quenched with methanol (1 mL). The resulting mixture was allowed to warm to room temperature. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (20.20 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.13 (m, 11H); 6.81-6.72 (m, 2H); 4.71-4.66 (m, 1H,); 4.04-3.60 (d, 4H, *J*=14.0 Hz); 3.90-3.82 (m, 3H); 3.78 (s, 6H); 2.91-2.86 (t, 2H,); 2.22-2.13 (m, 2H); 1.96-1.87 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7; 148.9; 147.6; 140.1; 131.8; 128.9; 128.7; 128.6; 128.4; 128.2; 126.9; 126.8; 120.8; 120.7; 112.1; 111.3; 111.1; 80.6; 59.1; 55.8; 55.5; 48.6; 34.0; 29.5; 21.5; IR (film) 3373, 3054, 2937, 2838, 1638, 1515, 1455, 1420, 1237 cm^{-1}**.**



17

(3S,11bR)-3-(dibenzylamino)-2,3,6,7-tetrahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one

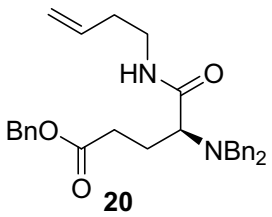
Hydroxylactam **16** (91.50 mg, 0.19 mmol) was dissolved in dry CH_2Cl_2 (14.82 mL) under an argon atmosphere at 0 °C. To this solution was added TMSOTf (0.07 mL., 0.39 mmol). The mixture was stirred for 3 h and water was added. The mixture was extracted with $CHCl_3$. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give an inseparable mixture of 2 diastereomers of the benzoquinolizidinone **17** as an oil (84.60 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.19 (m, 11H); 6.63-6.60 (d, 2H); 4.81-4.76 (t, 1H, *J*=8.4 Hz); 4.50-4.46 (t, 1H, *J*=5.4 Hz); 4.13 (d, 2H, *J*=14.1 Hz); 3.79 (d, 2H, *J*=14.1 Hz); 3.85 (m, 6H); 3.48-3.43 (dt, 1H, *J*=2.9 Hz, *J*=8.4 Hz); 2.99-2.80 (m, 2H); 2.71-2.61 (m, 1H); 2.22-1.80 (m, 3H); IR (film) 3054, 2986, 1638, 1513, 1421, 1359, 1224 cm^{-1}.



18

(3S,11bR)-3-amino-2,3,6,7-tetrahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one

To a solution of *N,N*-dibenzy amine **17** (58.9 mg, 0.13 mmol) in MeOH (3 mL) was added 10% (w/w) Pd/C (5.89 mg) and the mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered and the filtrate concentrated to give **18** as an oil (36.30 mg, quantitative).

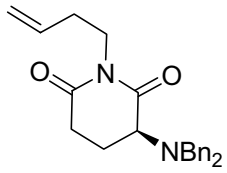


20

(S)-benzyl 4-(but-3-enylcarbamoyl)-4-(dibenzylamino)butanoate

Acid **5** (0.19 g, 0.46 mmol) was dissolved in dry CH_2Cl_2 (6 mL) under an argon atmosphere at room temperature. To this solution were added DMAP (0.01 g., 0.09 mmol), EDC (0.08 mL, 0.65 mmol) , Et_3N (0.06 mL, 0.46 mmol.) and 3-butenylamine hydrochloride (0.10 g., 0.90 mmol). The mixture was stirred vigorously. Upon completion adjudged by TLC (3 h), saturated $NaHCO_3$ solution (30mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (221 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46- 7.22 (m, 15H); 5.77-5.64 (m, 1H); 5.30 (d, 1H, *J*=14.7 Hz); 5.17 (d, 1H, *J*=14.7 Hz); 5.16-5.03 (m, 2H,); 3.92(d, 2H, *J*=13.8 Hz); 3.49 (d, 2H, *J*=13.8 Hz); 3.38 (t, 1H, *J*=8.1 Hz); 3.27-3.02 (m, 2H); 2.32-2.01 (m, 4H); 0.94-0.86 (m, 2H); **^{13}C**

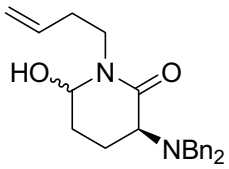
NMR (300 MHz, $CDCl_3$) δ 172.2; 172.2; 139.4; 135.3; 129.0; 128.7; 128.6; 128.5; 128.4; 128.3; 128.0; 127.8; 127.4; 127.1; 126.9; 116.9; 66.2; 60.3; 54.6; 38.4; 33.7; 33.1; 25.5; $[\alpha]_D^{24.9}$-72.15° (*c* = 2.10, CH_2Cl_2); IR (film) 3434, 2233, 3084, 3055, 3031, 2980, 2940, 2847, 1728, 1663, 1519, 1495, 1456, 1372, 1211 cm^{-1}.



21

(S)-1-(but-3-enyl)-3-(dibenzylamino)piperidine-2,6-dione

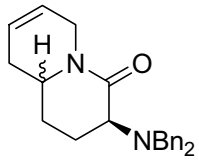
To a solution of amide **20** (559.60 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) was added dropwise DIBALH (3.4 mL, 1M in toluene) via syringe under an argon atmosphere at -78 °C. The mixture was allowed to slowly warm to room temperature and stirred for additional 2 h. After cooling to 0 °C, the reaction mixture was quenched by slow addition of MeOH (5 mL) and 1N HCl (5mL). The mixture was extracted with CH_2Cl_2. The combined organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography to afford imide **21** (137.70 mg, 31%) as an oil and recovered amide **20** (351.00 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.23 (m, 10H); 5.87-5.73 (m, 1H); 5.08-5.01 (m, 2H); 4.07 (d, 2H, *J*=3.9 Hz); 3.78 (d, 2H, *J*=3.9 Hz); 4.17-4.04 (m, 1H); 3.88-3.76 (m, 1H); 3.50 (t, 1H, *J*=8.3 Hz); 2.77-2.72(m, 1H); 2.46-2.27 (m, 3H); 2.05-2.00 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.3; 171.7; 139.7; 135.2; 128.6; 128.4; 128.2; 127.4; 127.2; 116.9; 59.3; 55.1; 38.8; 32.5; 22.6; $[\alpha]_D^{25.4}$-55.44° (*c* = 1.00, CH_2Cl_2); IR (film) 3061, 3029, 2964, 2853, 1726, 1675, 1494, 1455, 1347, 1319 cm^{-1}.



22

(S)-1-(but-3-enyl)-3-(dibenzylamino)-6-hydroxypiperidin-2-one

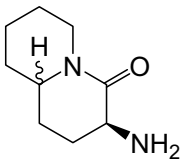
Imide **21** (156.00 mg, 0.40 mmol) was dissolved in dry toluene (10 mL) under an argon atmosphere at - 78 ^{o}C. To this solution was added DIBALH (2.2 mL, 2.2 mmol). The reaction was allowed to warm to -20 °C and stirred vigorously. Upon completion adjudged by TLC (2 h), the reaction was quenched with methanol (6.4 mL). The resulting mixture was allowed to warm to room temperature. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give a light yellow oil (37.00 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.21 (m, 10H); 5.90-5.72 (m, 1H); 5.12-5.03 (m, 2H); 4.89-4.82 (m, 1H); 4.02 (d, 4H, *J*=14.0 Hz); 3.71 (d, 4H, *J*=14.0 Hz); 3.85-3.69 (m, 1H); 3.48-3.38 (m, 1H); 2.47-2.32 (m, 2H); 2.27-2.18 (m, 1H); 1.97-1.88 (m, 1H); 1.81-1.68 (m, 1H); 1.55-1.42 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7; 140.2; 135.8; 128.7; 128.6; 128.2; 127.4; 126.8 (2); 117.3; 80.3; 59.1; 55.4; 45.7; 31.6; 29.50; 21.6; IR (film) 3380, 3054, 2984, 2940, 2850, 1641, 1493, 1454 cm^{-1}.



23

(3S,9aS)-3-(dibenzylamino)-2,3,9,9a-tetrahydro-1H-quinolizin-4(6H)-one

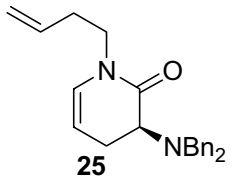
Hydroxylactam **22** (35.00 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (7 mL) under an argon atmosphere at 0 °C. To this solution was added TMSOTf (0.03 mL., 0.20 mmol). The mixture was stirred for 3h and subsequently extracted with $CHCl_3$. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This oil was further purified by column chromatography to give an inseparable mixture of 2 diastereomers of the quinolizidinone product (26.00 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.17 (m, 10H); 5.78-5.65 (m, 2H); 4.92-4.82 (m, 1H); 4.08 (d, 2H, *J*=14.0 Hz); 3.756 (d, 2H, *J*=14.0 Hz); 3.53-3.24 (m, 3H); 2.34-2.24 (m, 1H); 2.02-1.65 (m, 5H).



24

(3S,9aR)-3-amino-hexahydro-1H-quinolizin-4(6H)-one

To a solution of *N,N*-dibenzyl amine **23** (24.70 mg, 0.07 mmol) in hexane (1 mL) was added Pd/C (2.50 mg.) and the mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered and the filtrate concentrated to give **24** as an oil (15.50 mg, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67-4.62 (m, 2H); 3.30-3.25 (m, 3H); 2.46-1.29 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.3; 55.2; 52.0; 43.9; 32.9; 26.7; 26.3.

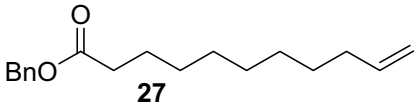


25

(S)-1-(but-3-enyl)-3-(dibenzylamino)-3,4-dihydropyridin-2(1H)-one

Hydroxylactam **22** (77.00 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (0.5 mL). Formic acid was slowly added and the mixture was stirred for 10 minutes at room temperature. Formic acid was removed under reduced pressure. The residue was purified by flash column chromatography to give a light yellow oil **25** (13.00 mg, 15%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.09 (m, 10H); 5.78-5.61 (m, 2H); 4.99-4.92 (m, 3H); 4.01 (d, 2H, *J*=14.1 Hz); 3.72 (d, 2H, *J*=14.1 Hz); 3.59-3.26 (m, 3H); 2.49-2.18 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.0; 140.5; 134.8; 128.9; 128.5; 128.2; 126.7; 117.0; 105.1; 57.2; 55.1; 45.4; 33.1; 25.8.

SYNTHESIS OF C21 FATTY ACID SIDE CHAIN

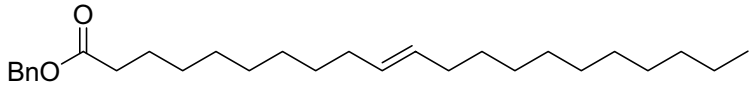


27

benzyl undec-10-enoate

A mixture of 10-Undecenoic acid (15.0 mL, 74.26 mmol), NaOH (4.46 g, 0.11 mol), and benzyl chloride (8.54 mL, 74.26 mmol) in H_2O:MeOH (1:1, 337.0 mL) was heated to reflux overnight. 1M HCl (50 mL) and H_2O were added and the mixture was extracted with $CHCl_3$ (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give the crude material as a yellow oil. The product was purified by column chromatography to give the pure product as a yellow oil (10.65 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.21

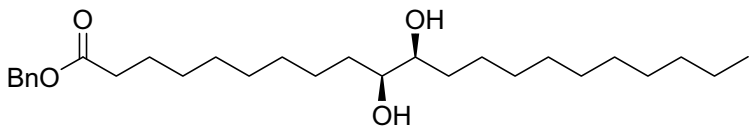
(m, 5H, Ph); 7.51-7.21 (m, 5H); 5.86-5.73 (m, 1H); 5.13 (s, 2H); 5.02-4.93 (dd, 1H, *J*=21.5 Hz, *J*=3.6 Hz); 2.36-2.31 (t, 2H, *J*=7.4 Hz); 2.03-1.99 (m, 2H); 1.65-1.58 (m, 2H); 1.13-1.27 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.6; 139.1; 136.1; 128.5; 128.1; 127.7; 114.1; 66.0; 34.3; 34.9; 29.2; 29.1; 29.1; 29.0; 28.9; 24.9; IR (film) 3055, 2929, 2856, 1732, 1497, 1455, 1382 cm^{-1}.



29

(E)-benzyl henicos-10-enoate

To a solution of benzyl-10-undecanoate **27** (1.20 g., 4.40 mmol) and 1-undecene **28** (9.8 mL, 44.0 mmol) in dry CH_2Cl_2 (88 mL) was added Grubbs' I catalyst (0.18 g, 0.22 mmol) and the mixture was heated to reflux overnight. The solvent was evaporated and the product was purified by column chromatography to give a light yellow oil **29** (1.19 g, 65%, *E:Z* ratio undetermined). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 5H); 5.39-5.38 (m, 2H); 5.11 (s, 2H); 2.37-2.32 (t, 2H, *J*=7.5 Hz); 1.98 (m, 4H,); 1.64 (m, 2H); 1.43-1.27 (m, 26H); 0.89-0.87 (m, 3H).

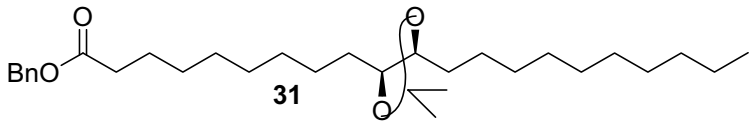


30

(10S,11S)-benzyl 10,11-dihydroxyhenicosanoate

AD-mix-α (4.06 g.) was dissolved in H_2O : *t*-BuOH (1:1). The bilayer mixture was stirred vigorously at room temperature for 5 minutes then cooled to 0 ^{o}C. To this solution was

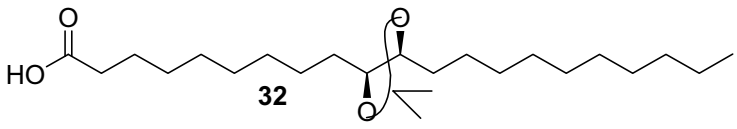
added diene **29** (1.19 g, 2.90 mmol) and the reaction was stirred vigorously at 0 ^{o}C for 48 h. The reaction was quenched with saturated aqueous solution of sodium sulfite at 0 ^{o}C. The resulting mixture was allowed to warm to room temperature, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude white powder. This product was further purified by column chromatography to give a white solid (1.12 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H); 5.13 (s, 2H); 3.39 (s, 2H); 2.37-2.32 (t, 2H, *J*=7.3 Hz); 1.66-1.59 (m, 2H); 1.47 (m, 4H); 1.29-1.26(m, 26H); 0.90-0.85 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.7; 136.1; 128.5; 128.1; 77.5; 66.0; 35.3; 34.0; 33.6; 33.5; 33.0; 31.9; 31.2; 31.1; 27.3; 26.1; 26.0; 25.9; 25.6; 24.9; 22.6; 14.1; $[\alpha]_D^{25.2}$-5.16° (*c* = 1.37, CH_2Cl_2).



31

benzyl 9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)nonanoate

Diol **31** (1.12 g, 2.50 mmol) was dissolved in 2,2-dimethoxypropane (56.8 mL) under argon atmosphere. To this solution was added TFA (0.32 mL) and the mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. This product was further purified by column chromatography to give a light yellow oil (1.15 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H); 5.13 (s, 2H); 3.59 (m, 2H); 2.39-2.31 (t, 2H); 1.68 (m, 2H); 1.395 (s, 6H); 1.30-1.28 (m, 30H); 0.98-0.87 (t, 3H, *J*=6.0 Hz) ; IR (film) 3054, 2929, 2856, 1731, 1421, 1169 cm^{-1}.

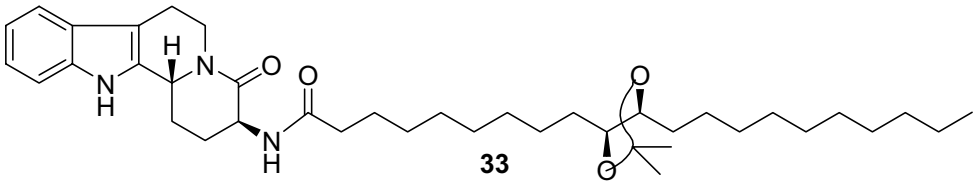


32

9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)nonanoic acid

To a solution of benzyl ester **31** (0.70 g, 1.43 mmol) in hexane was added 10% Pd/C (0.07 g) in hexane (5 mL). The mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered and the filtrate concentrated to give a light yellow oil **32** (0.54 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 2H); 2.38-2.33 (t, 2H, *J*=7.5 Hz); 1.66-1.66 (m, 2H); 1.32-1.27 (m, 30H); 0.91-0.87 (t, 3H, *J*=6.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 179.3; 107.7; 80.9; 33.9; 31.8; 31.6; 31.0; 29.7; 29.6; 29.5; 29.4; 29.2; 29.1; 28.9; 28.5; 27.4; 27.1; 26.8; 26.0; 25.8; 24.8; 24.6; 22.61; $[\alpha]_D^{25.5}$-17.71° (*c* = 1.91, CH_2Cl_2); IR (film) 3053, 2986, 2929, 1711, 1463, 1421, 1378, 1370 cm^{-1}.

COMPLETION OF NON-NATURAL ANALOGUES OF SCHULZEINES

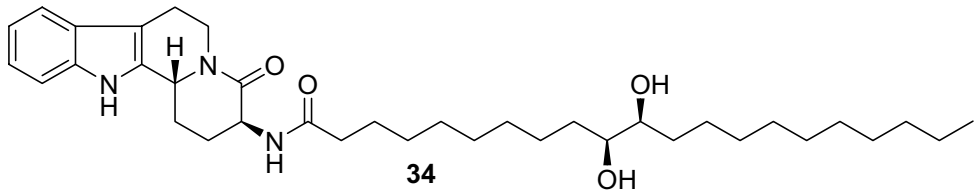


33

9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-N-((3S,12bR)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizin-3-yl)nonanamide

To a solution of acid **32** (50.00 mg, 0.12 mmol) in dry THF (1 mL) under argon atmosphere at room temperature were added DMAP (1.50 mg, 0.01 mmol), DDC (0.04 g., 0.20 mmol) and indoloquinolizidinone **11** (16.30 mg, 0.06 mmol). The mixture was heated to reflux overnight. Solvent was evaporated and the product was purified by column chromatography to give amide **33** as an oil (24.10 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.31 (dd, 2H, *J*=7.5 Hz, *J*=28.2 Hz); 7.12-6.98 (dtd, 2H, *J*=1.1 Hz, *J*=7.1 Hz, *J*=25.7 Hz), 4.97-4.87 (m, 2H); 4.62-

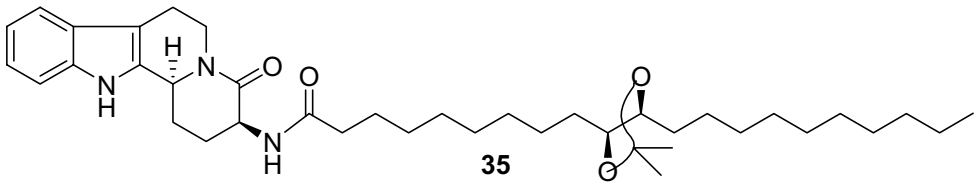
4.60 (m, 2H); 3.11-2.87 (m, 2H); 2.80-2.77 (m, 1H); 2.52-2.45 (m, 1H); 2.23-2.07 (m, 1H), 1.89-1.08 (m, 34H); 0.93-0.91 (t, 3H, *J*=2.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.6; 169.3; 133.1; 126.7; 121.1; 118.6; 117.3; 110.7; 108.2; 107.5 ; 80.9; 54.5; 49.5; 41.8; 35.5; 33.8; 33.3; 32.9; 32.5; 31.6; 29.3; 29.2; 29.0; 28.9; 28.8; 28.7; 26.1; 25.7; 20.3; 13.0; IR (film) 3757, 3449, 3054, 2987, 2931, 1712, 1646, 1421, 1263 cm^{-1}.



34

(10S,11S)-N-((3S,12bR)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizin-3-yl)-10,11-dihydroxyhenicosanamide

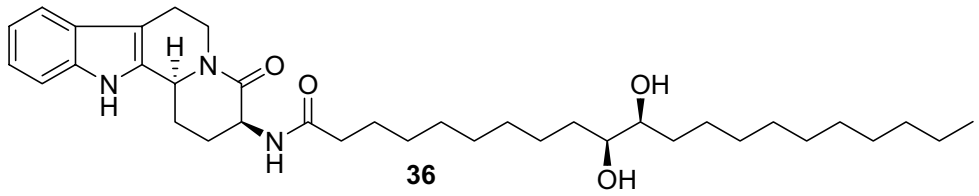
Acetonide **33** (24.10 mg, 0.03 mmol) was dissolved in 1 N HCl in THF . The mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. The product was purified by column chromatography to give the diol **34** (9.90 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H); 7.51-7.26 (dd, 2H, *J*=7.6 Hz, *J*=77.4 Hz); 7.21-7.09 (m, 2H); 6.67-6.66 (d, 1H, *J*=4.8 Hz); 4.94-4.90 (m, 1H); 4.82-4.76 (m, 1H); 4.46-4.39 (m, 1H); 3.39 (s, 2H); 3.15-2.92 (m, 2H); 2.82-2.76 (m, 2H); 2.64-2.39 (m, 2H); 2.26-2.21 (t, 2H , *J*=14.2 Hz); 1.66-1.12); 0.89-0.85 (t, 3H, *J*=6.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.6; 170.1; 136.9; 132.5; 126.9; 122.2; 119.8; 118.2; 111.1; 109.9; 74.5; 52.9; 50.6; 42.1; 36.6; 33.6; 33..5; 31.9; 29.7; 29.6; 29.3; 29.1; 28.9; 26.0; 25,7; 25.5; 25.4; 24.7; 22.6; 20.4; 14.1.



35

9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-N-((3S,12bS)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizin-3-yl)nonanamide

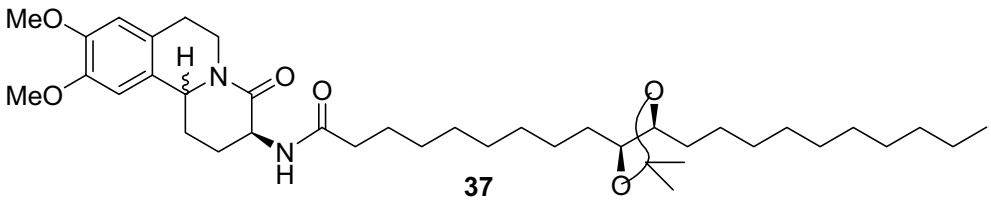
Acid **32** (60.00 mg, 0.15 mmol) was dissolved in dry THF (1 mL) under argon atmosphere at room temperature. To this solution were added DMAP (1.80 mg, 0.01 mmol), DDC (0.05 g, 0.24 mmol) and indoloquinolizidinone **12** (18.70 mg., 0.07 mmol). The mixture was heated to reflux overnight. Solvent was evaporated and the product was purified by column chromatography to give the pure product **35** as an oil (26.50 mg, 62%). ^{1}H NMR (300 MHz, MeOD) δ 7.44-7.31 (dd, 2H, *J*= 8.87 Hz, *J*=32.1 Hz); 7.12-6.98 (td, 2H, *J*=7.1 Hz, *J*=25.9 Hz); 5.08-5.04 (m, 1H); 4.87 (s, 1H); 4.34-4.28 (q, 1H, *J*=6.0 Hz); 3.60 (s, 2H); 3.00-2.90 (m, 1H); 2.79-2.77 (m, 1H); 2.71-2.67 (m, 1H); 1.85-1.08 (m, 34H); 0.93-0.89 (t, 3H, *J*=5.9 Hz); ^{13}C NMR (300 MHz, MeOD) δ 174.6; 168.8; 136.8; 133.2; 126.5; 121.1; 118.6; 117.4; 110.6; 107.4; 80.9; 54.8; 50.4; 40.4 ; 35.6 ; 33.3; 32.5; 31.6; 29.2; 29.0; 28.9; 28.8; 27.3; 26.9; 25.9; 25.8; 25.4; 25.3; 20.6; 13.0; IR (film) 3392, 3055, 2941, 1636, 1558, 1449, 1266, 1112, 1020 cm^{-1}.



36

(10S,11S)-N-((3S,12bS)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizin-3-yl)-10,11-dihydroxyhenicosanamide

Acetonide **33** (17.70 mg, 0.03 mmol) was dissolved in 1N HCl in THF . The mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. the product was purified by column chromatography to give diol **36** (9.70 mg, 54%). ^{1}H NMR (300 MHz, MeOD) δ 7.44-7.31 (m, 2H, *J*=30.0 Hz, *J*=7.642 Hz); 7.12-6.99 (m, 2H); 5.07-5.02 (m, 1H); 4.89-4.89 (m, 1H); 4.32-4.26 (m, 1H,); 3.36 (s, 2H); 2.98-2.86 (m, 1H); 2.80-2.78 (m, 1H); 2.73-2.65 (m, 1H); 2.28-2.19 (m, 2H); 2.06-1.07 (m, 34H); 0.89-0.86 (t, 3H, *J*=7.82 Hz); ^{13}C NMR (300 MHz, MeOD) δ 174.7; 168.8; 136.7; 133.2; 121.2; 118.7; 110.8; 107.5; 73.9; 54.8; 50.5; 40.5; 35.8; 33.4; 32.7; 31.6; 29.2; 29.0; 28.9; 27.3; 25.9; 25.6; 25.4; 25.3; 24.6; 22.3; 20.7; 13.26.

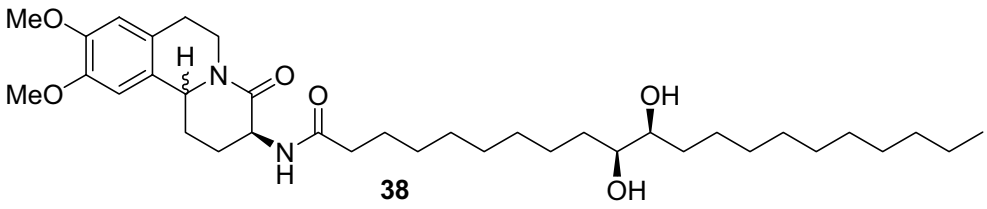


37

9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-N-((3S)-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-1H-pyrido[2,1-a]isoquinolin-3-yl)nonanamide

The acid **32** (0.06 g, 0.17 mmol) was dissolved in dry CH_2Cl_2 (1 mL) under argon atmosphere at room temperature. To this solution were added DMAP (2.20 mg, 0.02 mmol),

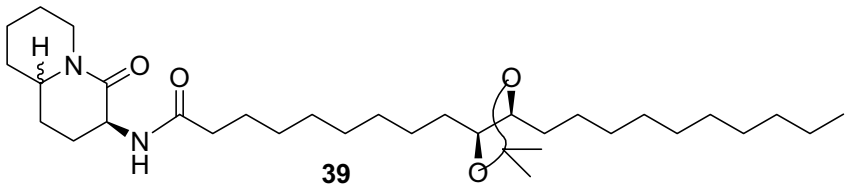
DDC (59.00 mg, 0.28 mmol) and 3,4-dimethoxybenzo-quinolizidinone **18** (24.80 mg., 0.09 mmol). The mixture was stirred vigorously. Upon completion adjudged by TLC (2 days), solvent was evaporated and the product was purified by column chromatography to give amide **37** as an oil (22.30 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65-6.63 (d, 2H, *J*=6.7 Hz); 4.70-4.51 (m, 3H); 3.87 (s, 6H); 3.58 (s, 2H); 3.08-2.59 (m, 3H); 2.27-2.22 (t, 2H, *J*=7.7 Hz); 1.88-1.64 (m, 4H); 1.50-1.26 (m, 32H); 0.90-0.86 (t, 3H, *J*=6.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.3; 170.3; 148.5; 127.5; 111.5; 108.7; 81.0; 56.1; 53.4; 49.4; 39.8; 36.7; 33.0; 31.9; 29.9; 29.8; 29.7; 29.6; 29.5; 29.3; 29.2; 29.1; 28.3; 27.3; 26.1; 25.6; 24.8; 22.6; 14.12; IR (film) 3408, 3321, 3054, 2986, 2930, 1670, 1634, 1506, 1470, 1445, 1264 cm^{-1}.



38

(10S,11S)-N-((3S,11bR)-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-1H-pyrido[2,1-a]isoquinolin-3-yl)-10,11-dihydroxyhenicosanamide

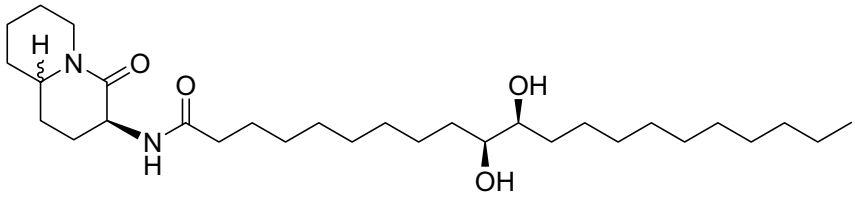
Acetonide **37** (22.30 mg, 0.03 mmol) was dissolved in 1N HCl in THF (1 mL). The mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. The product was purified by column chromatography to give diol **38** (7.60 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70-6.56 (m, 2H); 4.68-4.45 (m, 3H); 3.92 (s, 3H); 3.86 (s, 3H); 3.39 (s, 2H); 3.07-2.80 (m, 3H); 2.26-2.21 (m, 2H); 1.77-1.25 (m, 34H); 0.89-0.85 (t, 3H, *J*=5.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.2; 170.2; 148.0; 127.6; 126.9; 111.5; 108.7; 74.5; 56.2; 55.9; 59.4; 39.9; 33.6; 31.9; 29.9; 29.7; 29.6; 29.4; 29.3; 29.1; 29.0; 28.3; 28.0; 25.7; 25.5; 24.9; 22.6; 14.1.



39

9-((4S,5S)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-N-((3S,9aR)-octahydro-4-oxo-1H-quinolizin-3-yl)nonanamide

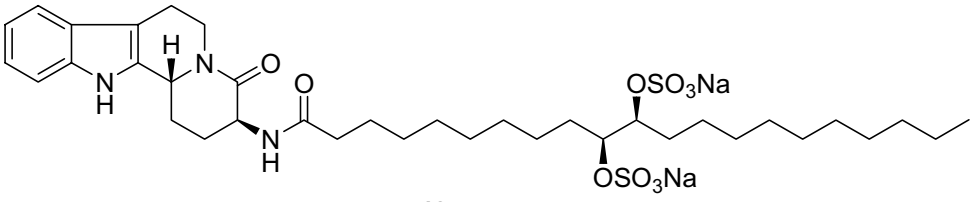
Acid **32** (71.00 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (1 mL) under argon atmosphere at room temperature. To this solution were added DMAP (2.20 mg, 0.01 mmol), DDC (61.00 mg, 0.30 mmol), and quinolizidinone **24** (15.50 mg, 0.09 mmol). The mixture was stirred vigorously. Upon completion adjudged by TLC (2 days), solvent was evaporated and the product was purified by column chromatography to give amide **39** as an oil (20.50 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H); 4.68-4.63 (m, 2H); 4.18-4.13 (m, 1H); 3.58 (s, 2H); 3.47-3.43 (m, 2H); 2.53-2.45 (m, 1H); 2.24-2.19 (t, 2H, *J*=11.5 Hz); 1.91-1.09 (m, 40H); 0.90-0.85 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.6; 157.9; 107.7; 81.0; 56.9; 51.6; 44.5; 36.9; 34.11; 33.9; 33.0; 32.6; 31.9; 29.8; 29.7; 29.6; 29.5; 27.3; 27.0; 26.1; 25.6; 25.2; 24.3; 14.12; IR (film) 3405, 3054, 2986, 2929, 1649, 1602, 1513, 1466, 1438, 1264 cm^{-1}.



40

(10S,11S)-N-((3S,9aR)-octahydro-4-oxo-1H-quinolizin-3-yl)-10,11-dihydroxyhenicosanamide

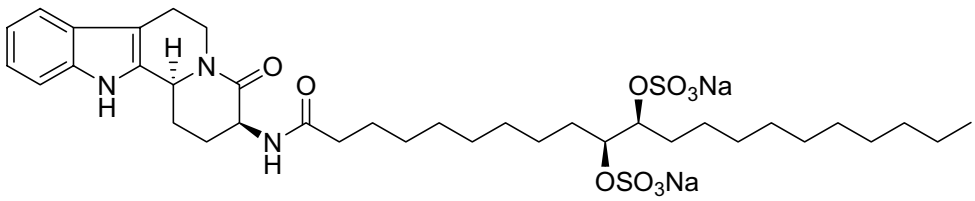
Acetonide **39** (20.50 mg, 0.04 mmol) was dissolved in 1N HCl in THF (1 mL). The mixture was stirred for 30 minutes at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a crude yellow oil. The product was purified by column chromatography to give diol **40** (5.80 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H); 4.67-4.62 (m, 2H); 4.18-4.15 (m, 1H); 3.41 (s, 3H); 2.53-2.45 (m, 2H); 2.24-2.19 (t, 2H, *J*=7.2 Hz); 1.93-1.26 (m, 40H); 0.90 -0.85 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.7; 168.0; 74.5; 56.9; 51.6; 44.5; 36.7; 33.6; 33.5; 33.0; 32.6; 31.1; 29.7; 29.1; 26.7; 26.0; 25.7; 25.5; 25.1; 25.0; 24.3; 22.7; 21.9; 14.1.



48

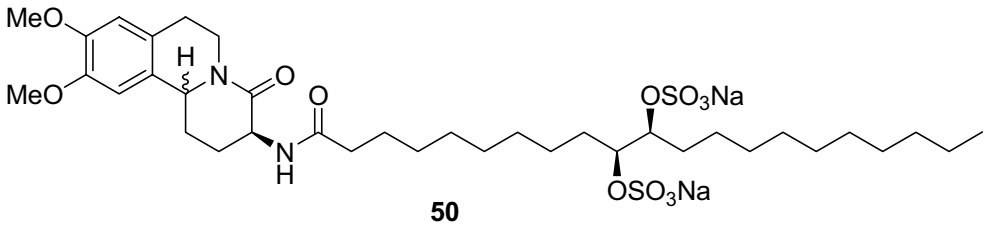
A solution of diol **34** (9.90 mg, 0.01 mmol) and sulfur trioxide-pyridine complex (57.29 mg, 0.36 mmol) in DMF (1.5 mL) was stirred at room temperature for 30 h. Then sat. aq. $NaHCO_3$ was added and the mixture was stirred for 30 min. The resulting solution was concentrated under reduced pressure. The residue was triturated with ethyl acetate and filtered. The crude material was purified by flash column chromatography to give sulfate salt **48** (1.10 mg, 8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (dd, 2H, *J*=7.7 Hz, *J*=22.54 Hz); 7.70-6.86 (td,

2H, *J*=7.0 Hz, *J*=25.8 Hz); 4.76 (m, 2H); 4.51-4.49 (m, 1H); 3.62-3.44 (m, 2H); 2.67-2.62 (m, 2H); 2.11-2.2.05 (m, 2H); 1.49-1.19 (m, 32H); 0.79-0.77 (m, 3H); $[\alpha]_D^{24.3}$+20.00° (*c* = 0.11, MeOH).



49

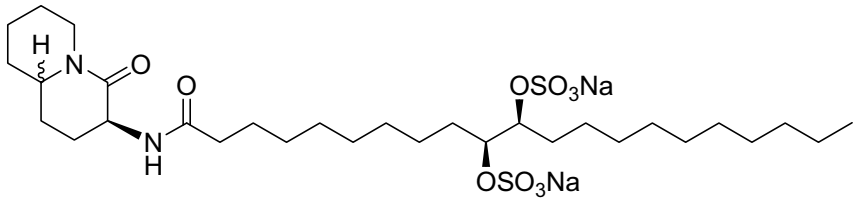
A solution of diol **36** (9.70 mg, 0.01 mmol) and sulfur trioxide-pyridine complex (57.29 mg, 0.36 mmol) in DMF (1.5 mL) was stirred at room temperature for 30 h. Then sat. aq. $NaHCO_3$ was added and the mixture was stirred for 30 min. The resulting solution was concentrated under reduced pressure. The residue was triturated with ethyl acetate and filtered. The crude material was purified by flash column chromatography to give sulfate salt **48** (0.70 mg, 5%).



50

A solution of diol **38** (7.60 mg, 0.01 mmol) and sulfur trioxide-pyridine complex (57.29 mg, 0.36 mmol) in DMF (1.5 mL) was stirred at room temperature for 30 h. Then sat. aq. $NaHCO_3$ was added and the mixture was stirred for 30 min. The resulting solution was concentrated under reduced pressure. The residue was triturated with ethyl acetate and filtered. The crude material was purified by flash column chromatography to give sulfate salt **48** (1.7 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87-6.85 (m, 2H); 4.86 (m, 2H); 4.59 (m, 1H); 3.89 (s,

3H); 3.63-3.42 (m, 3H); 3.32-3.29 (m, 2H); 2.94-2.89 (m, 3H); 2.24-1.59 (m, 42H); 0.89-0.87 (m, 3H).

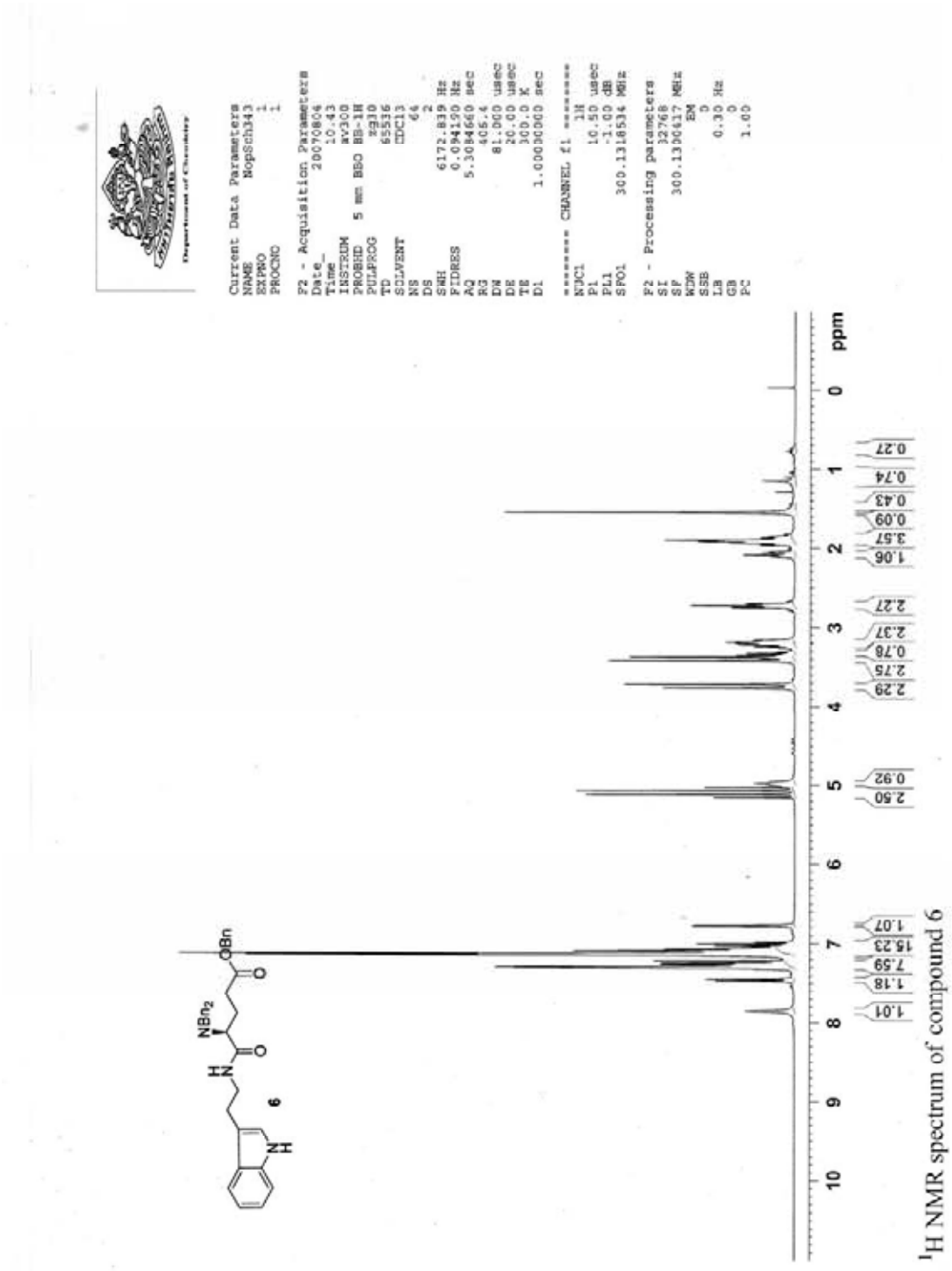


51

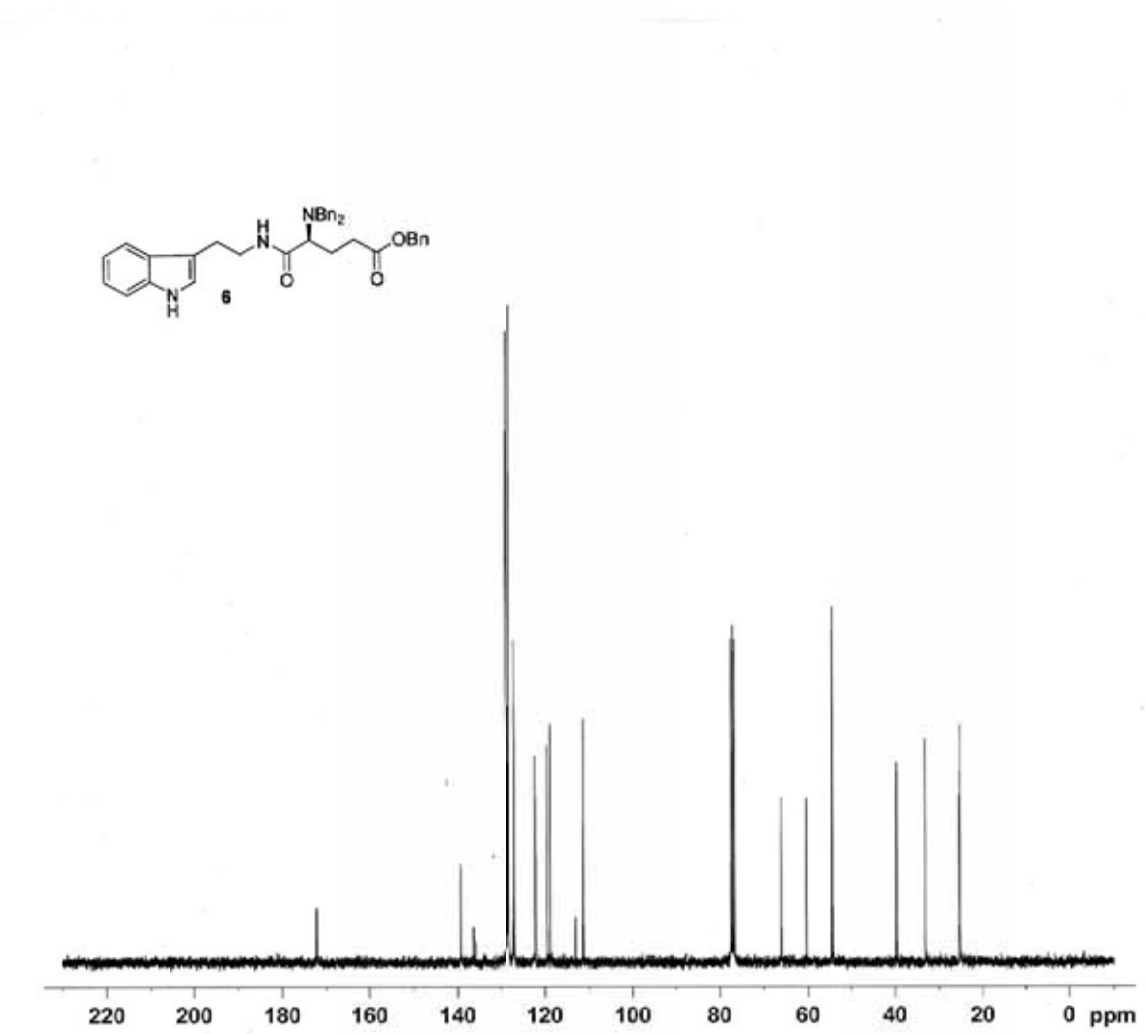
A solution of diol **40** (5.8 mg, 0.01 mmol) and sulfur trioxide-pyridine complex (57.29 mg, 0.36 mmol) in DMF (1.5 mL) was stirred at room temperature for 30 h. Then sat. aq. $NaHCO_3$ was added and the mixture was stirred for 30 min. The resulting solution was concentrated under reduced pressure. The residue was triturated with ethyl acetate and filtered. The crude material was purified by flash column chromatography to give sulfate salt **48** (2.5 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58-4.57 (m, 2H); 4.33-4.20 (m, 1H); 3.78-3.69 (m, 2H); 3.68-3.58 (m, 1H); 3.41-3.28 (m, 2H); 2.58-2.48 (m, 2H); 2.25-2.20 (t, 2H, *J*=6.8 Hz); 1.91-1.28 (m, 40H); 0.91-0.87 (t, 3H, *J*=6.2 Hz)

Appendix

^{1}H NMR and ^{13}C NMR spectra of compounds



^{1}H NMR spectrum of compound 6



^{13}C NMR spectrum of compound 6

Department of Chemistry

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PROCNO                        1

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SOLVENT                  CDCl3
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FIDRES                0.552855 Hz
AQ                    0.9044468 sec
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DE                       20.00 usec
TE                       300.0 K
D1                    1.00000000 sec
d11                   0.03000000 sec

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P1                        5.20 usec
PL1                      -3.00 dB
SFO1                75.4760505 MHz

======== CHANNEL f2 ========
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NUC2                       1H
PCPD2                    92.00 usec
PL2                      -1.00 dB
PL12                     16.00 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
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SF                 75.4677490 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.00
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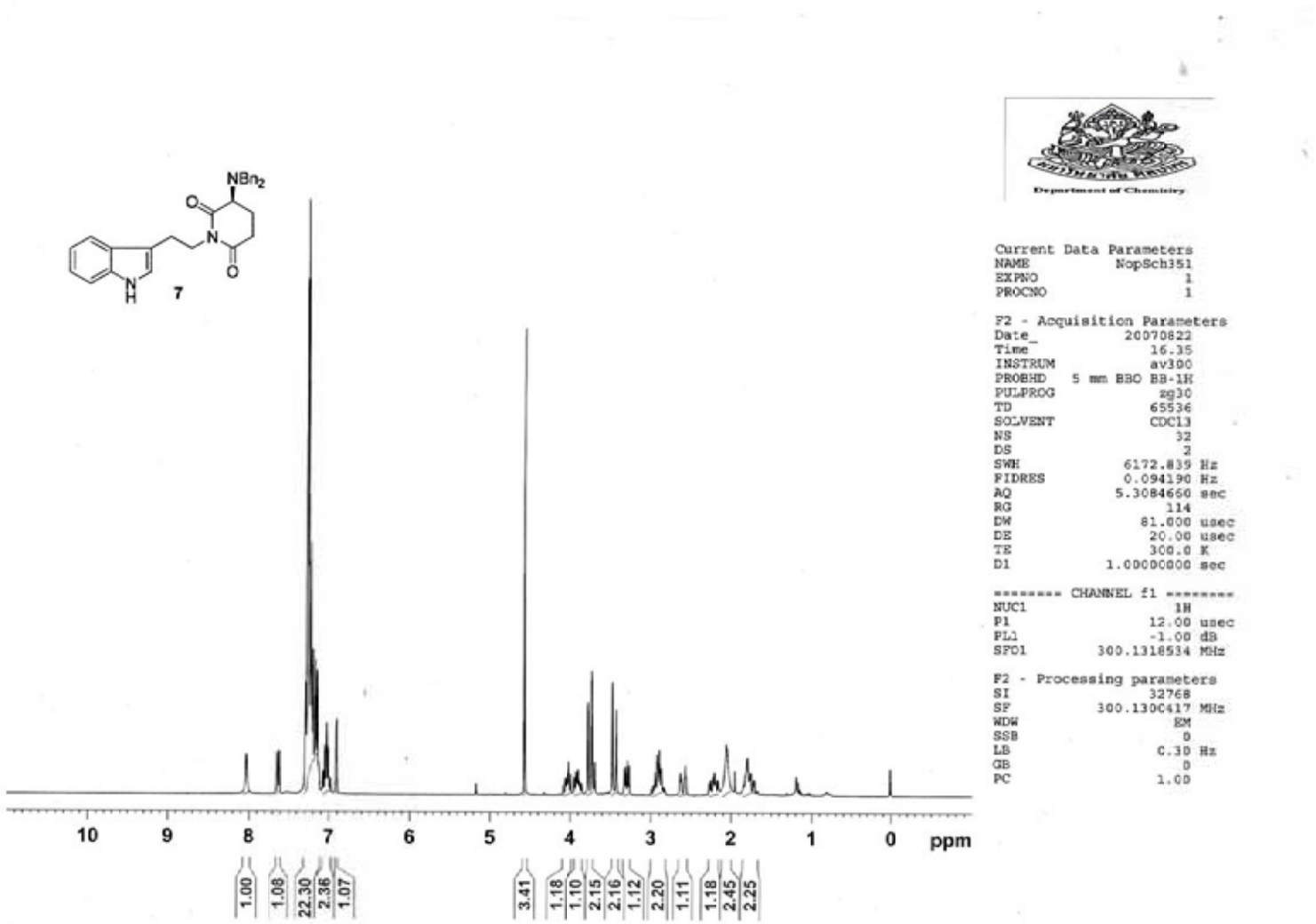
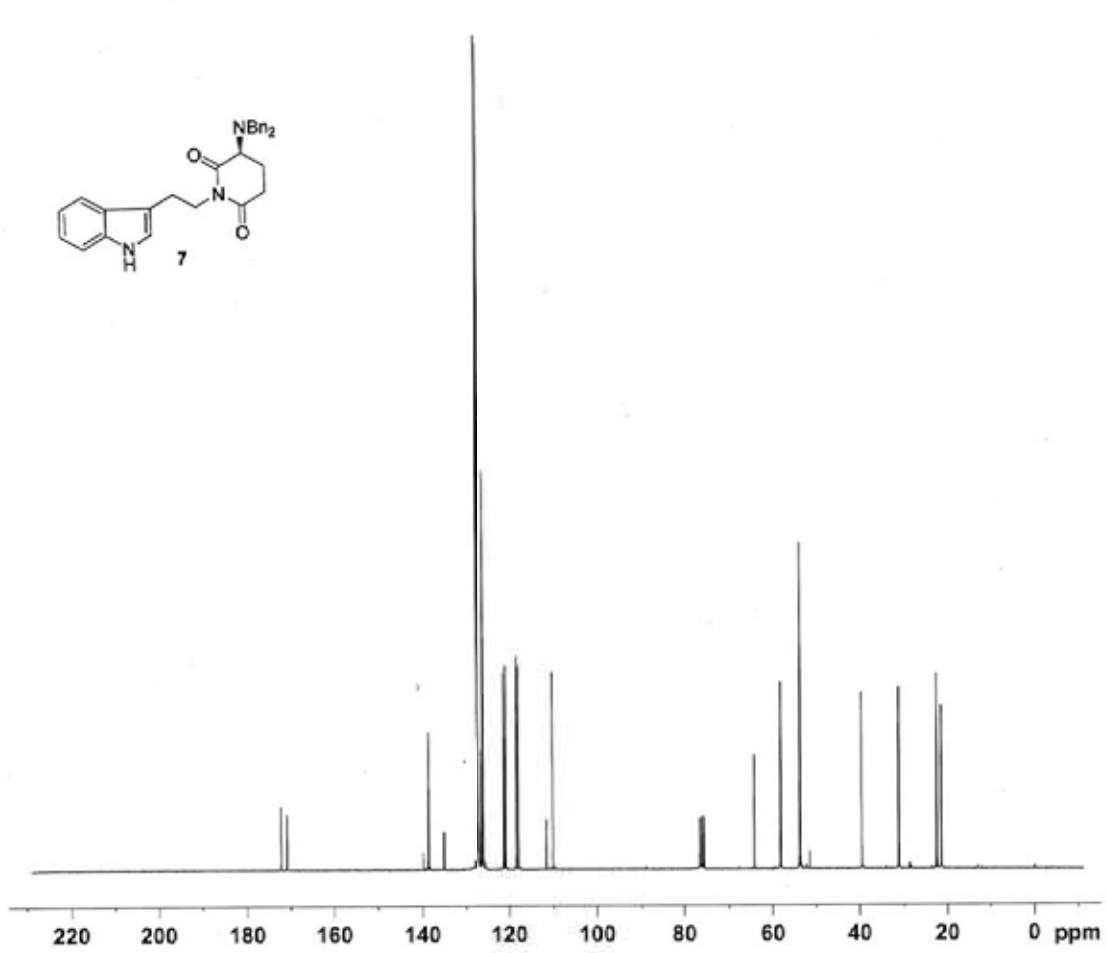


^{1}H NMR spectrum of compound 7



^{13}C NMR spectrum of compound 7

Department of Chemistry

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PROCNO                        1

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PULPROG                  zgdc
TD                      32768
SOLVENT                 CDCl3
NS                      10240
DS                          4
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FIDRES                0.552855 Hz
AQ                    0.9044468 sec
RG                        13004
DW                       27.600 usec
DE                       20.00 usec
TE                       308.0 K
D1                  1.00000000 sec
d11                 0.03000000 sec

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PL1                      -3.00 dB
SFO1                75.4760505 MHz

======== CHANNEL f2 ========
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NUC2                       1H
PCPD2                    92.00 usec
PL2                      -1.00 dB
PL12                     16.00 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
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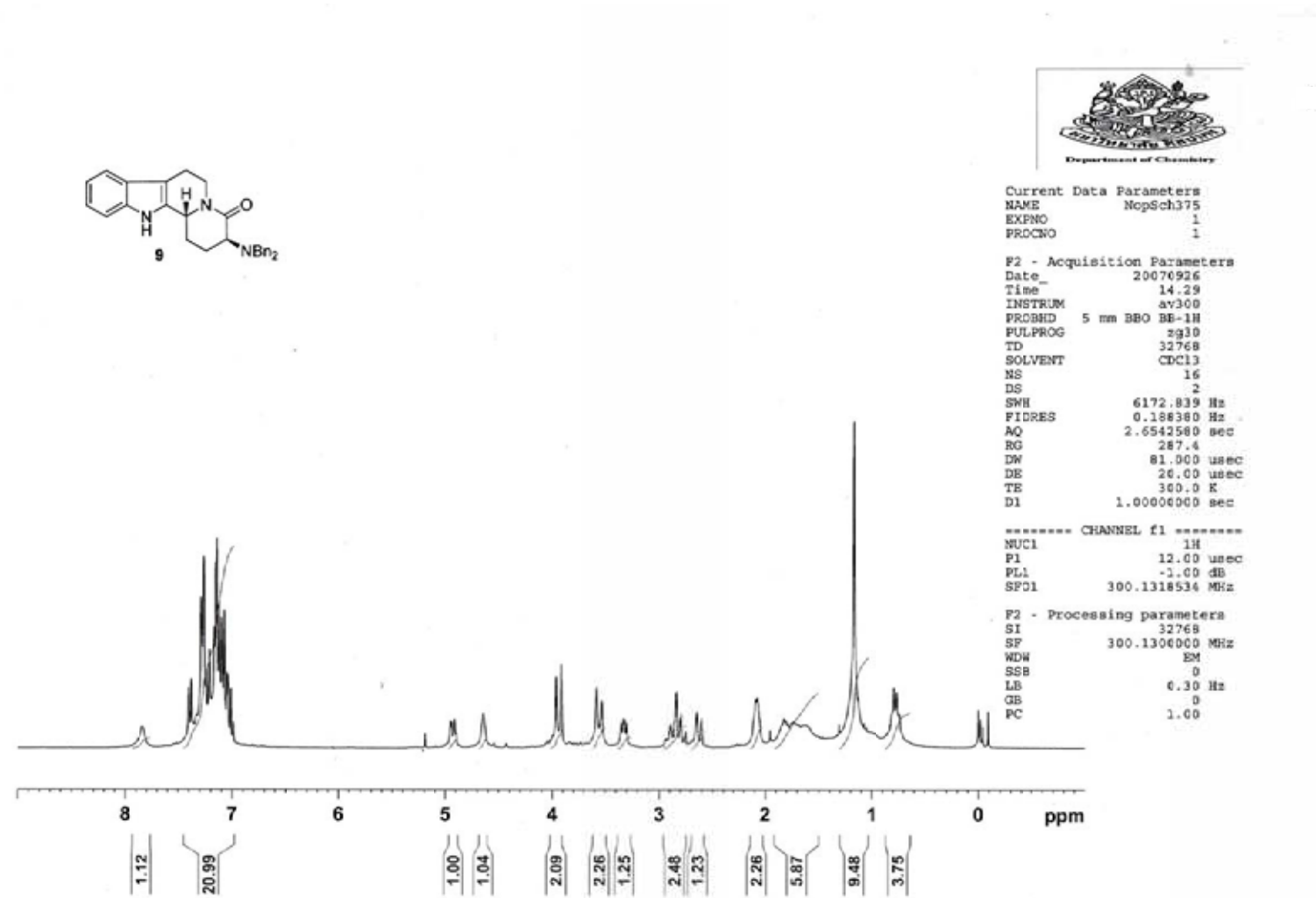
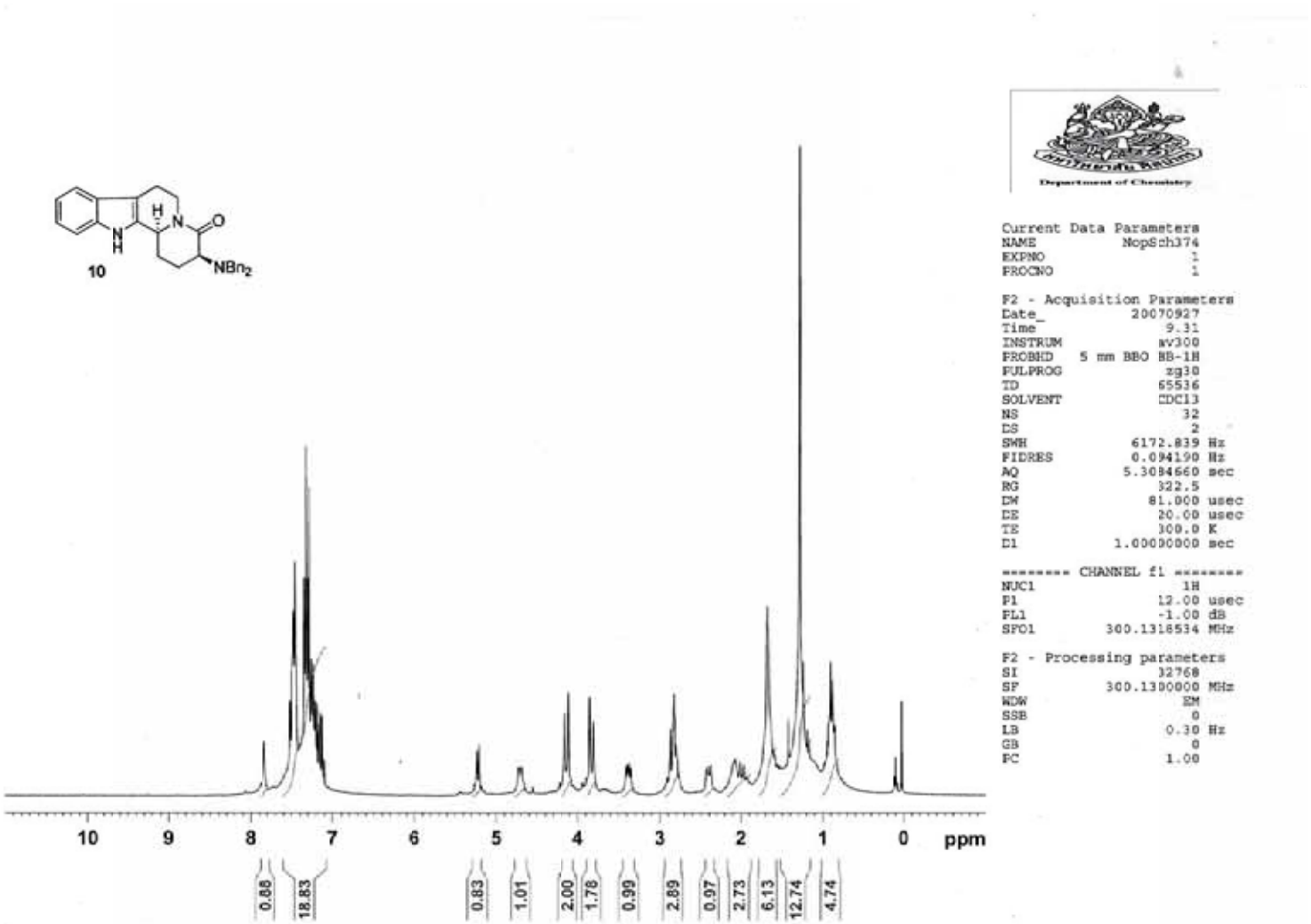
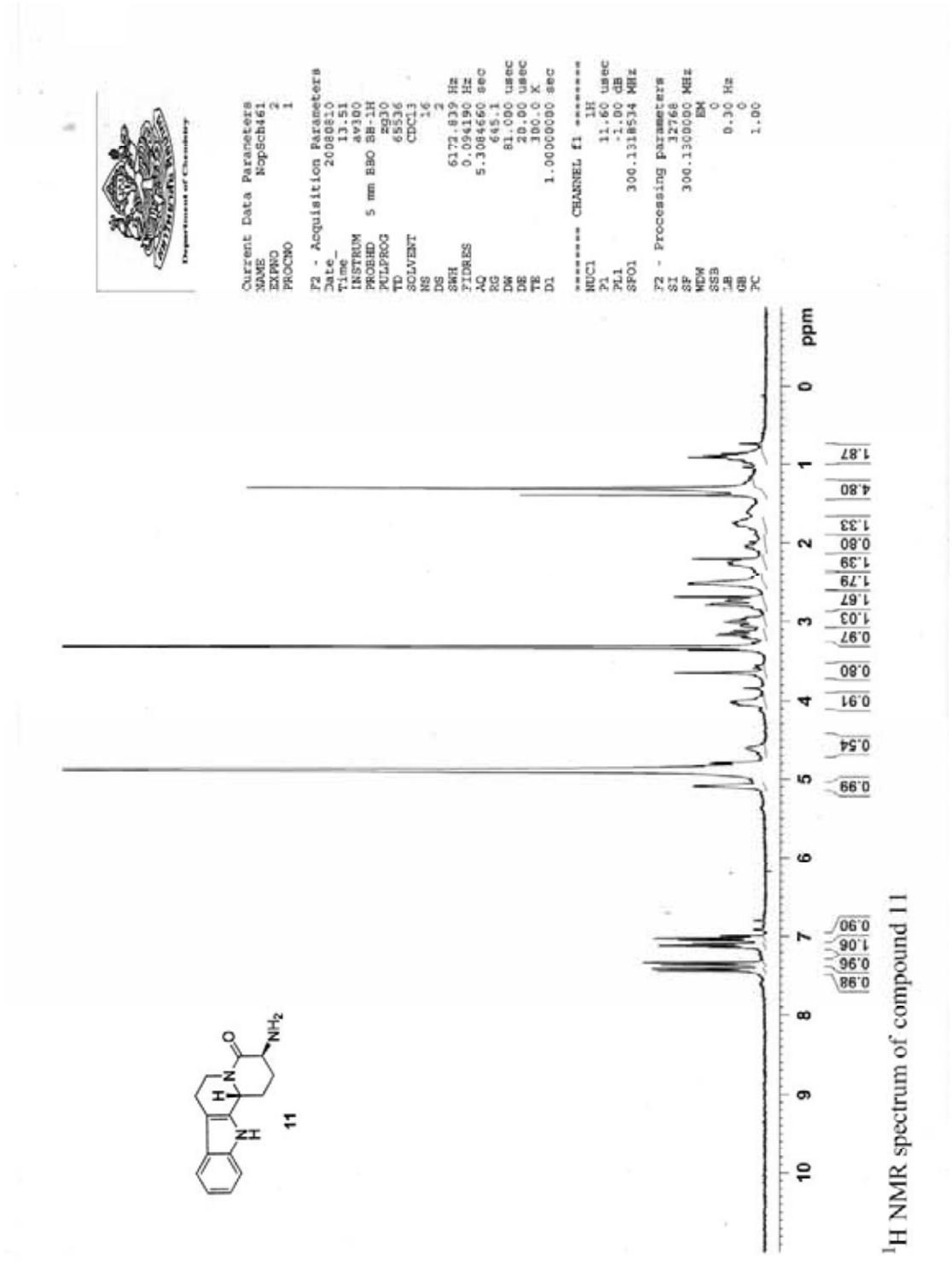


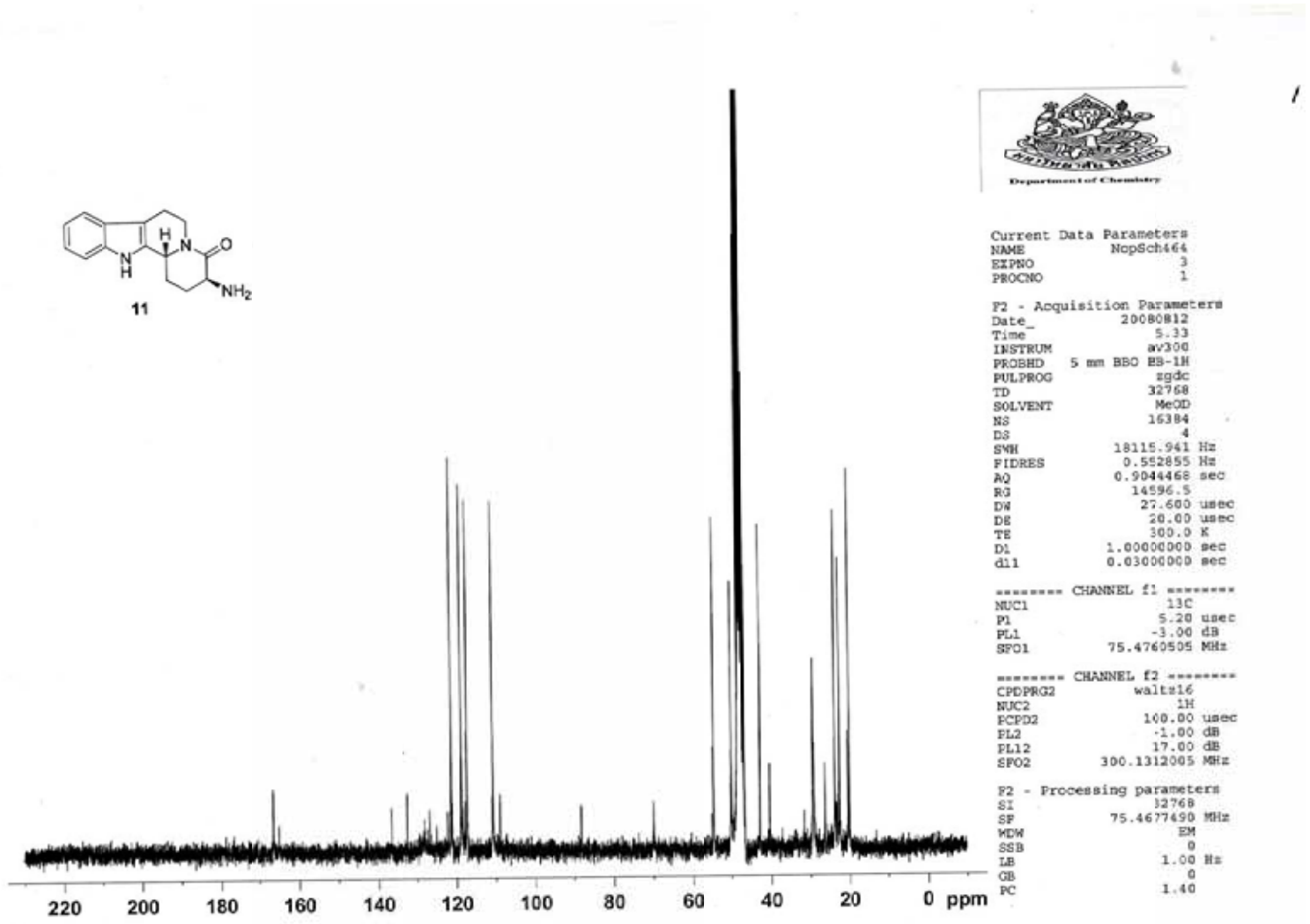
^{1}H NMR spectrum of compound 9



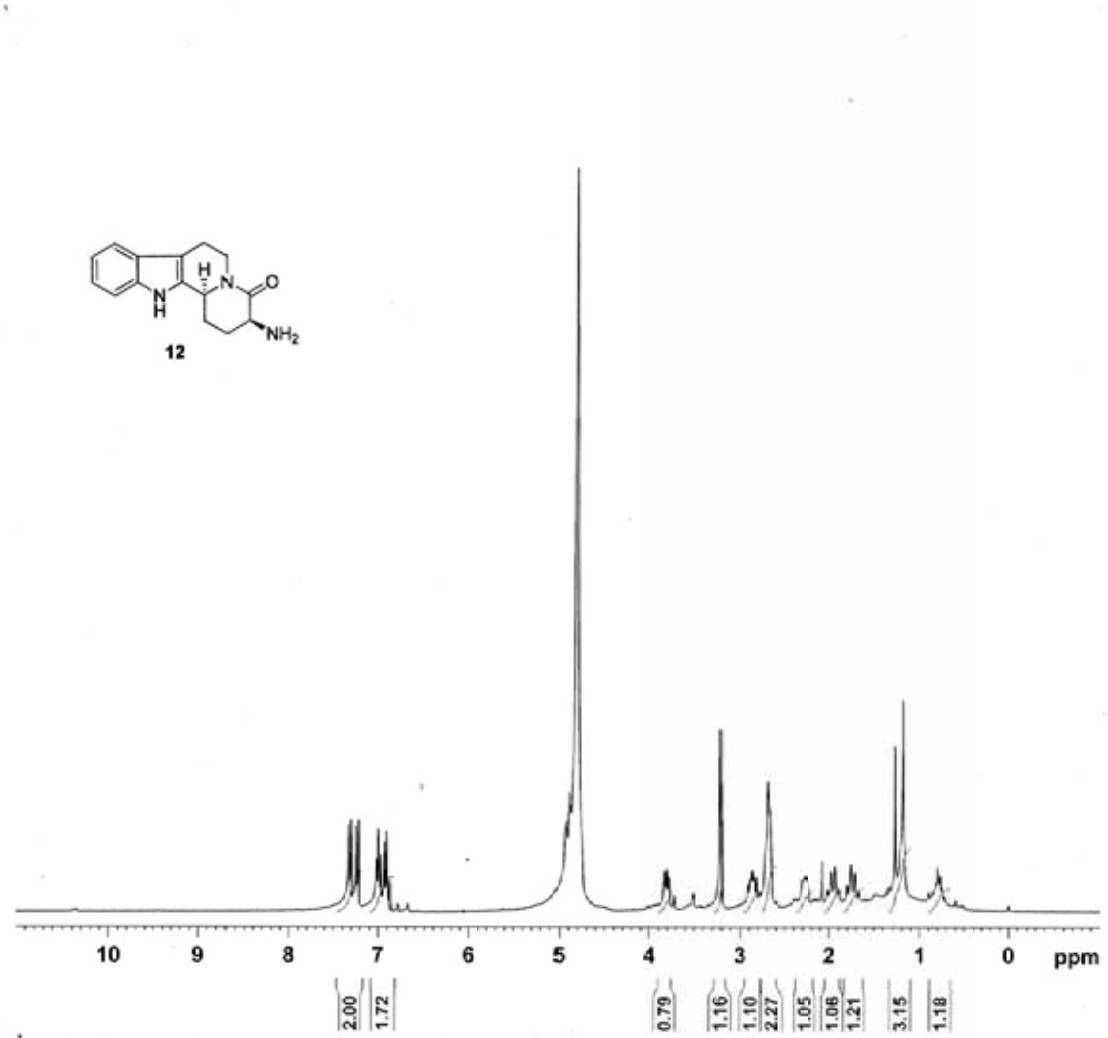
^{1}H NMR spectrum of compound 10



^{1}H NMR spectrum of compound 11



^{13}C NMR spectrum of compound 11



Department of Chemistry

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PROCNO                        1

F2 - Acquisition Parameters
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PULPROG                   zg30
TD                       32768
SOLVENT                   MeOD
NS                          16
DS                           2
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FIDRES              0.188380 Hz
AQ                  2.6542580 sec
RG                      287.4
DW                     81.000 usec
DE                     20.00 usec
TE                     300.0 K
D1                 1.00000000 sec

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PL1                    -1.00 dB
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F2 - Processing parameters
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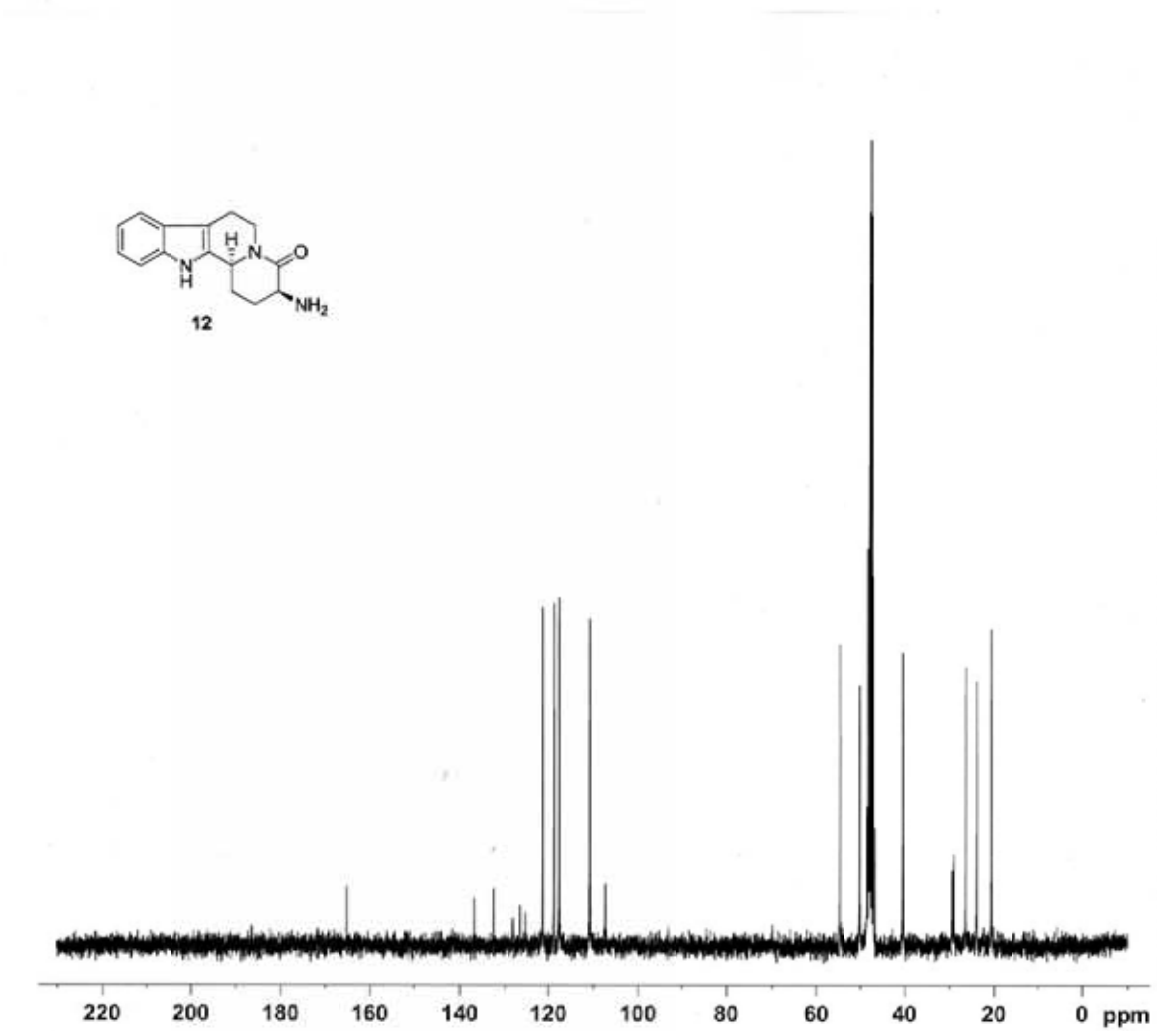
^{1}H NMR spectrum of compound 12



^{13}C NMR spectrum of compound 12

Department of Chemistry

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Current Data Parameters
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EXPNO                         2
PROCNO                        1

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Time                      15.19
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PULPROG                   zgdc
TD                       32768
SOLVENT                  CDCl3
NS                         800
DS                           4
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FIDRES                0.552855 Hz
AQ                    0.9044468 sec
RG                      10321.3
DW                       27.600 usec
DE                       20.00 usec
TE                       300.0 K
D1                  1.00000000 sec
d11                 0.03000000 sec

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P1                         5.20 usec
PL1                       -3.00 dB
SFO1                75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    100.00 usec
PL2                       -1.00 dB
PL12                      17.00 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
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SF                  75.4677490 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
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PC                        1.00
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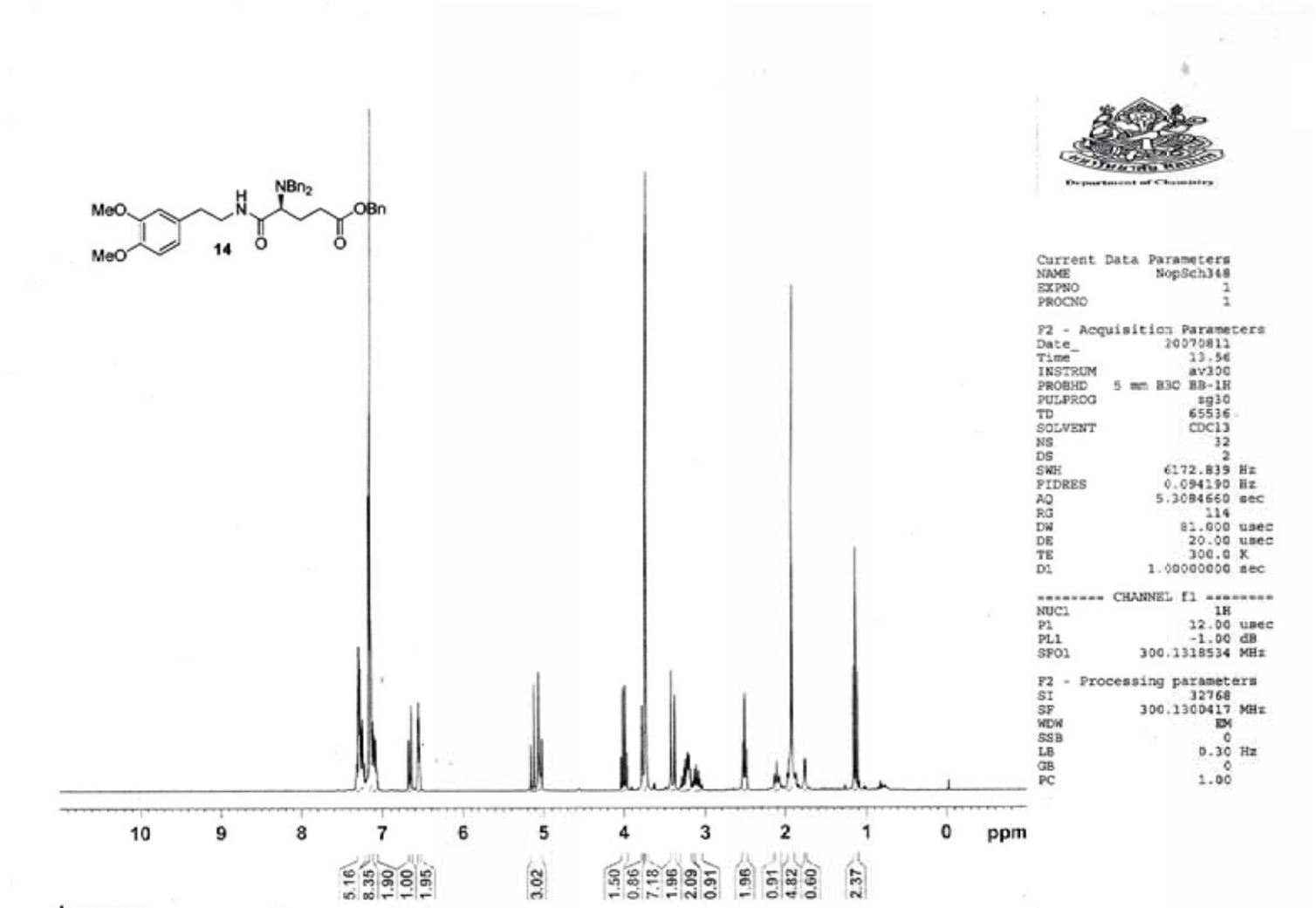

^{1}H NMR spectrum of compound 14

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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
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FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 114
DW 81.000 usec
DE 20.00 usec
TE 300.0 K
D1 1.00000000 sec

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P1 12.00 usec
PL1 -1.00 dB
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F2 - Processing parameters
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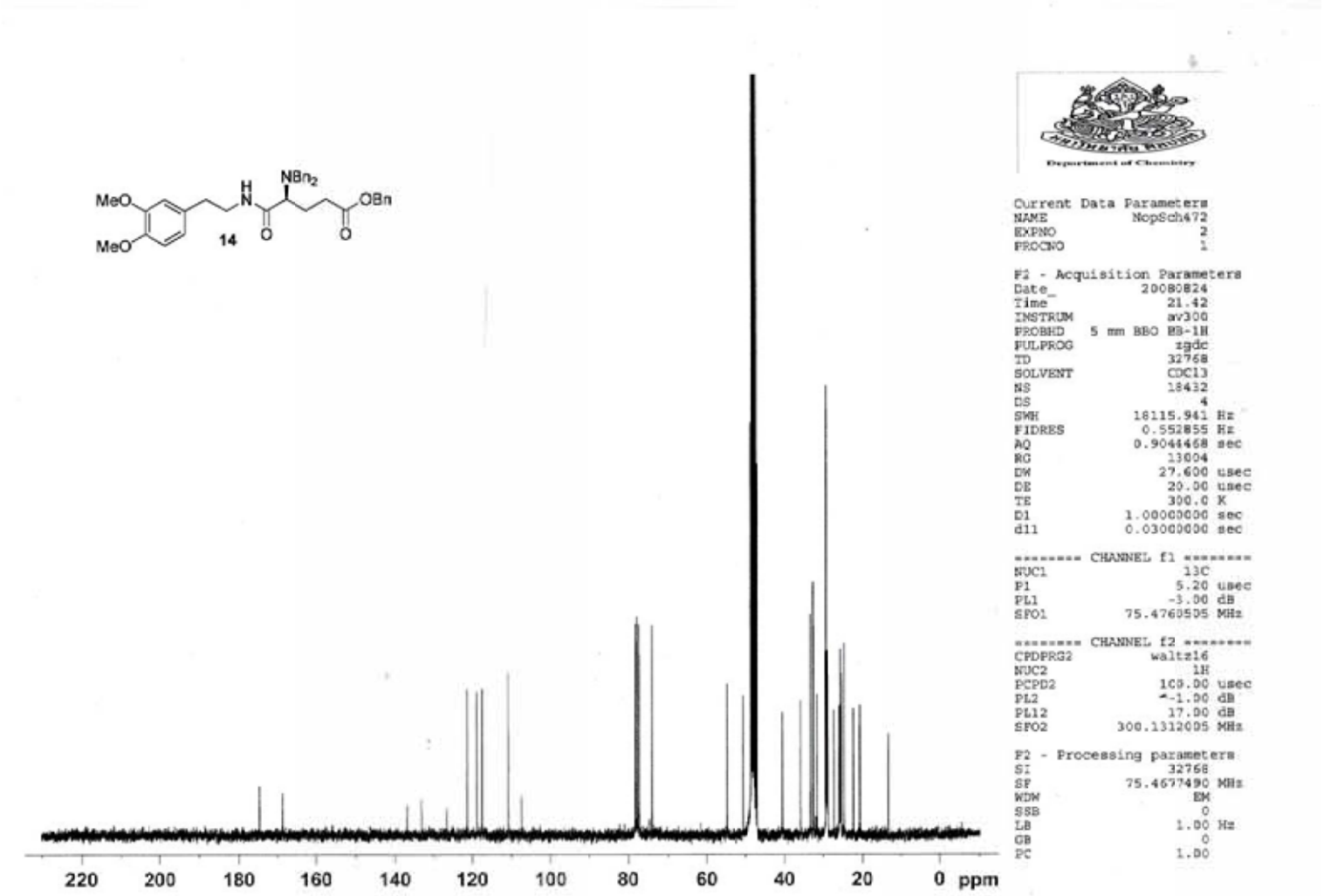
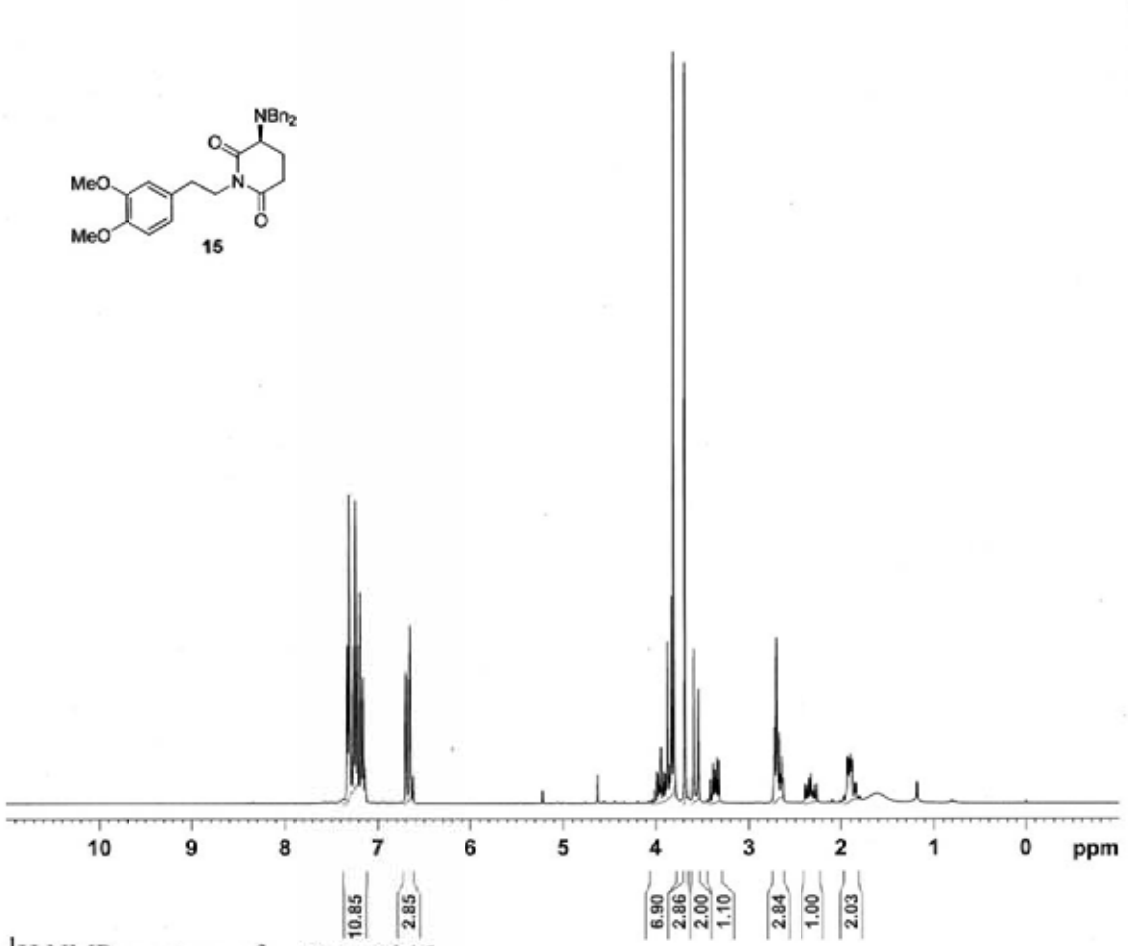


^{13}C NMR spectrum of compound 14



Department of Chemistry

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PROCNO                        1

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PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          32
DS                           2
SWH                 6172.839 Hz
FIDRES              0.094190 Hz
AQ                  5.3084660 sec
RG                       287.4
DW                     81.000 usec
DE                     20.00 usec
TE                     300.0 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
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PL1                    -1.00 dB
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F2 - Processing parameters
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PC                        1.00
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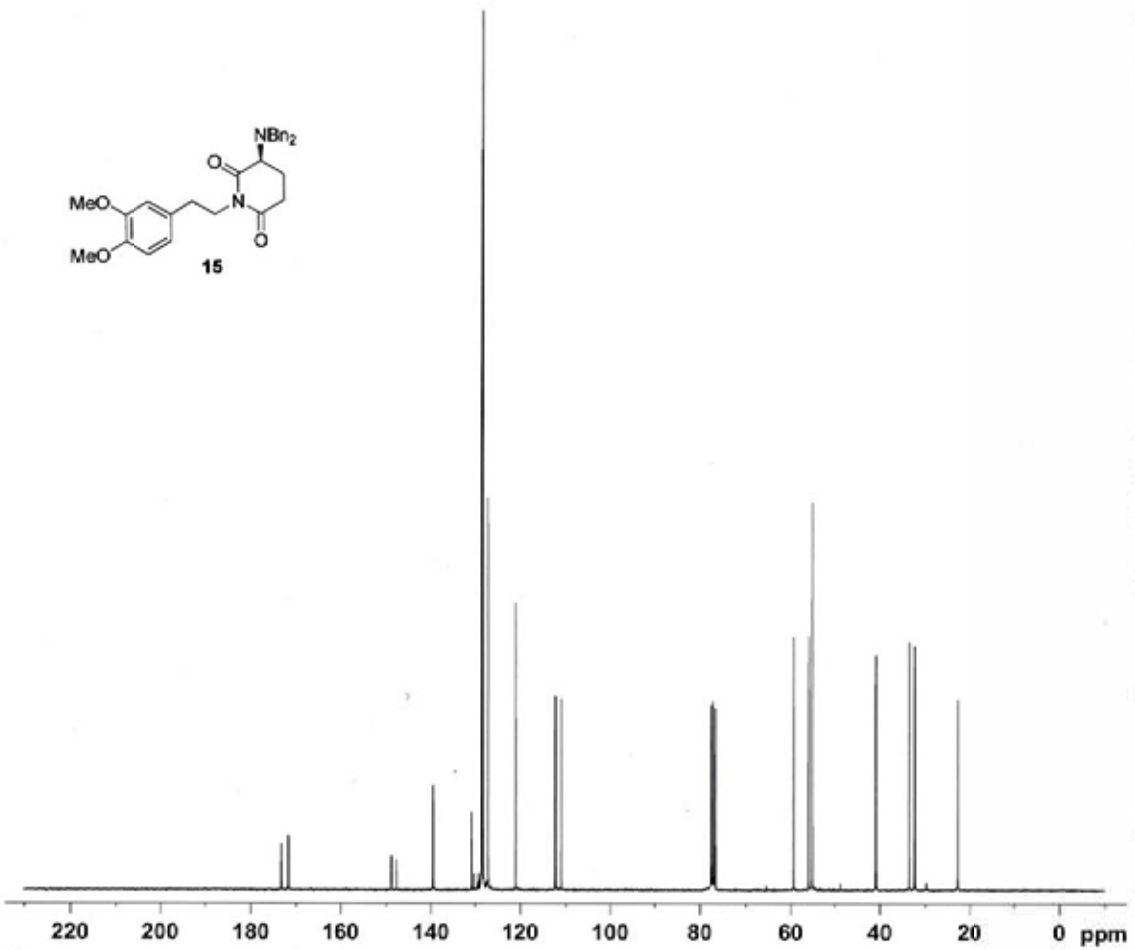
^{1}H NMR spectrum of compound 15



Department of Chemistry

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PROCNO                        1

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TD                    32768
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NS                    20480
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FIDRES                0.552855 Hz
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DE                      20.00 usec
TE                      300.0 K
D1                1.00000000 sec
d11               0.03000000 sec

======== CHANNEL f1 ========
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P1                       5.20 usec
PL1                     -3.00 dB
SFO1              75.4760505 MHz

======== CHANNEL f2 ========
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NUC2                       1H
PCPD2                   92.00 usec
PL2                     -1.00 dB
PL12                    16.00 dB
SFO2             300.1312005 MHz

F2 - Processing parameters
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PC                         1.00
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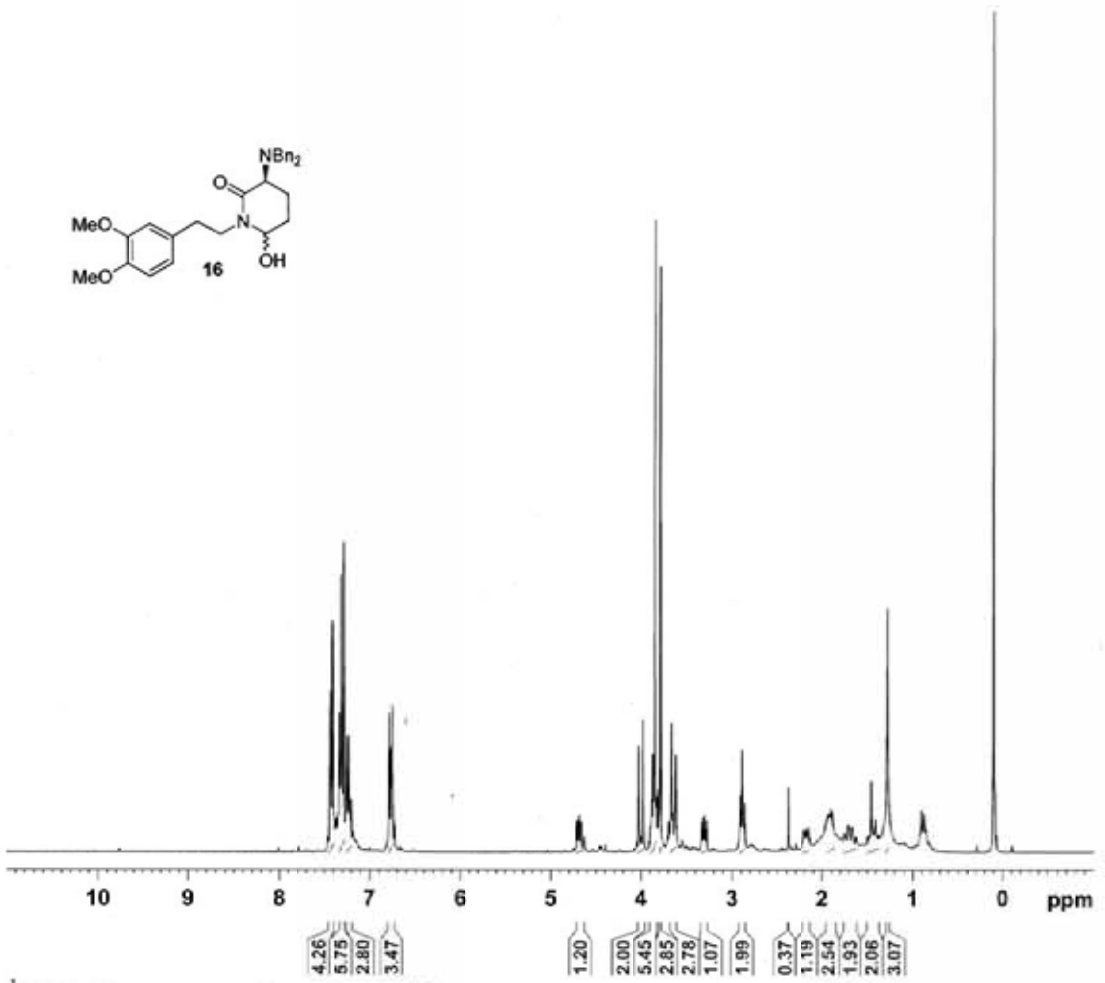
^{13}C NMR spectrum of compound 15



^{1}H NMR spectrum of compound 16

Department of Chemistry

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Current Data Parameters
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RG                     287.4
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TE                    300.0 K
D1                 1.00000000 sec

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SFO1           300.1318534 MHz

F2 - Processing parameters
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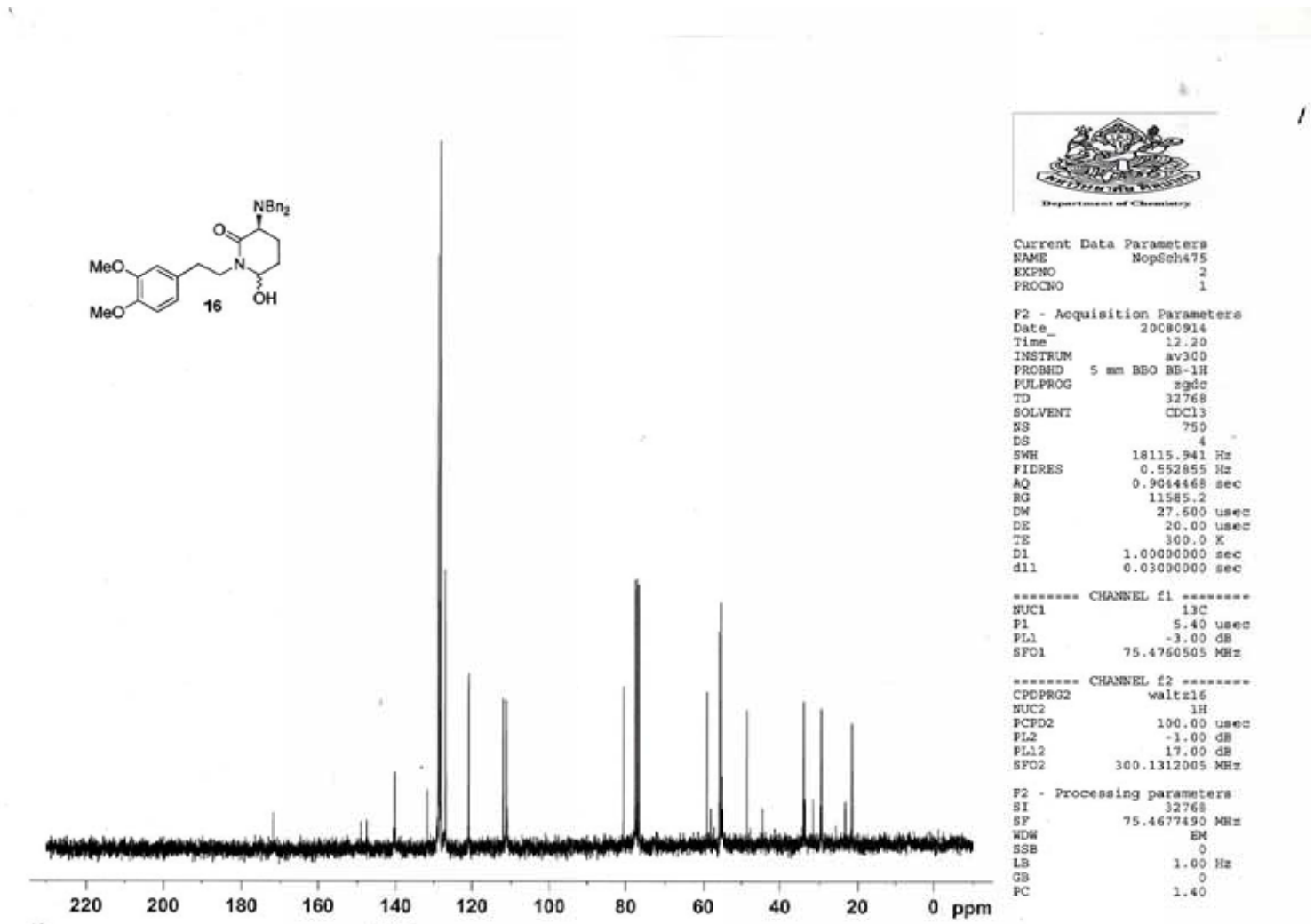
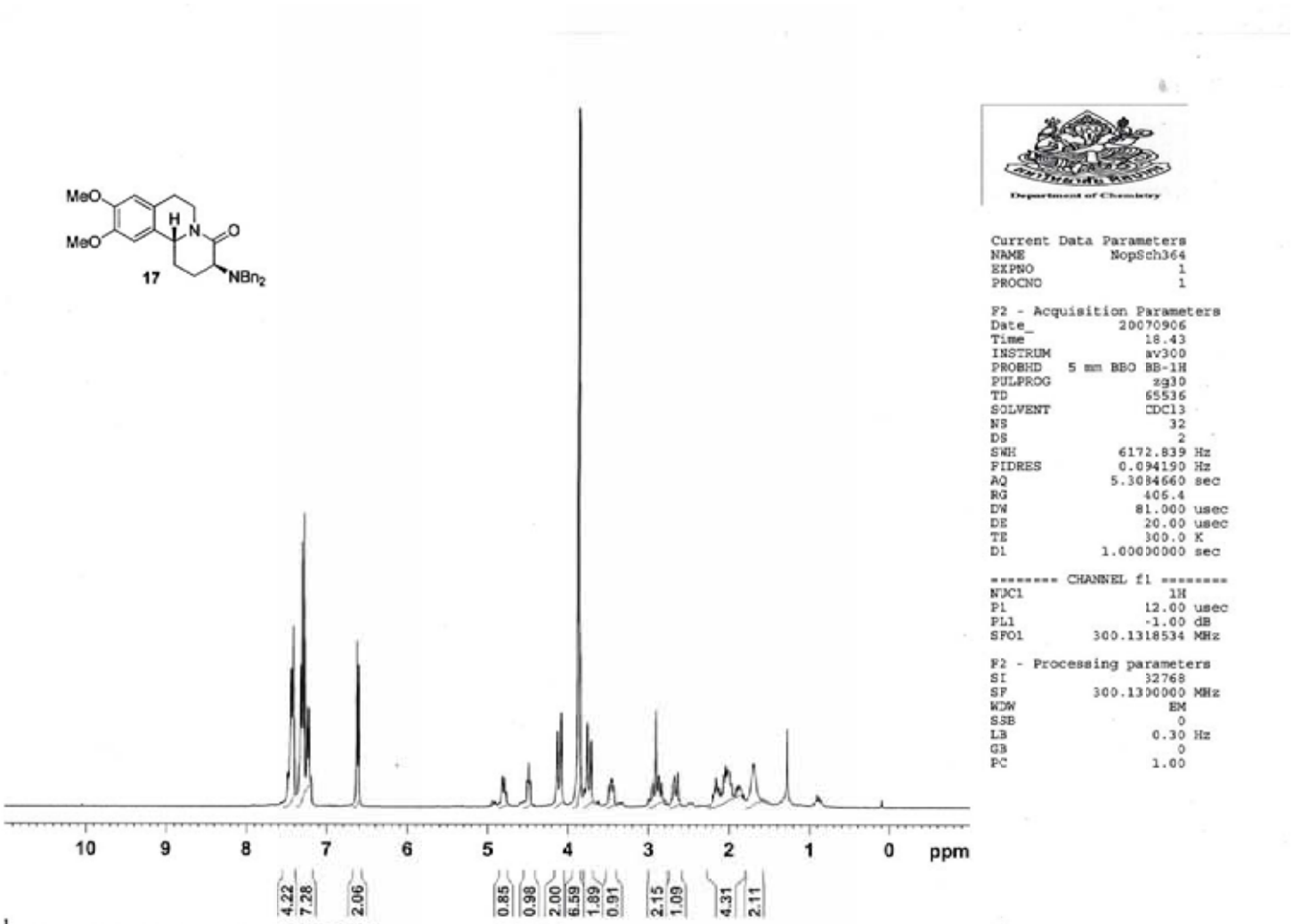
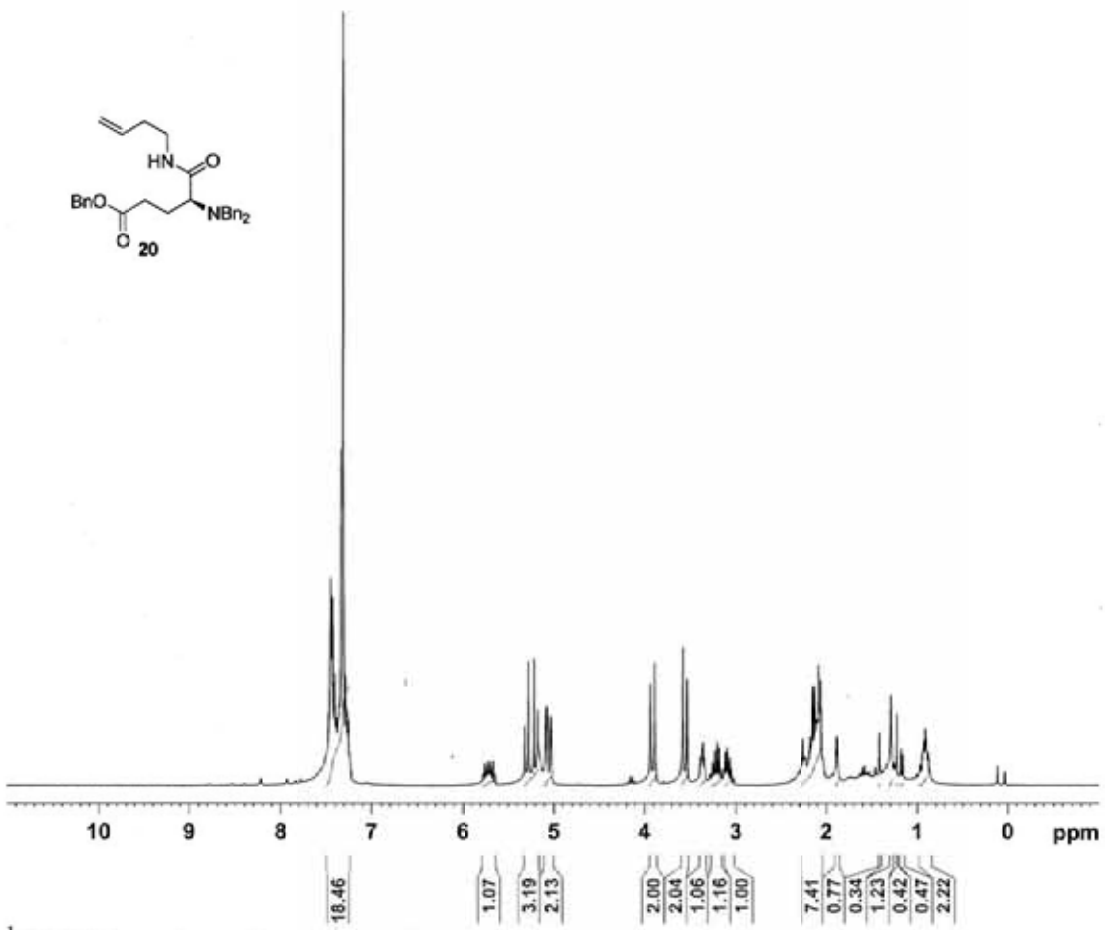
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



^{13}C NMR spectrum of compound 16



^{1}H NMR spectrum of compound 17



^{1}H NMR spectrum of compound 20

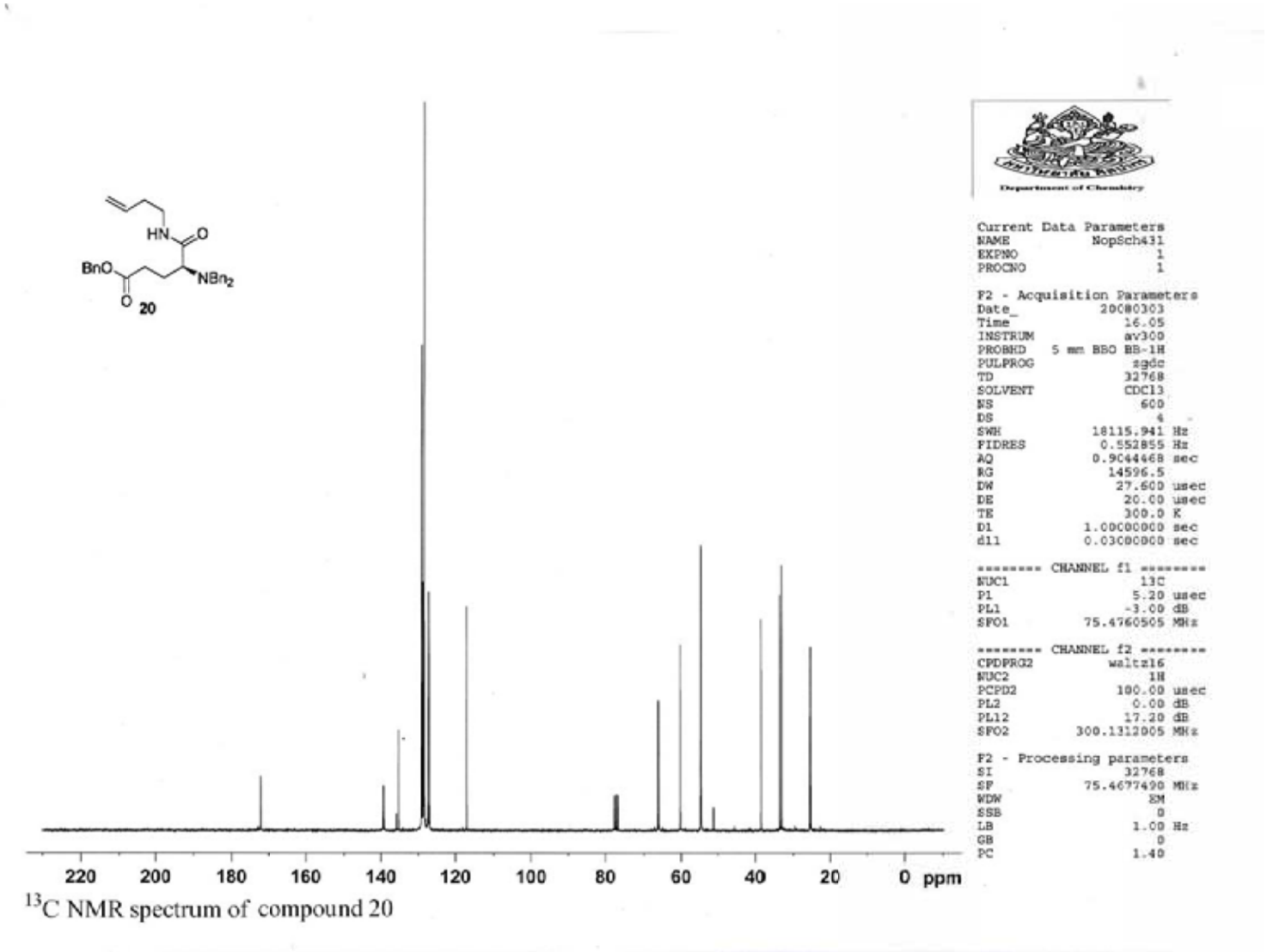
Department of Chemistry

```
Current Data Parameters
NAME                  NopSch381
EXPNO                         1
PROCNO                        1

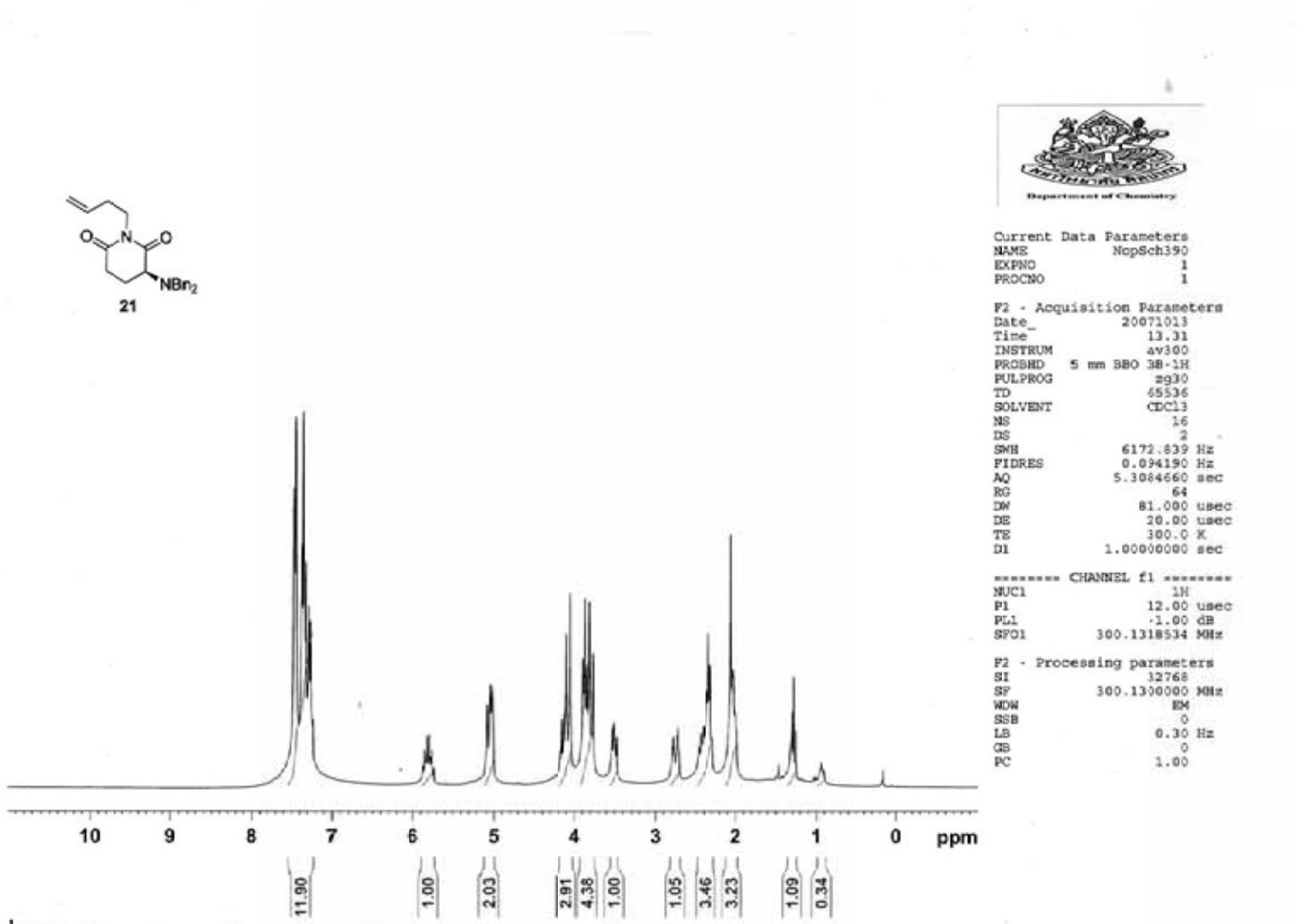
F2 - Acquisition Parameters
Date_               20071004
Time                    16.00
INSTRUM                 av300
PROBHD     5 mm BBO BB-1H
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 6172.839 Hz
FIDRES              0.094190 Hz
AQ                  5.3084560 sec
RG                      143.7
DW                     81.000 usec
DE                     20.00 usec
TE                     300.0 K
D1                  1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.00 usec
PL1                     -1.00 dB
SFO1               300.1318534 MHz

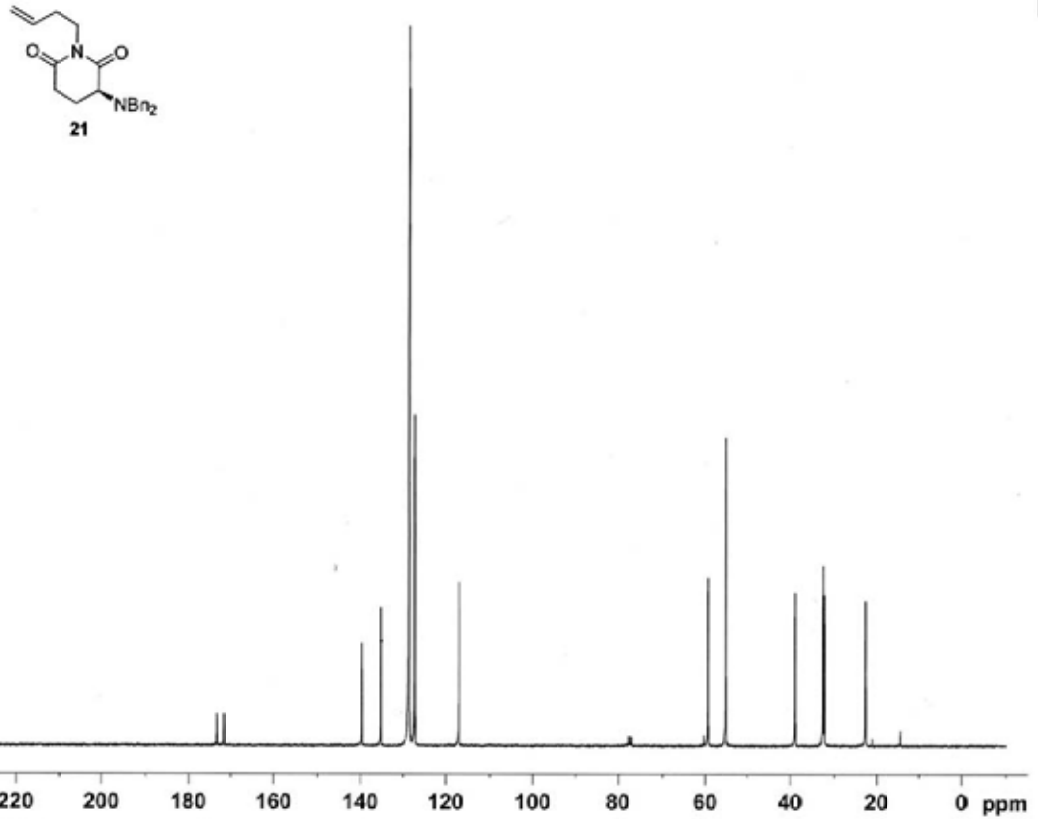
F2 - Processing parameters
SI                        32768
SF                 300.1300000 MHz
WDW                          EM
SSB                           0
LB                       0.30 Hz
GB                            0
PC                         1.00
```



^{13}C NMR spectrum of compound 20



^{1}H NMR spectrum of compound 21



^{13}C NMR spectrum of compound 21

Department of Chemistry

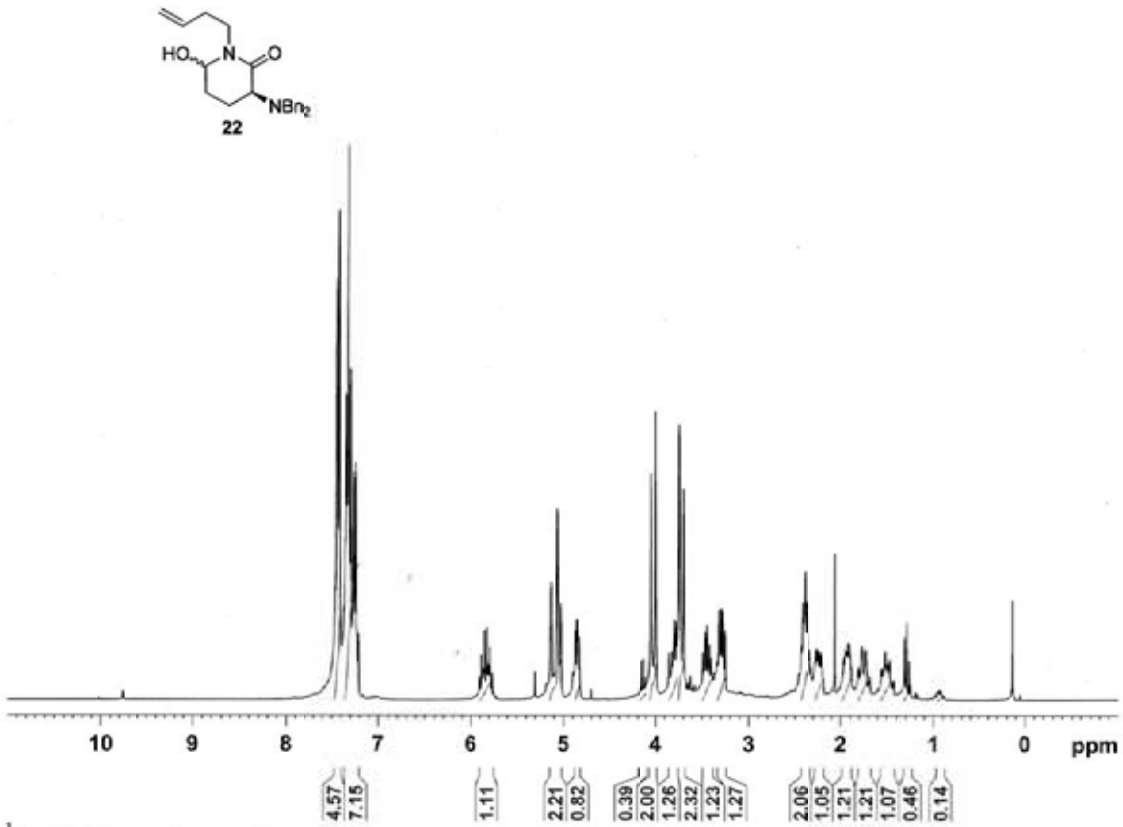
```
Current Data Parameters
NAME                  NopSch390
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20071013
Time                      13.44
INSTRUM                    av300
PROBHD    5 mm BBO BB-1H
PULPROG                    zgdc
TD                        32768
SOLVENT                   CDCl3
NS                          250
DS                            4
SWH                   18115.941 Hz
FIDRES                0.552855 Hz
AQ                    0.9044468 sec
RG                         8192
DW                       27.600 usec
DE                       20.00 usec
TE                       300.0 K
D1                    1.00000000 sec
d11                   0.03000000 sec

======== CHANNEL f1 ========
NUC1                        13C
P1                         5.20 usec
PL1                       -3.00 dB
SFO1                 75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     92.00 usec
PL2                       -1.00 dB
PL12                      16.00 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
SI                        32768
SF                   75.4677490 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.00
```



^{1}H NMR spectrum of compound 22

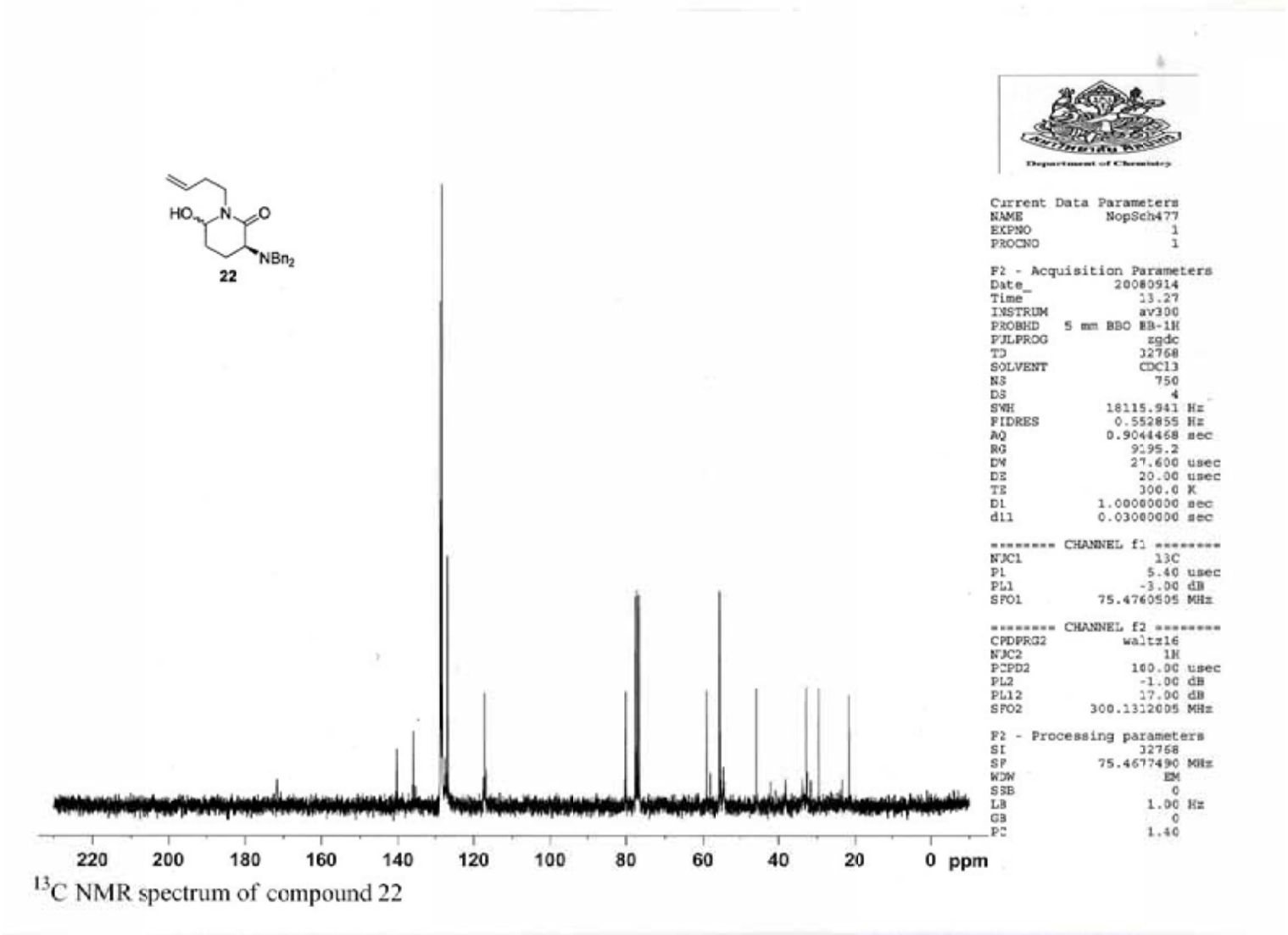
Department of Chemistry

```
Current Data Parameters
NAME                  NopSch398
EXPNO                         1
PROCNO                        1

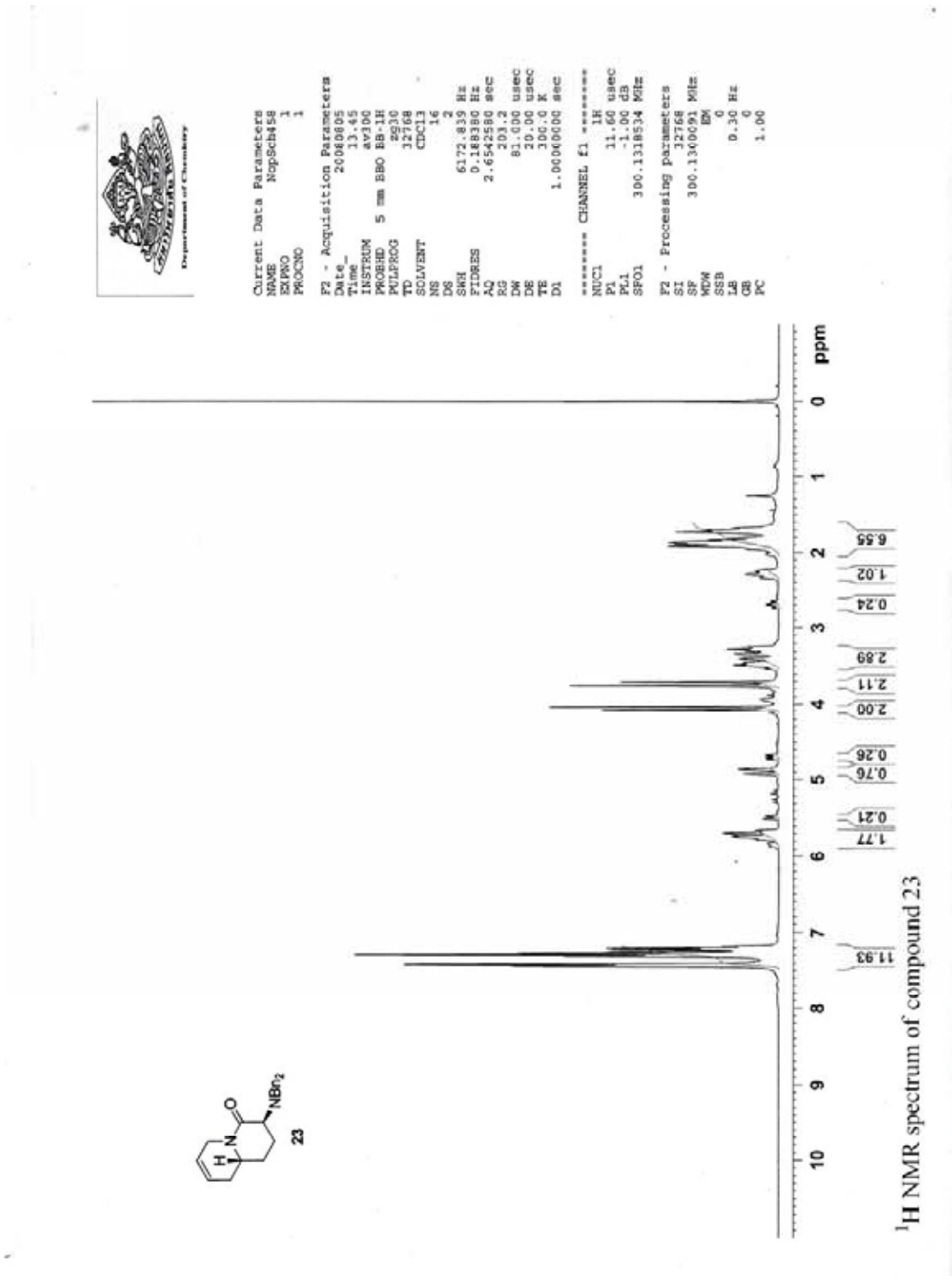
F2 - Acquisition Parameters
Date_                  20071030
Time                      16.23
INSTRUM                   av300
PROBHD    5 mm BBO BB-1H
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 6172.839 Hz
FIDRES              0.094190 Hz
AQ                  5.3084660 sec
RG                         71.8
DW                    81.000 usec
DE                    20.00 usec
TE                      300.0 K
D1                 1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                    12.00 usec
PL1                    -1.00 dB
SFO1              300.1318534 MHz

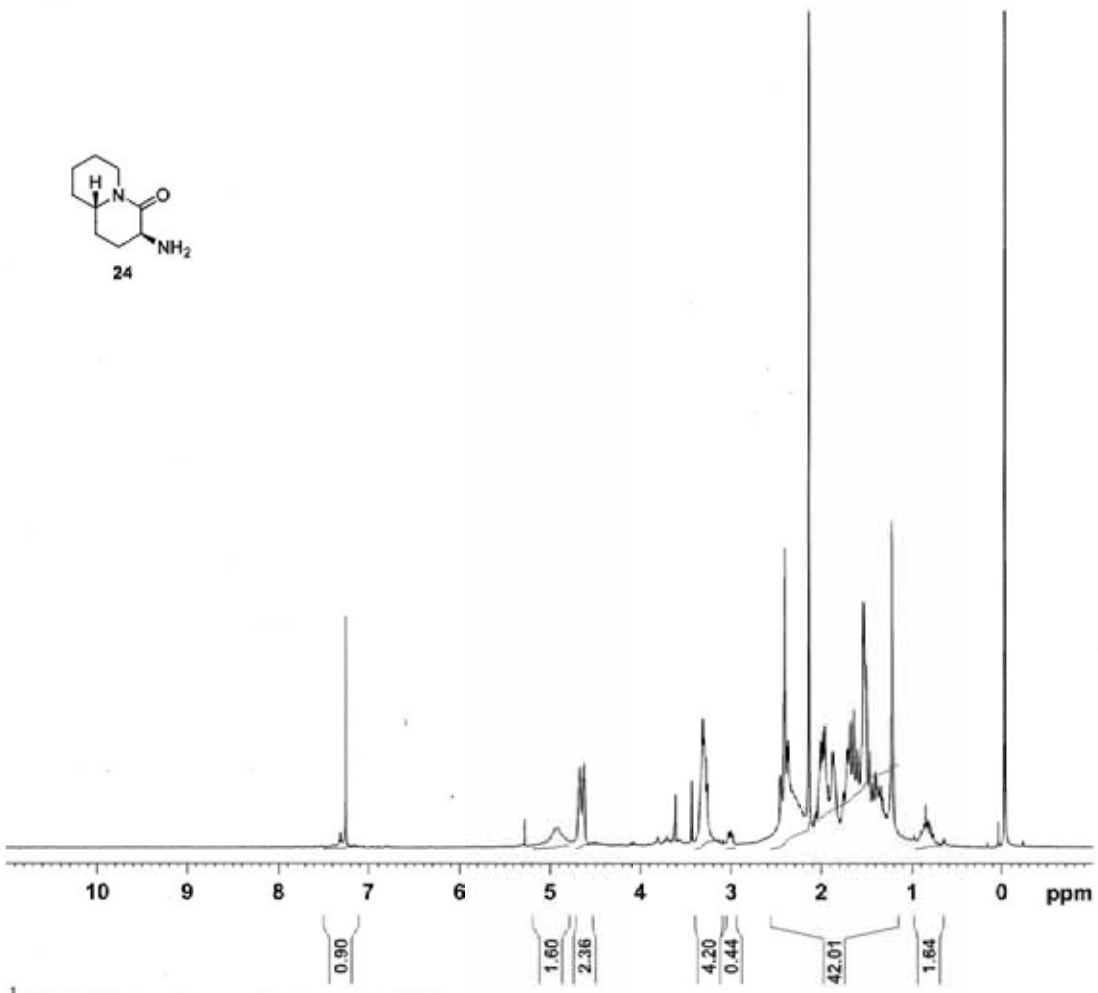
F2 - Processing parameters
SI                       32768
SF                300.1300000 MHz
WDW                         EM
SSB                          0
LB                     0.30 Hz
GB                           0
PC                        1.00
```



^{13}C NMR spectrum of compound 22



^{1}H NMR spectrum of compound 23



Department of Chemistry

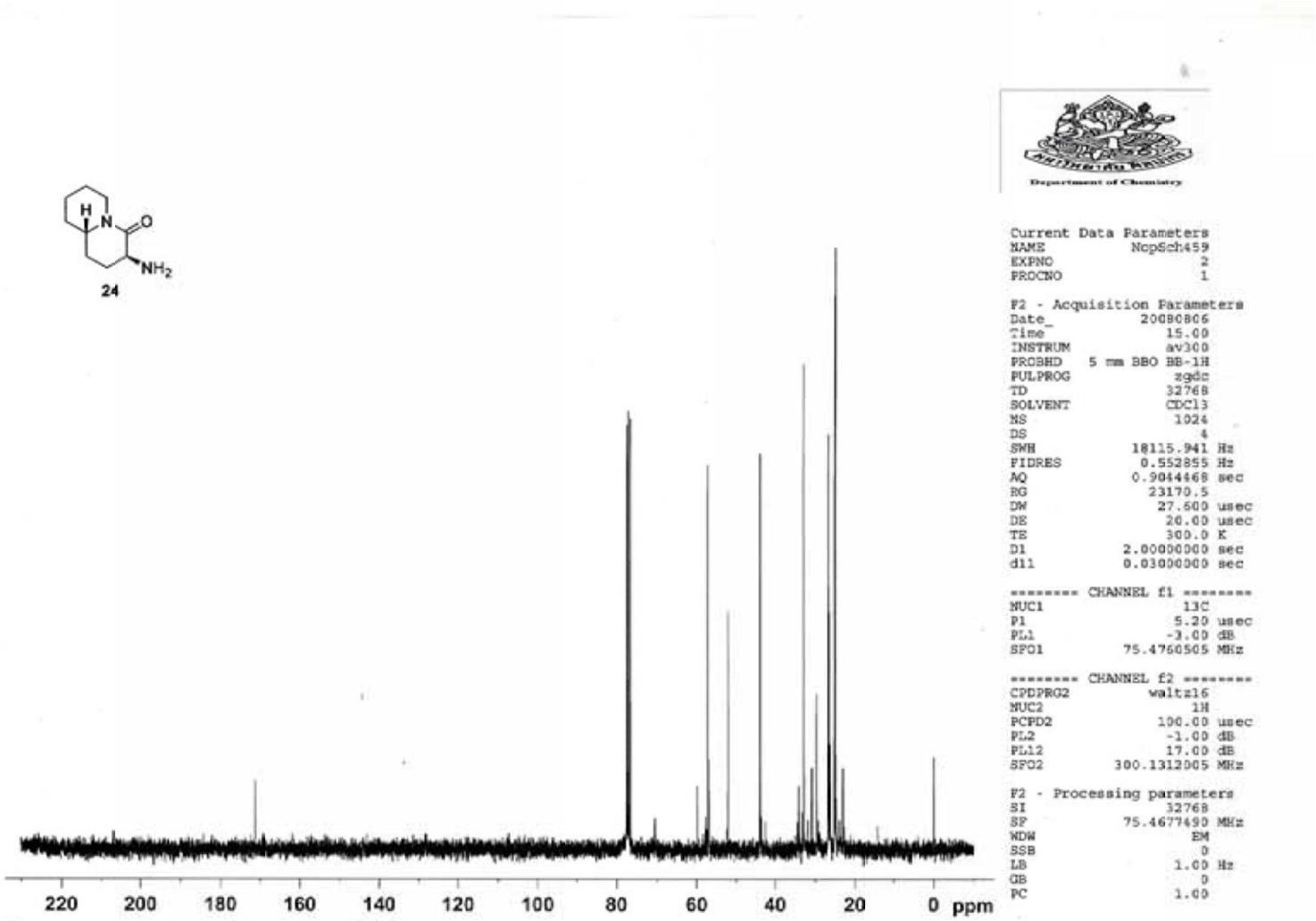
```
Current Data Parameters
NAME                  NopSch459
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20080806
Time                      14.07
INSTRUM                   av300
PROBHD    5 mm BBO BB-1H
PULPROG                    zg30
TD                        32768
SOLVENT                   CDCl3
NS                           48
DS                            2
SWH                    6172.839 Hz
FIDRES                 0.188360 Hz
AQ                     2.6542580 sec
RG                          181
DW                        81.000 usec
DE                        20.00 usec
TE                        300.0 K
D1                    1.00000000 sec

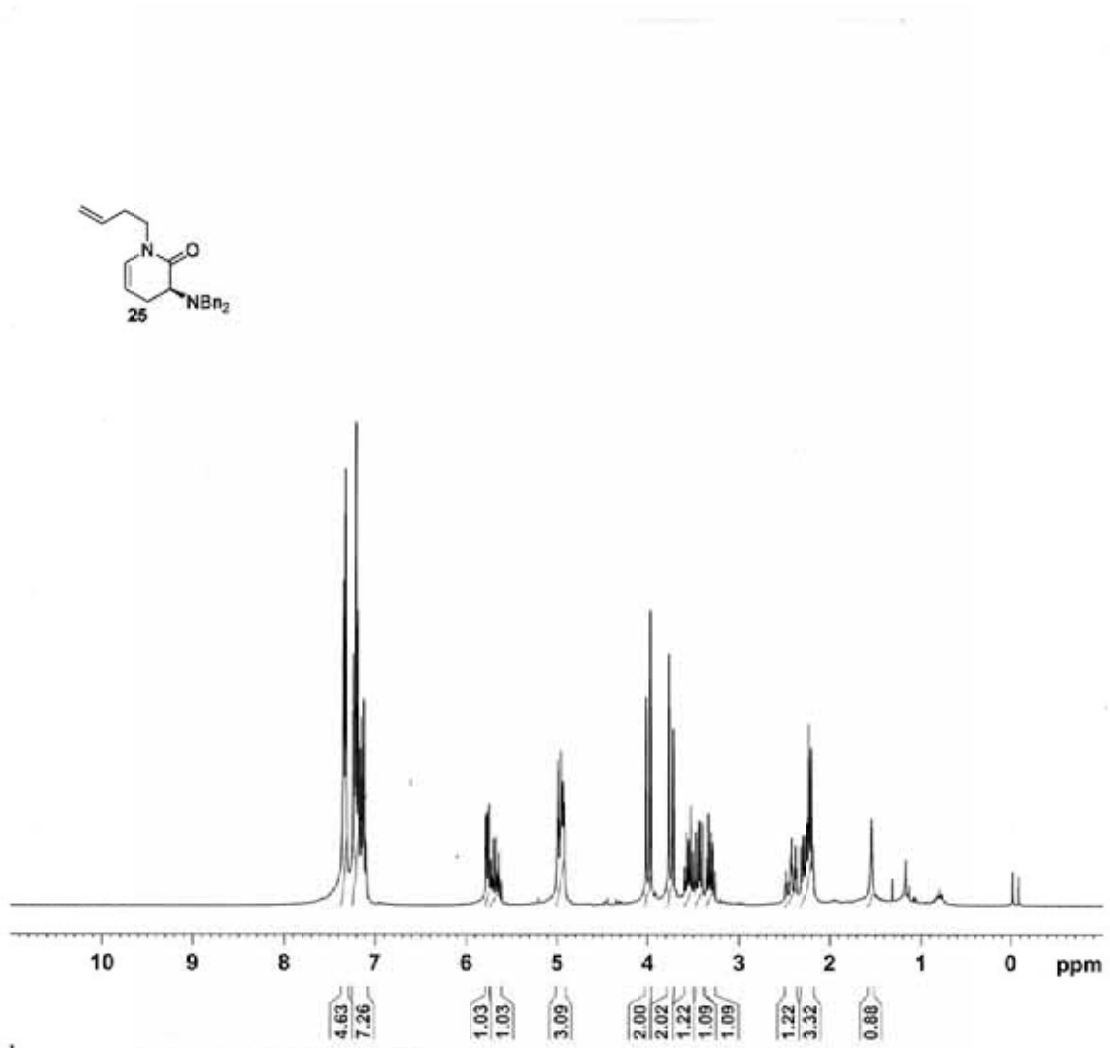
======== CHANNEL f1 ========
NUC1                         1H
P1                        11.60 usec
PL1                       -1.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                        32768
SF                  300.1300091 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

^{1}H NMR spectrum of compound 24



^{13}C NMR spectrum of compound 24



Department of Chemistry

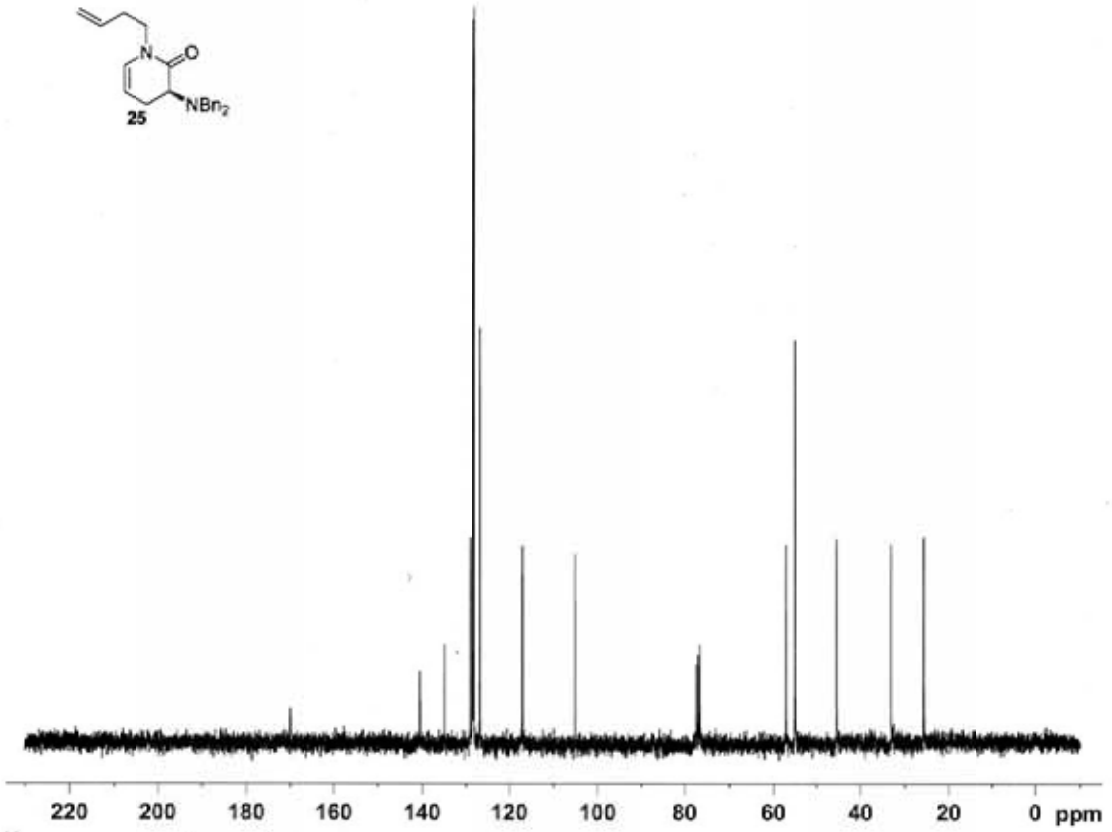
```
Current Data Parameters
NAME                  NopSch396
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20071025
Time                      14.49
INSTRUM                   av300
PROBHD    5 mm BBO BB-1H
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   6172.839 Hz
FIDRES                0.094190 Hz
AQ                    5.3084660 sec
RG                         256
DW                      81.000 usec
DE                      20.00 usec
TE                        300.0 K
D1                   1.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                       12.00 usec
PL1                      -1.00 dB
SFO1                300.1318534 MHz

F2 - Processing parameters
SI                        32768
SF                  300.1300364 MHz
WDW                          EM
SSB                           0
LB                         0.30 Hz
GB                            0
PC                         1.00
```

^{1}H NMR spectrum of compound 25



^{13}C NMR spectrum of compound 25

Department of Chemistry

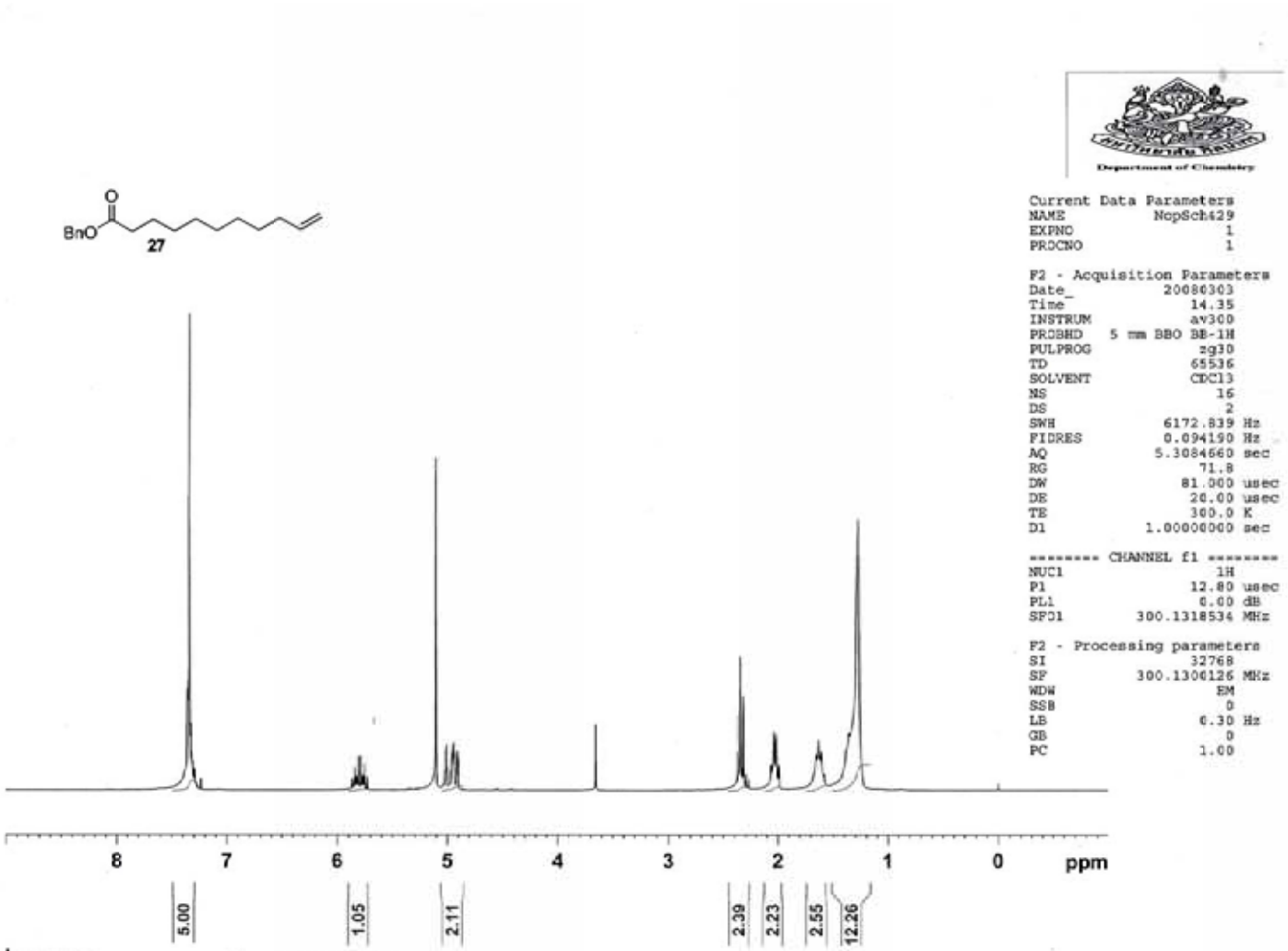
```
Current Data Parameters
NAME                  NopSch396
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20071025
Time                      15.01
INSTRUM                   av300
PROBHD    5 mm BBO BB-1H
PULPROG                   zgdc
TD                       32768
SOLVENT                  CDCl3
NS                         200
DS                           4
SWH                  18115.941 Hz
FIDRES                0.552855 Hz
AQ                    0.9044468 sec
RG                         8192
DW                       27.600 usec
DE                       20.00 usec
TE                       300.0 K
D1                  1.00000000 sec
d11                 0.03000000 sec

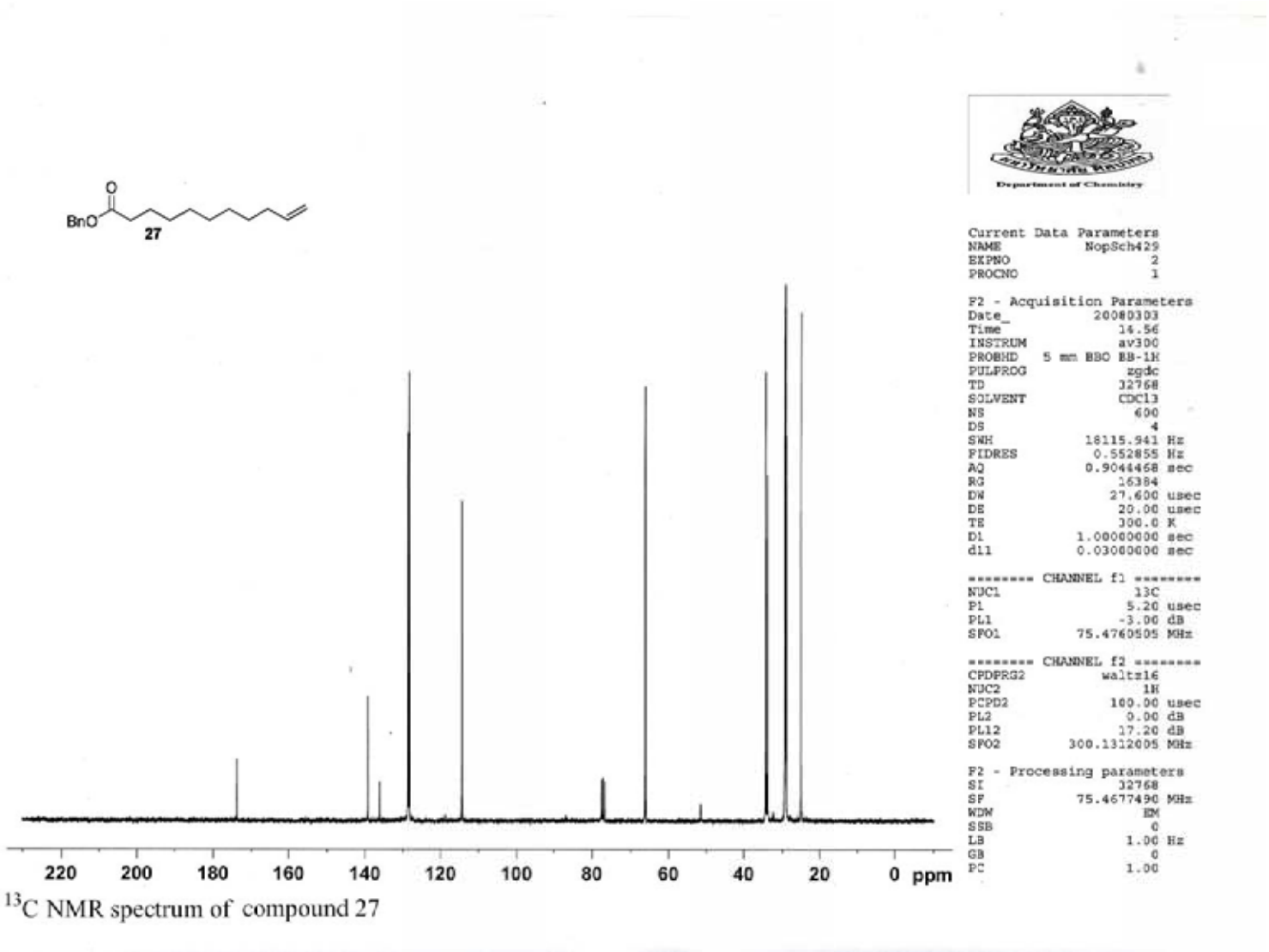
======== CHANNEL f1 ========
NUC1                        13C
P1                         5.20 usec
PL1                       -3.00 dB
SFO1                75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     92.00 usec
PL2                       -1.00 dB
PL12                      16.00 dB
SFO2                300.1312005 MHz

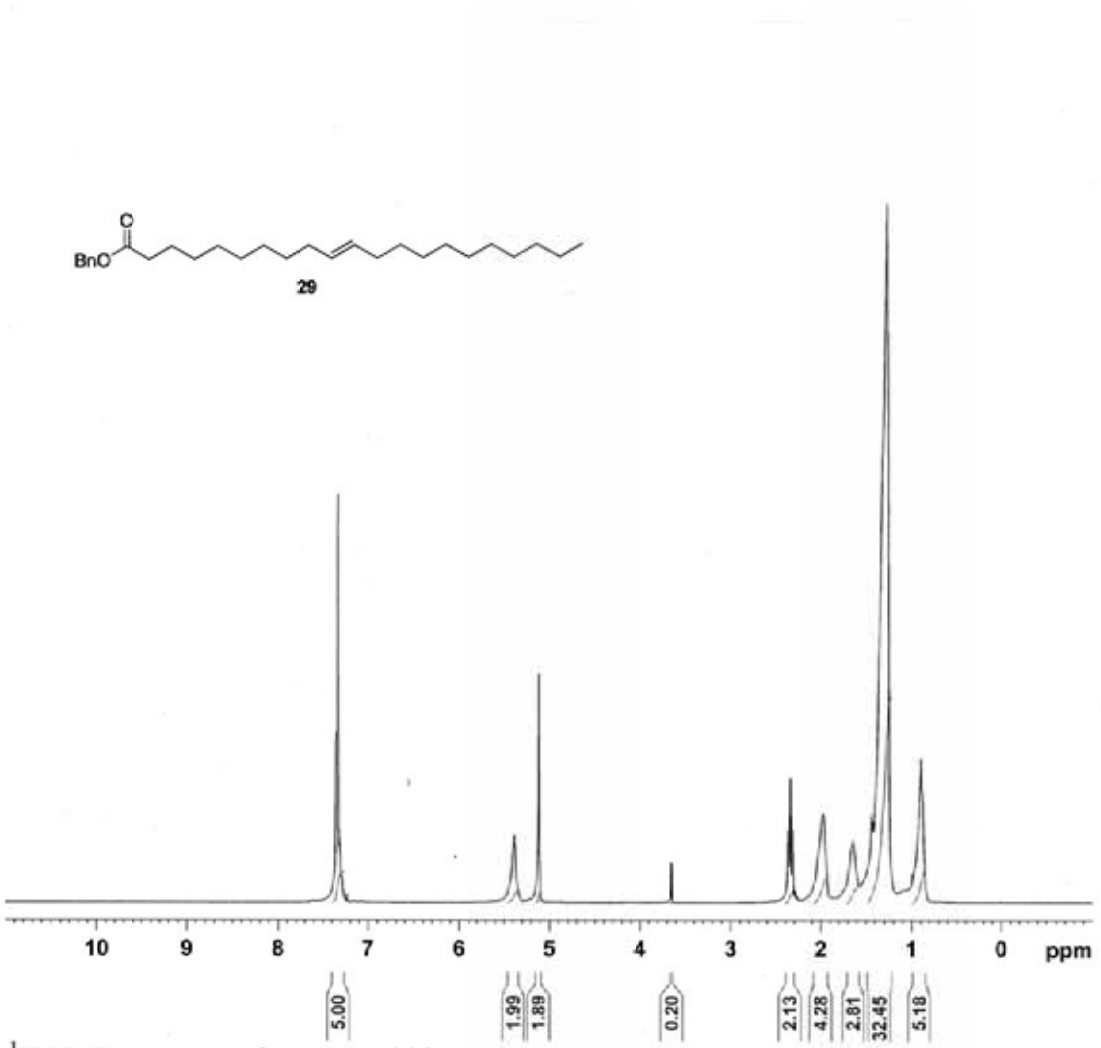
F2 - Processing parameters
SI                       32768
SF                  75.4677490 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.00
```



^{1}H NMR spectrum of compound 27



^{13}C NMR spectrum of compound 27



Department of Chemistry

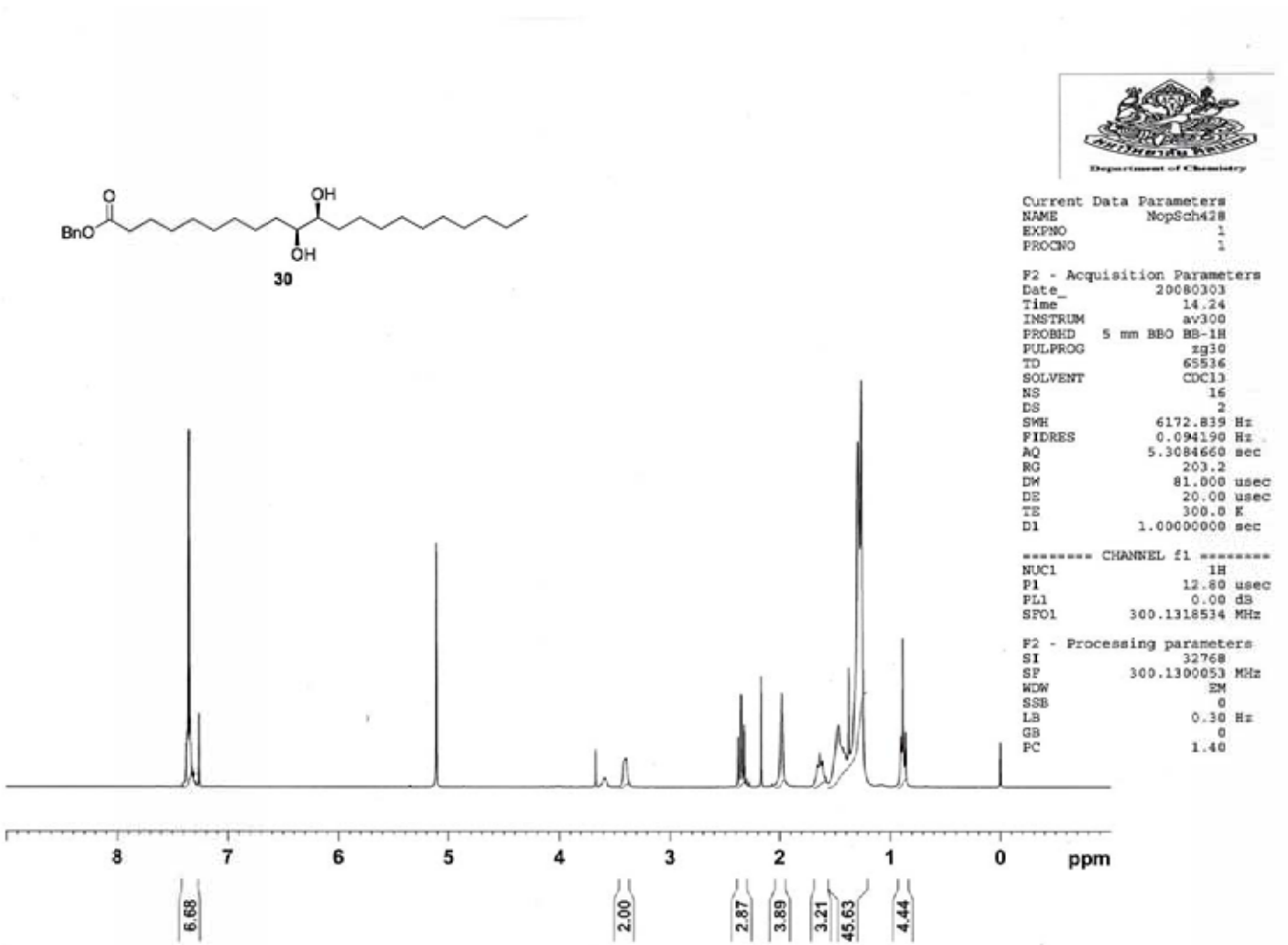
```
Current Data Parameters
NAME                  NopSch401
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20071105
Time                       9.46
INSTRUM                   av300
PROBHD     5 mm BBO BB-1H
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 6172.839 Hz
FIDRES              0.094190 Hz
AQ                  5.3084660 sec
RG                       25.4
DW                     81.000 usec
DE                     20.00 usec
TE                     300.0 K
D1                1.00000000 sec

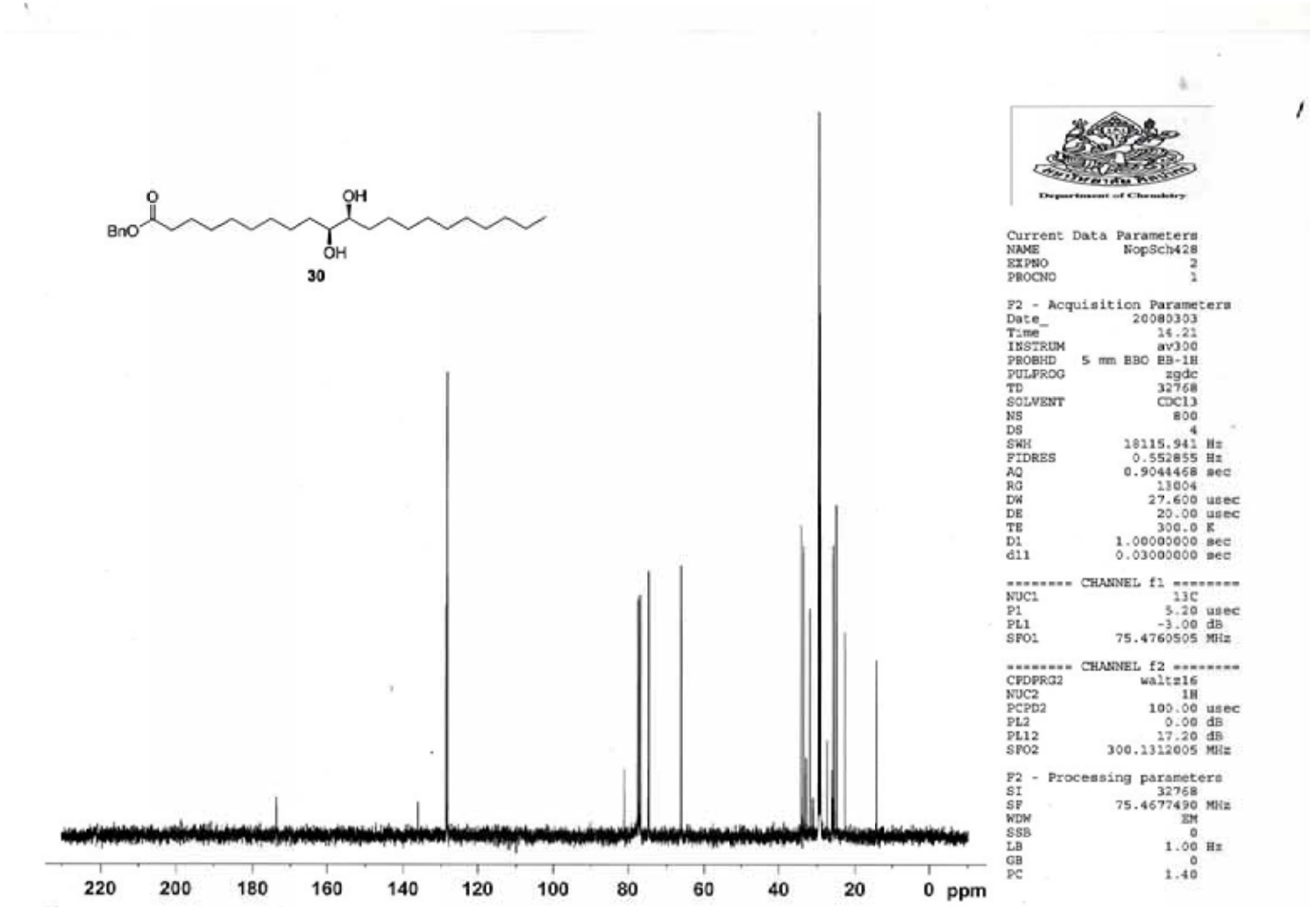
======== CHANNEL f1 ========
NUC1                       1H
P1                      19.60 usec
PL1                     -2.00 dB
SFO1             300.1318534 MHz

F2 - Processing parameters
SI                       32768
SF                300.1300140 MHz
WDW                         EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                       1.00
```

^{1}H NMR spectrum of compound 29



^{1}H NMR spectrum of compound 30



^{13}C NMR spectrum of compound 30

Department of Chemistry

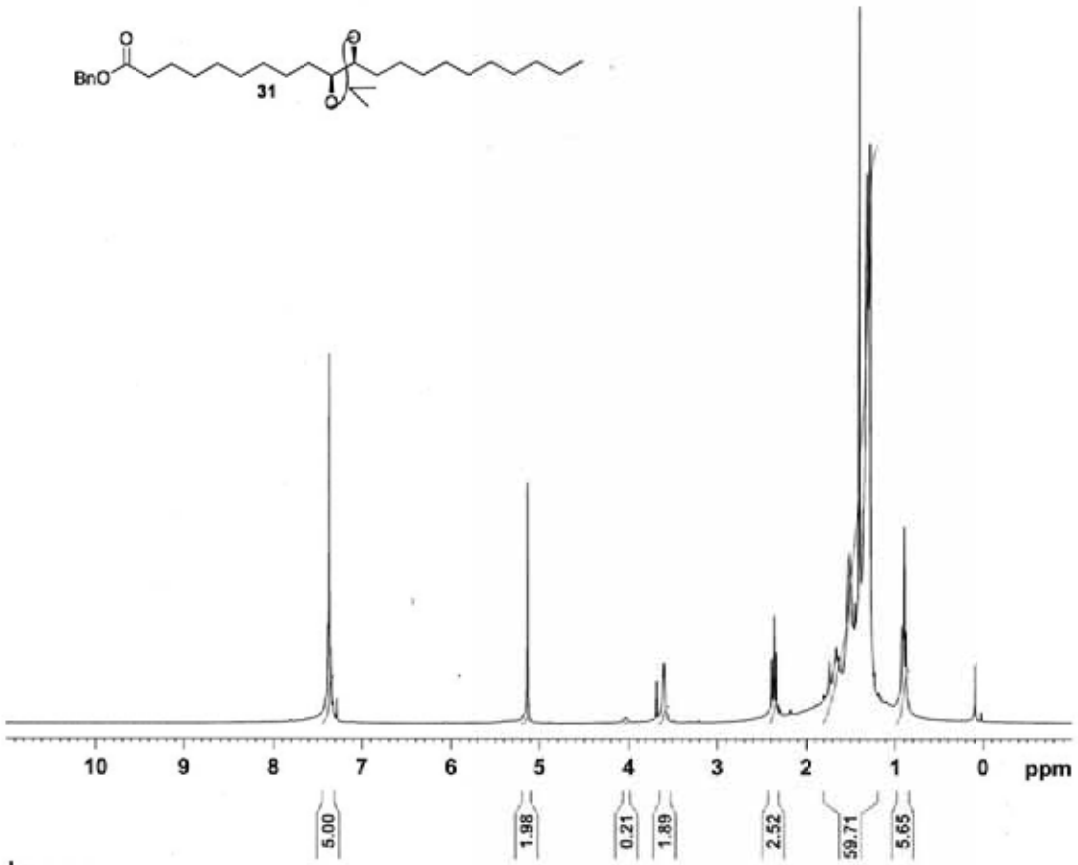
```
Current Data Parameters
NAME                 NopSch428
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20080303
Time                   14.21
INSTRUM                av300
PROBHD    5 mm BBO BB-1H
PULPROG                 zgdc
TD                     32768
SOLVENT                CDCl3
NS                       800
DS                         4
SWH                10115.941 Hz
FIDRES             0.552855 Hz
AQ                 0.9044468 sec
RG                     13804
DW                    27.600 usec
DE                    20.00 usec
TE                    300.0 K
D1                 1.00000000 sec
d11                0.03000000 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                       5.20 usec
PL1                     -3.00 dB
SFO1               75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                      0.00 dB
PL12                    17.20 dB
SFO2              300.1312005 MHz

F2 - Processing parameters
SI                       32768
SF                 75.4677490 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```



^{1}H NMR spectrum of compound 31

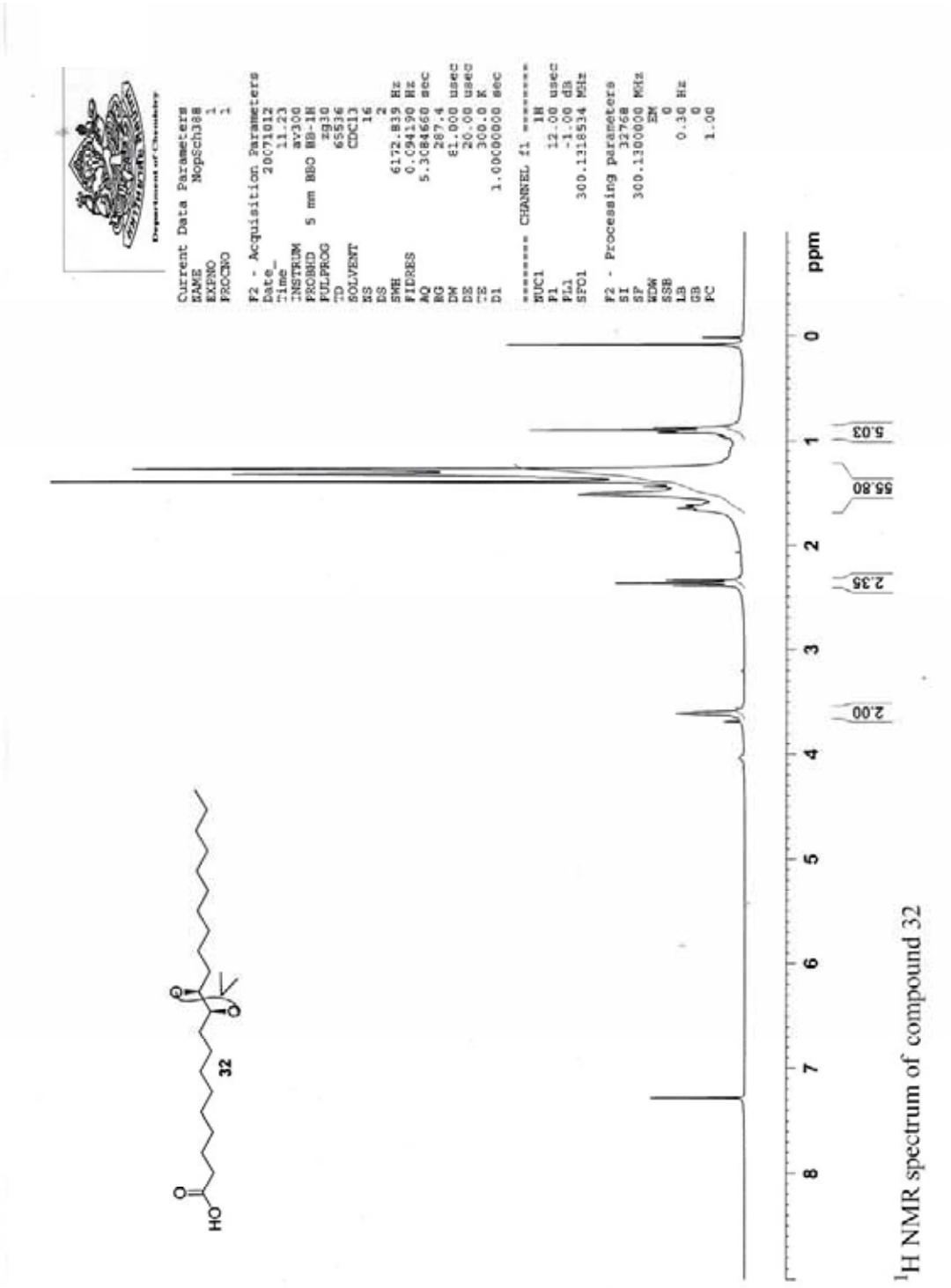
Department of Chemistry

```
Current Data Parameters
NAME                  NopSch384
EXPNO                         1
PROCNO                        1

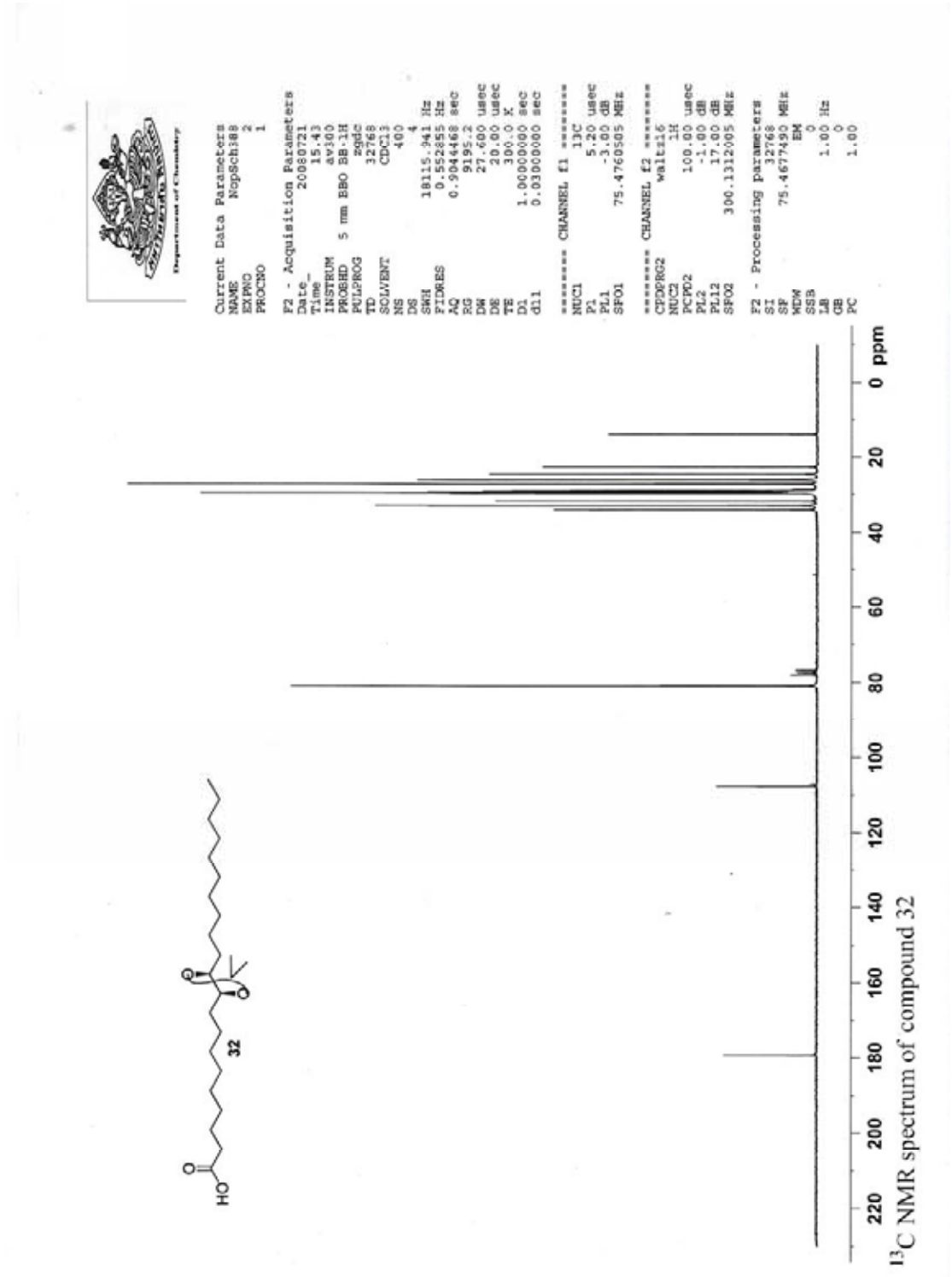
F2 - Acquisition Parameters
Date_                  20071008
Time                      15.01
INSTRUM                   av300
PROBHD    5 mm BBO BB-1H
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   6172.839 Hz
FIDRES                0.094190 Hz
AQ                    5.3084660 sec
RG                         90.5
DW                       81.000 usec
DE                       20.00 usec
TE                       300.0 K
D1                    1.00000000 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                       12.00 usec
PL1                      -1.00 dB
SFO1                300.1318534 MHz

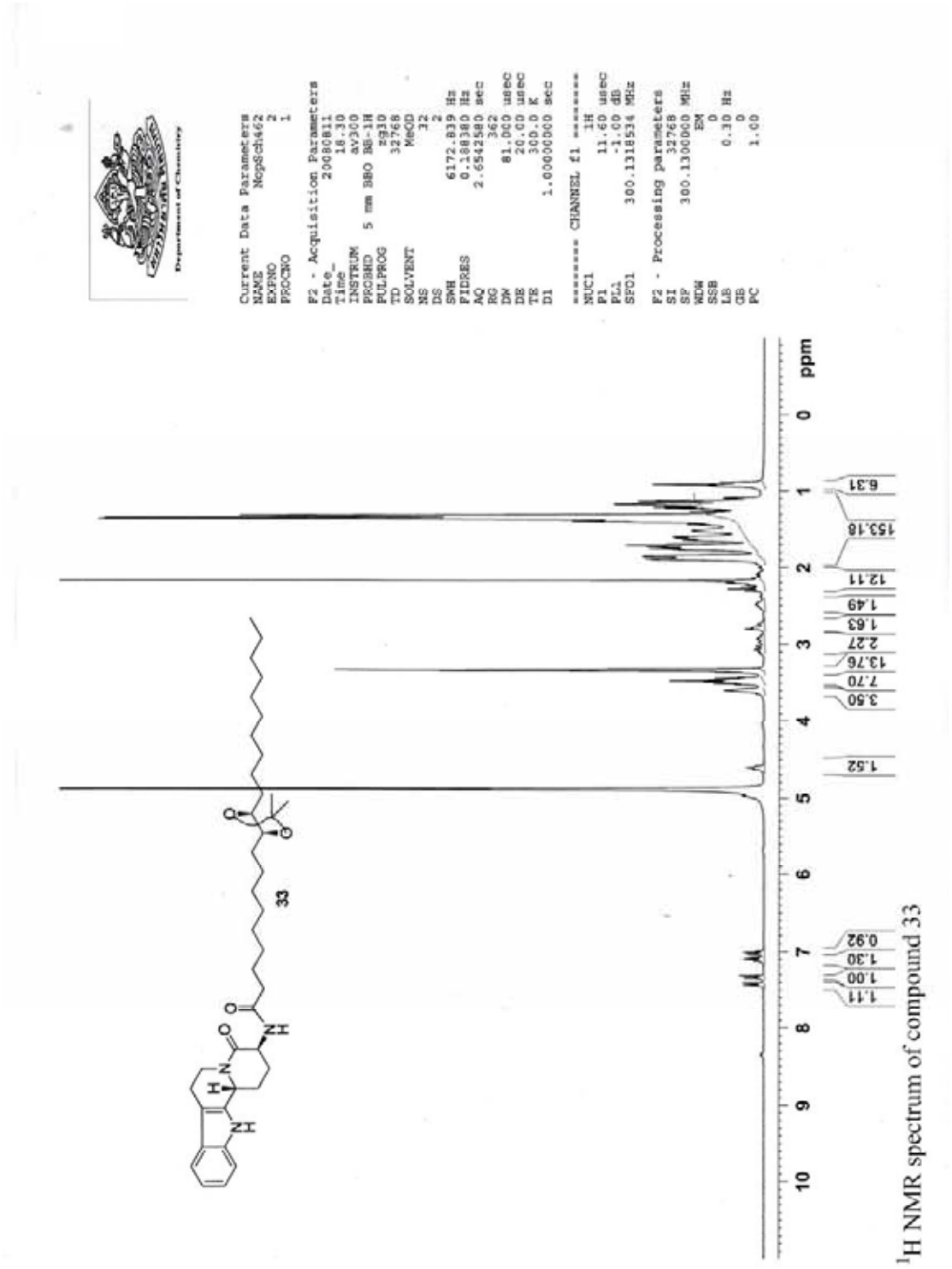
F2 - Processing parameters
SI                         32768
SF                  300.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00
```



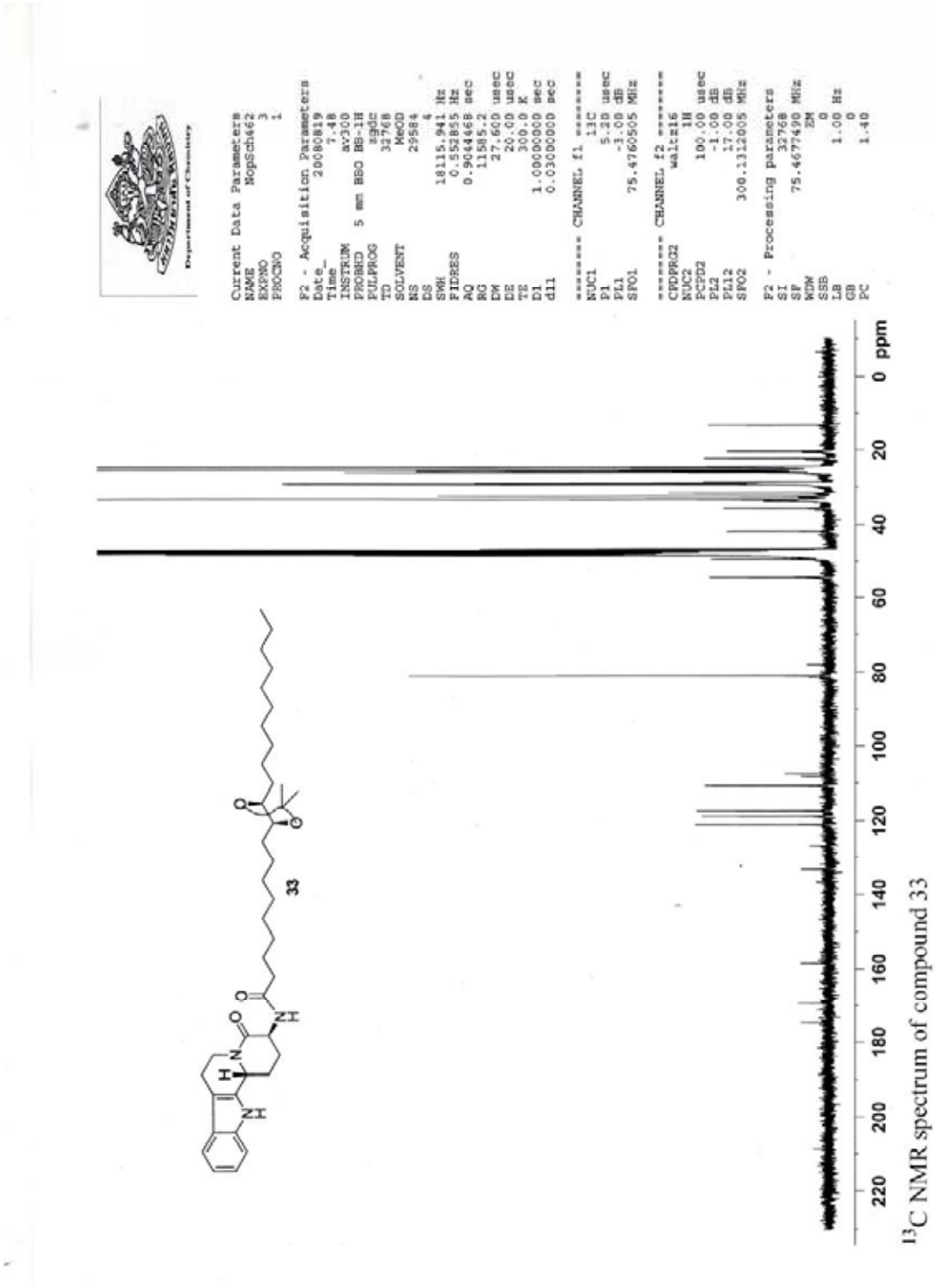
^{1}H NMR spectrum of compound 32



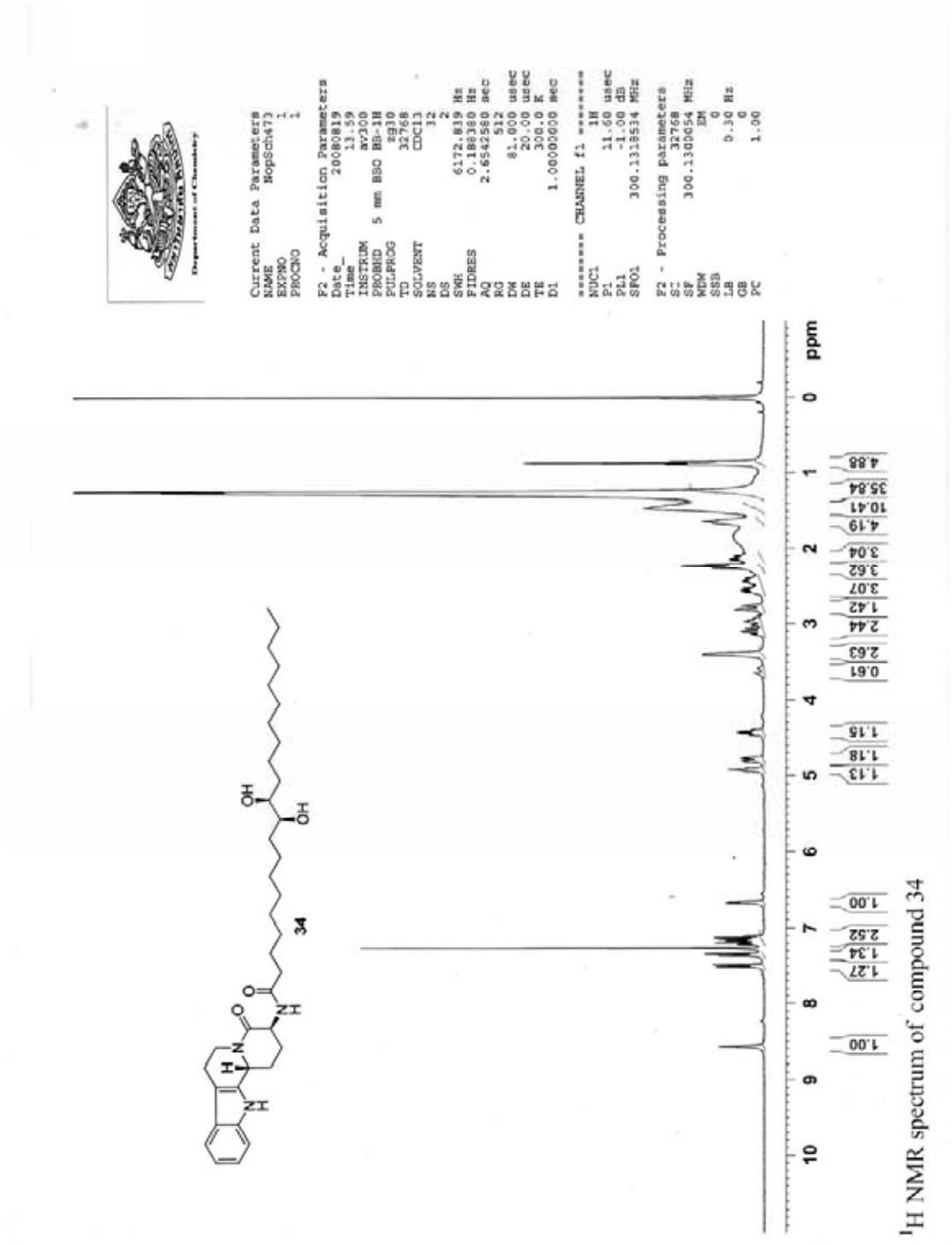
^{13}C NMR spectrum of compound 32



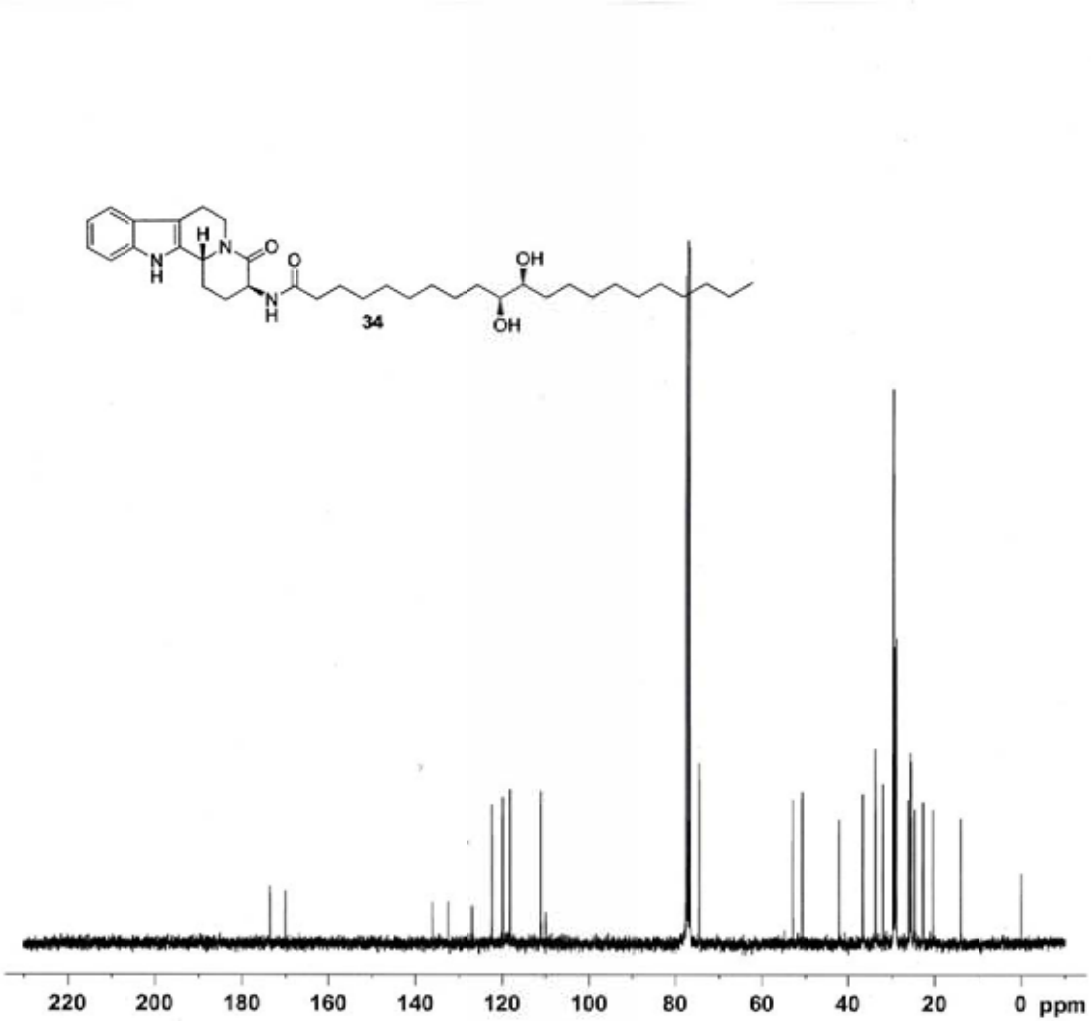
^{1}H NMR spectrum of compound 33



^{13}C NMR spectrum of compound 33



^{1}H NMR spectrum of compound 34



^{13}C NMR spectrum of compound 34

Department of Chemistry

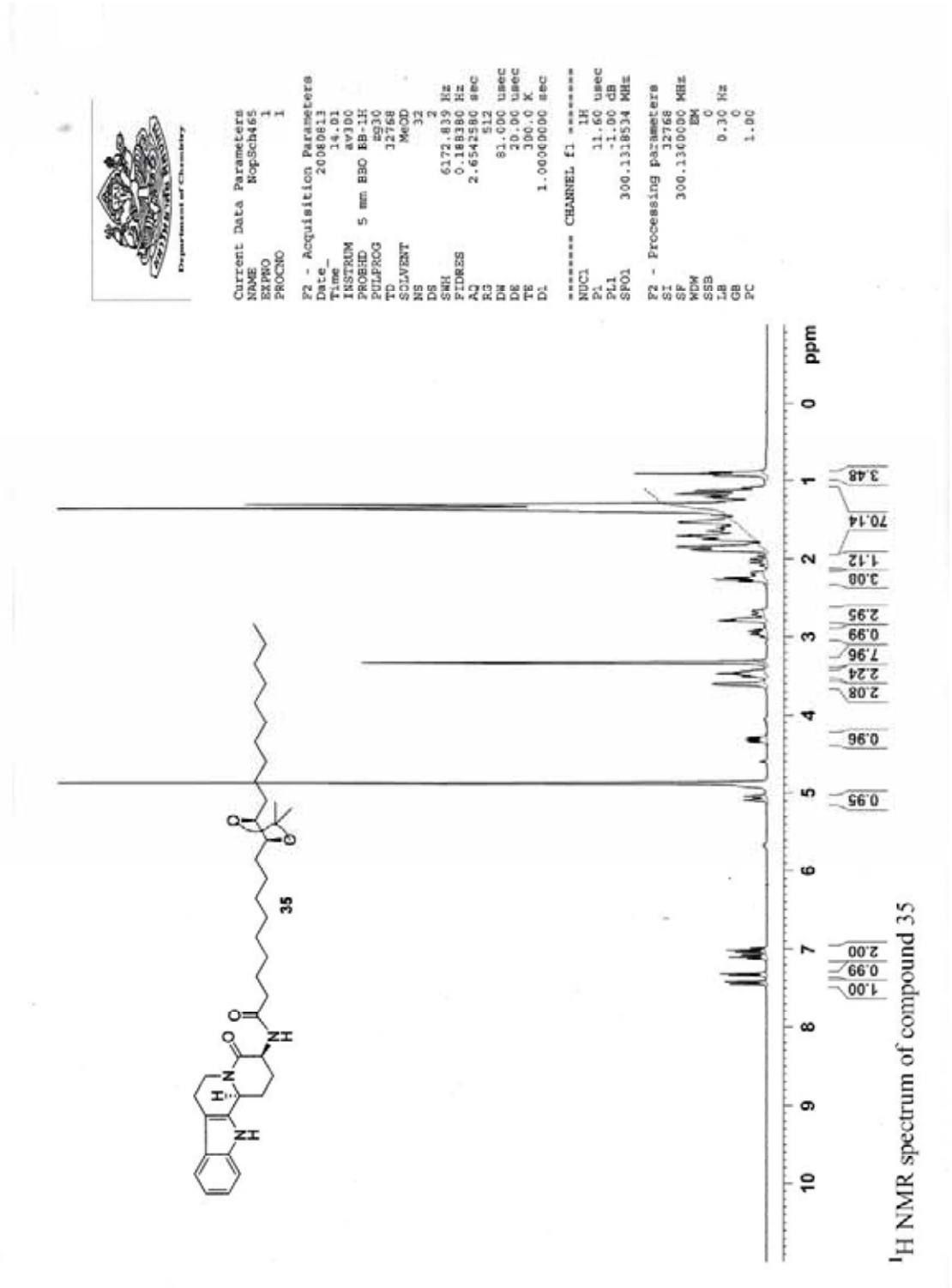
```
Current Data Parameters
NAME                  NopSch473
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_               20080824
Time                    14.59
INSTRUM                 av300
PROBHD   5 mm BBO BB-1H
PULPROG                 zgdc
TD                      32768
SOLVENT                 CDCl3
NS                       9216
DS                          4
SWH                 18115.941 Hz
FIDRES              0.552855 Hz
AQ                  0.9044468 sec
RG                      13004
DW                    27.600 usec
DE                    20.00 usec
TE                     300.0 K
D1                1.00000000 sec
d11               0.03000000 sec

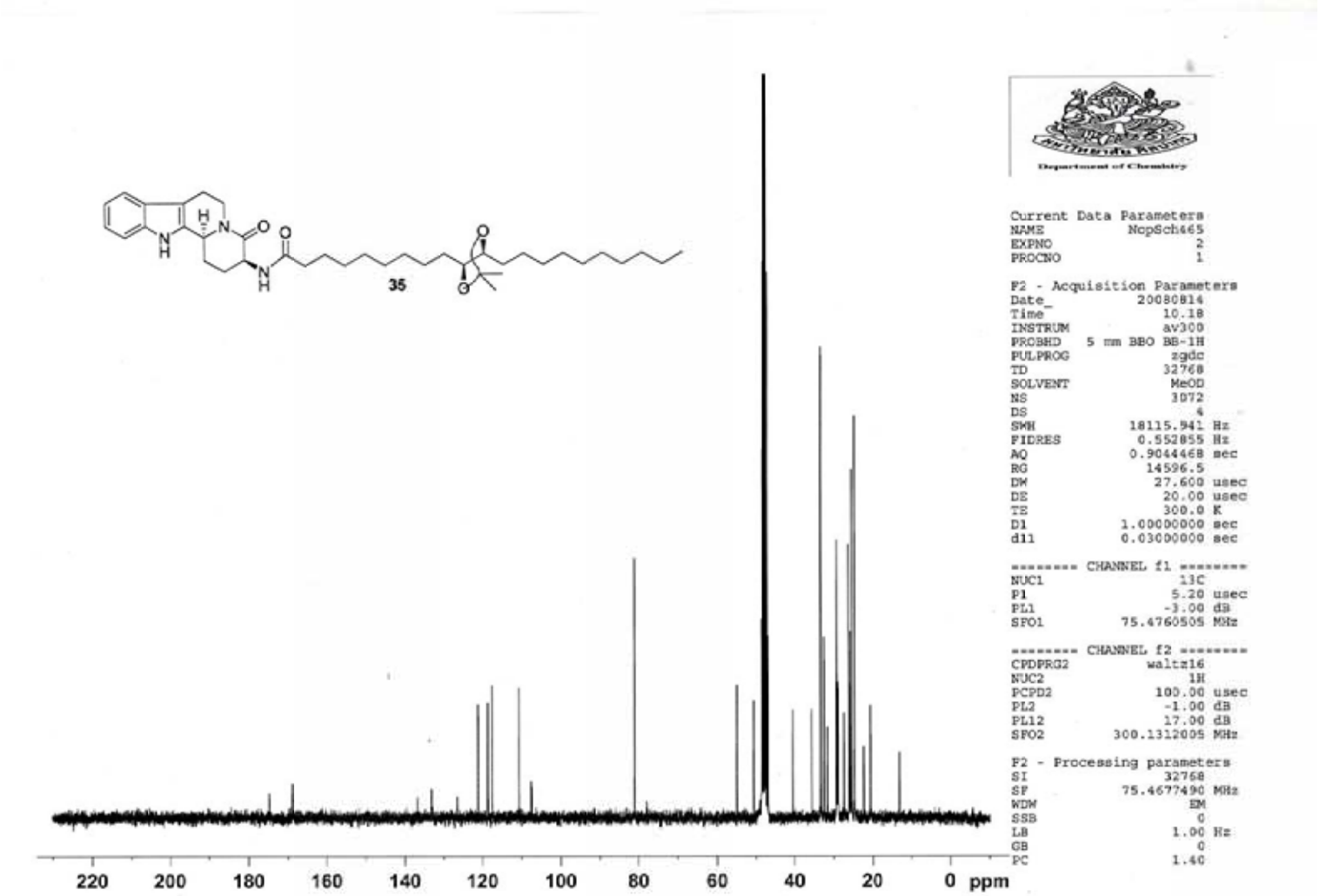
======== CHANNEL f1 ========
NUC1                      13C
P1                       5.20 usec
PL1                     -3.00 dB
SFO1              75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  100.00 usec
PL2                     -1.00 dB
PL12                    17.00 dB
SFO2             300.1312005 MHz

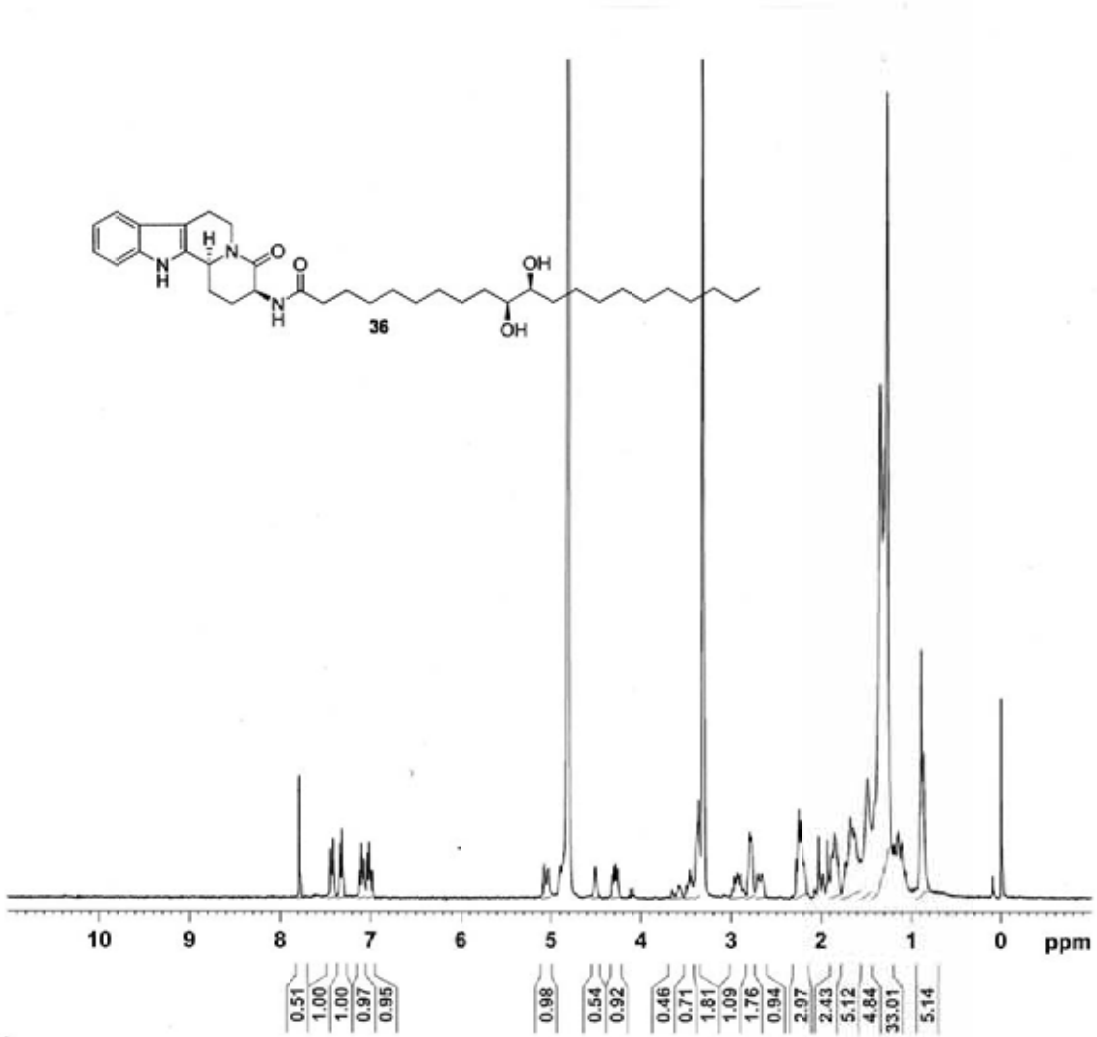
F2 - Processing parameters
SI                      32768
SF                75.4677474 MHz
WDW                        EM
SSB                         0
LB                       1.00 Hz
GB                          0
PC                       1.00
```



^{1}H NMR spectrum of compound 35



^{13}C NMR spectrum of compound 35



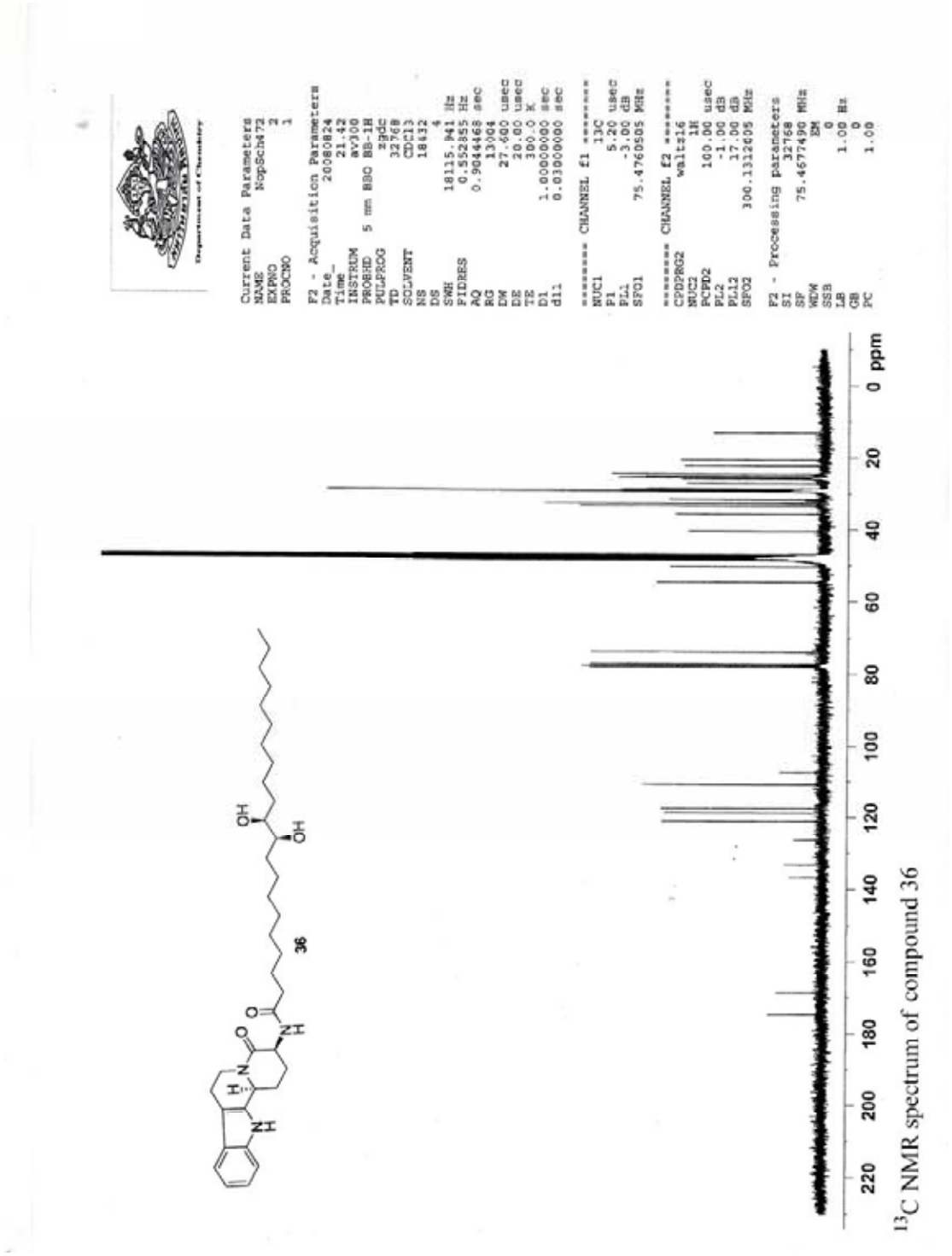
^{1}H NMR spectrum of compound 36

```
Current Data Parameters
NAME                  NopSch472
EXPNO                         1
PROCNO                        1

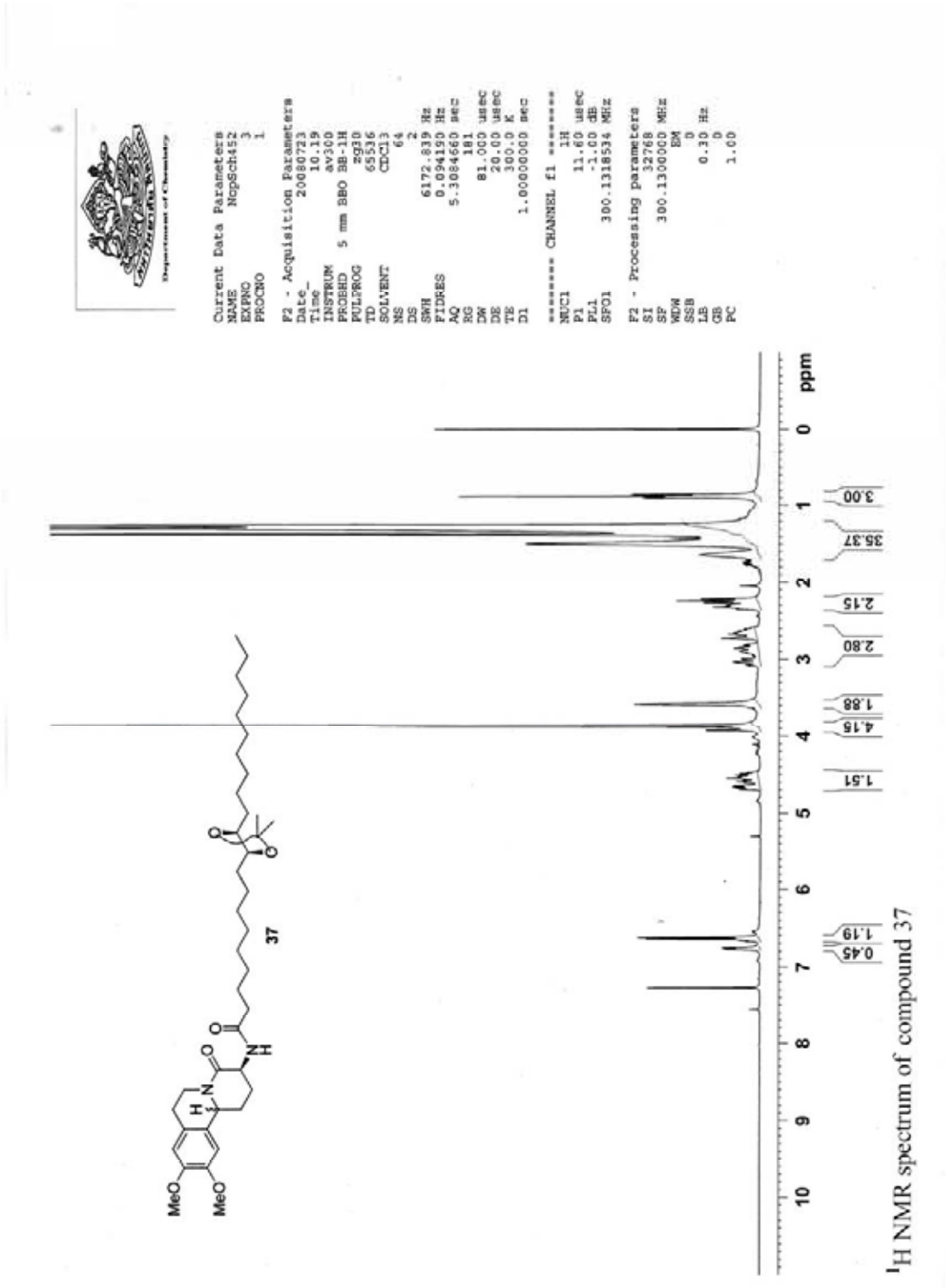
F2 - Acquisition Parameters
Date_              20080819
Time                    13.51
INSTRUM                 av300
PROBHD    5 mm BBO BB-1H
PULPROG                 zg30
TD                     32768
SOLVENT                 MeOD
NS                        32
DS                         2
SWH                6172.839 Hz
FIDRES             0.188380 Hz
AQ                 2.6542580 sec
RG                     724.1
DW                  81.000 usec
DE                  20.00 usec
TE                     300.0 K
D1                 1.0000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     11.60 usec
PL1                    -1.00 dB
SFO1           300.1318534 MHz

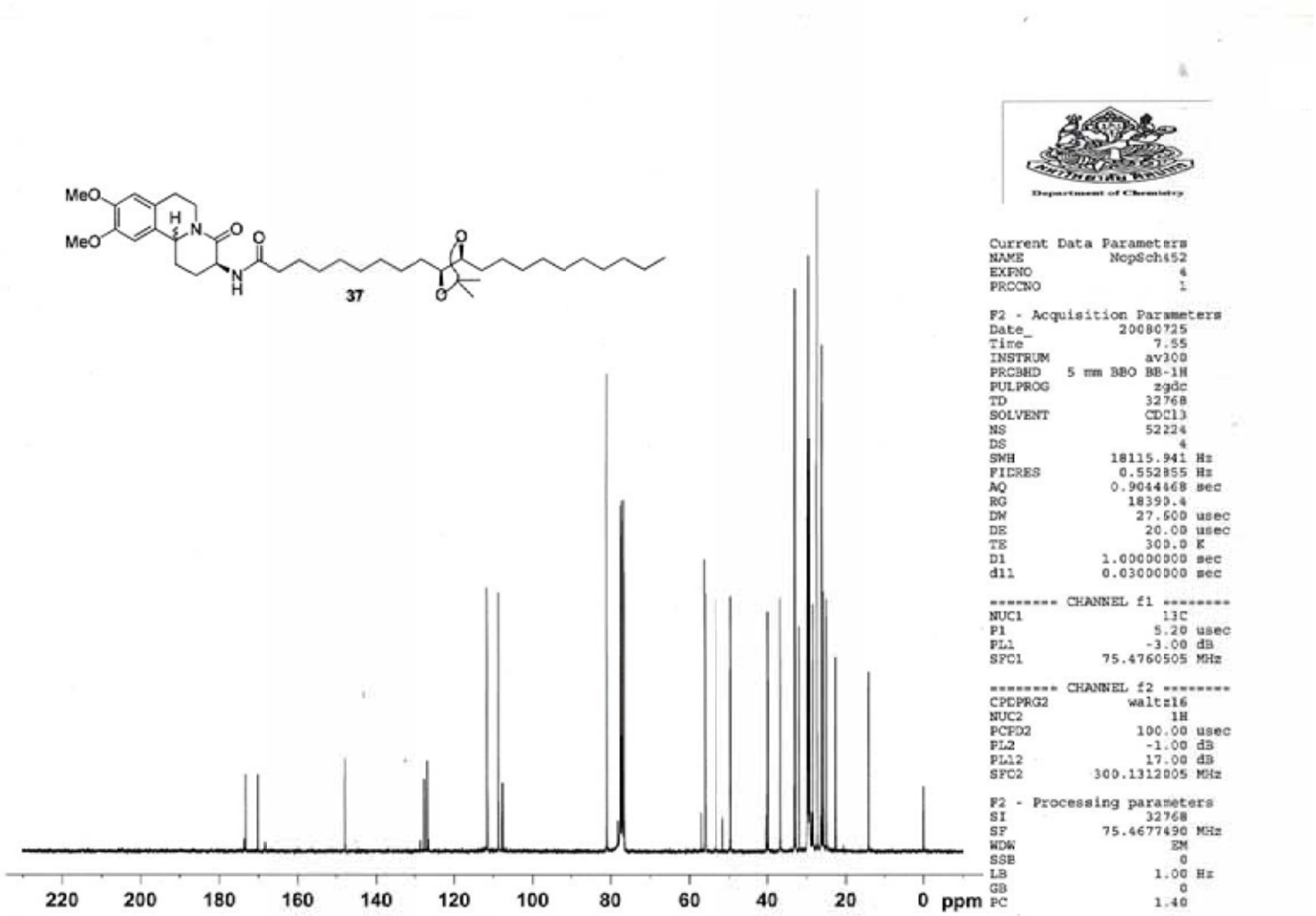
F2 - Processing parameters
SI                     32768
SF             300.1300014 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



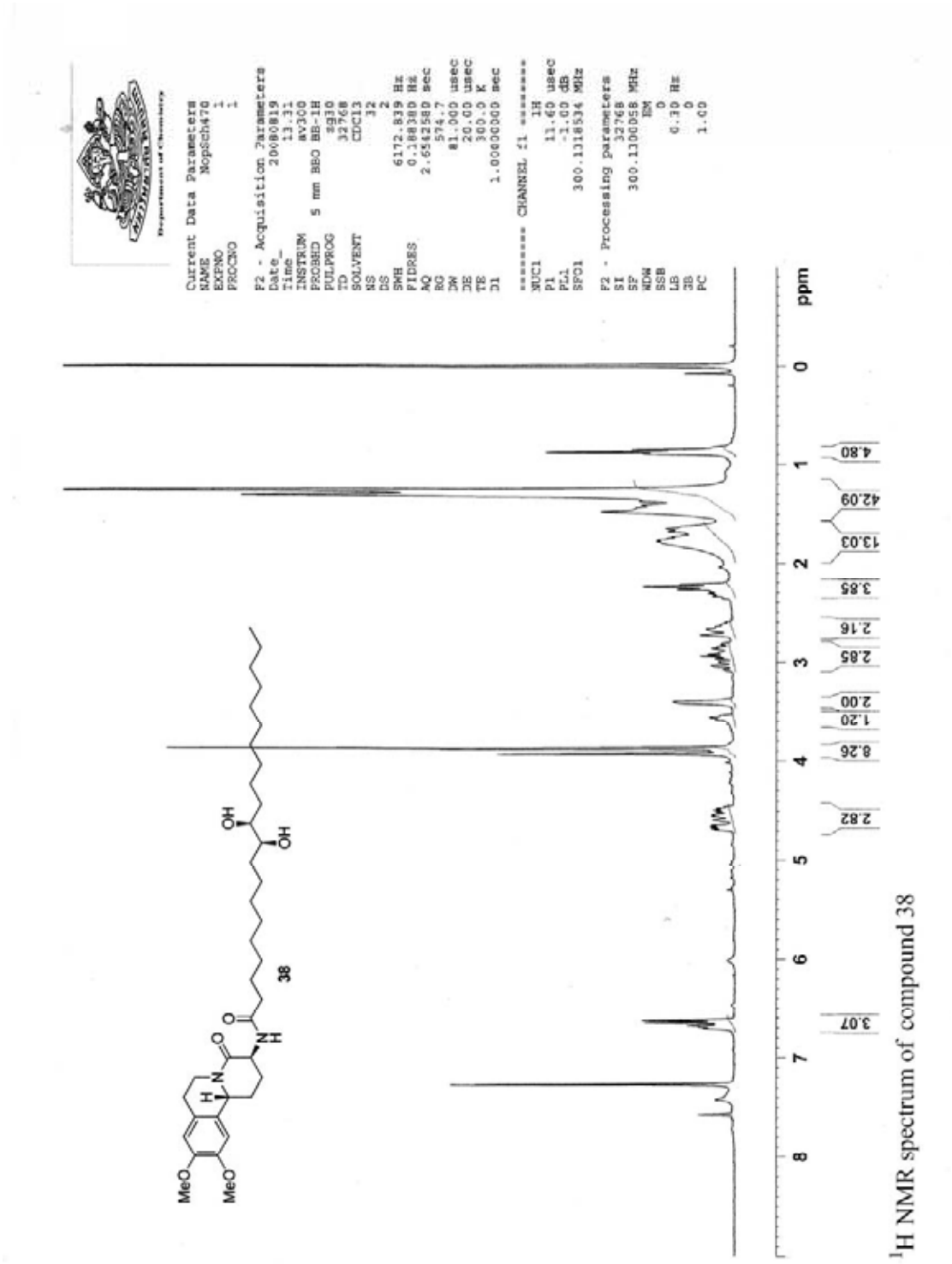
^{13}C NMR spectrum of compound 36



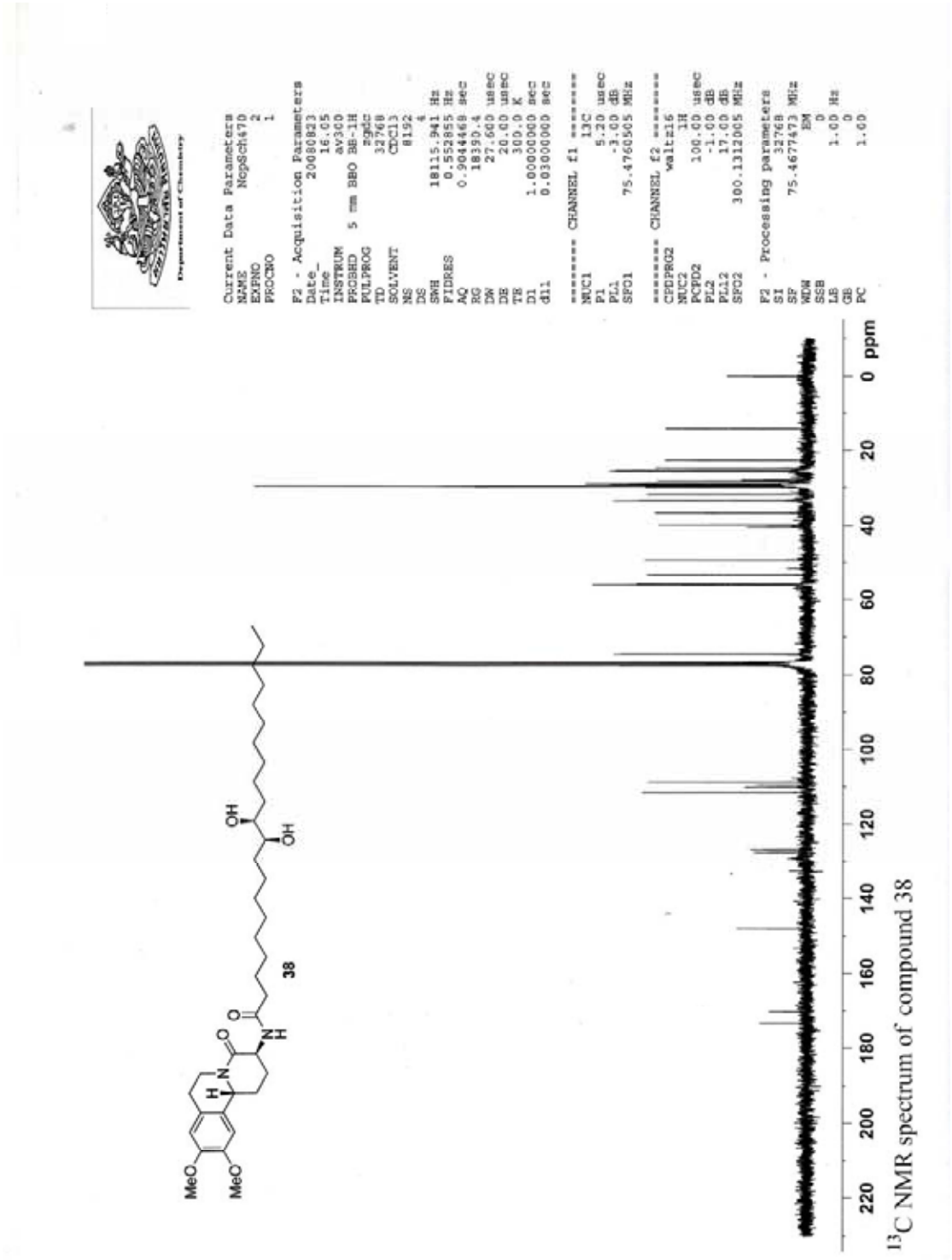
^{1}H NMR spectrum of compound 37



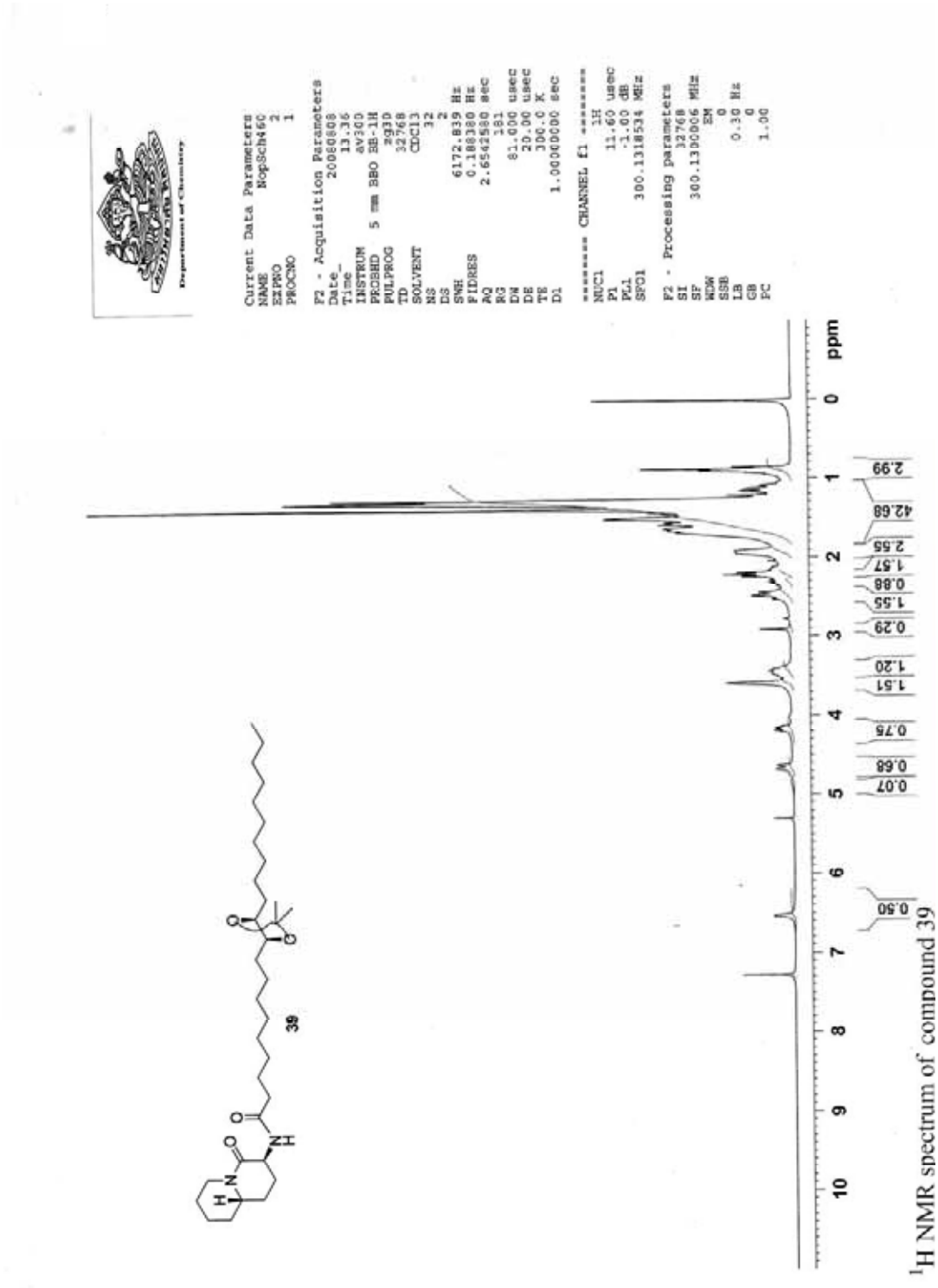
^{13}C NMR spectrum of compound 37



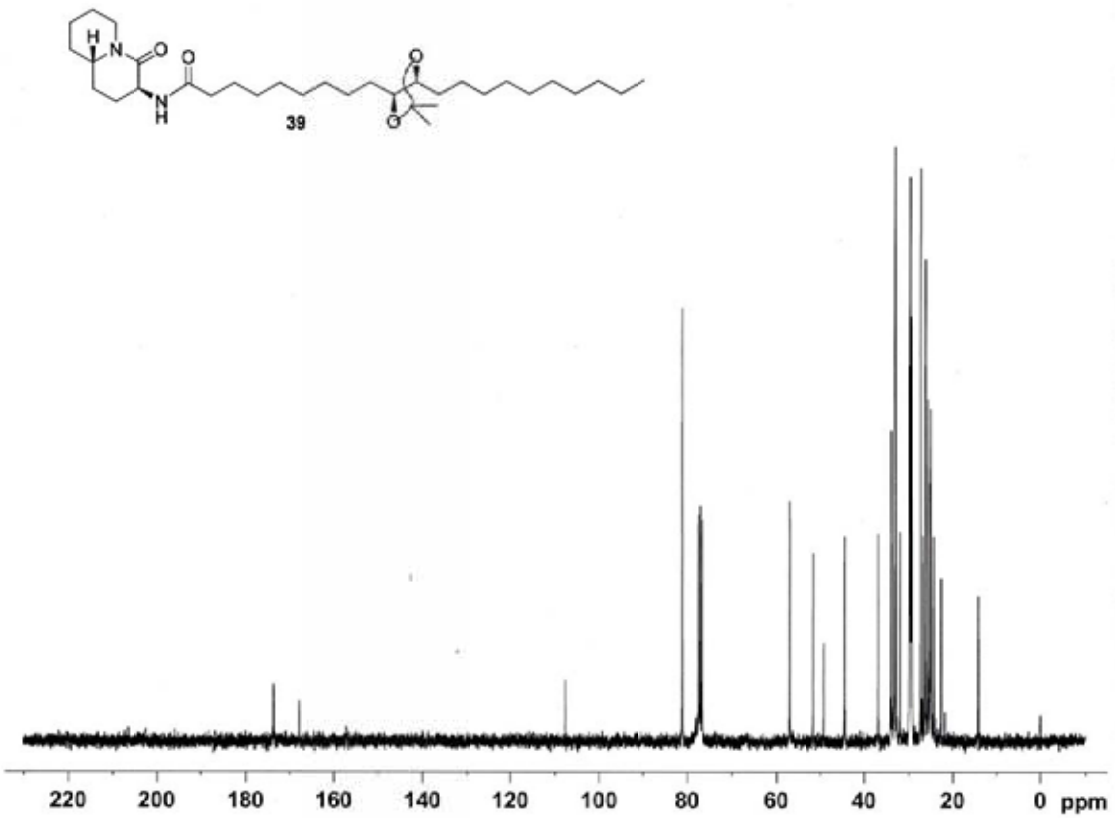
^{1}H NMR spectrum of compound 38



^{13}C NMR spectrum of compound 38



^{1}H NMR spectrum of compound 39



Department of Chemistry

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Current Data Parameters
NAME                  NopSch460
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
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Time                      14.44
INSTRUM                    av360
PROBHD   5 mm BBO BB-1H
PULPROG                    zgdc
TD                        32768
SOLVENT                   CDCl3
NS                         2048
DS                            4
SWH                   18115.941 Hz
FIDRES                0.552855 Hz
AQ                    0.9044468 sec
RG                      20642.5
DW                       27.600 usec
DE                       20.00 usec
TE                       300.0 K
D1                  1.00000000 sec
d11                 0.03000000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                        5.20 usec
PL1                      -3.00 dB
SFO1                75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                    100.00 usec
PL2                      -1.00 dB
PL12                     17.00 dB
SFO2               300.1312005 MHz

F2 - Processing parameters
SI                        32768
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WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
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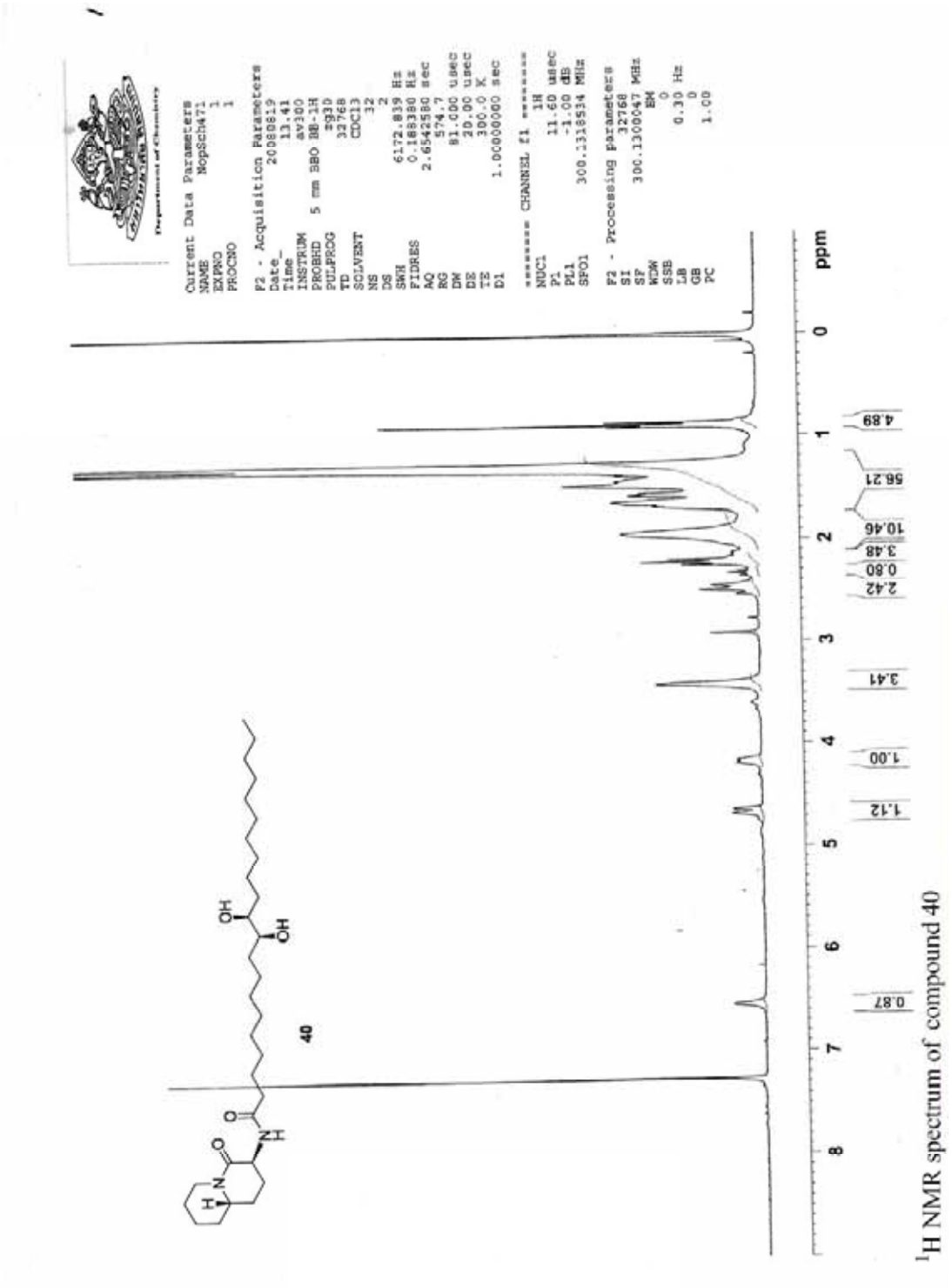
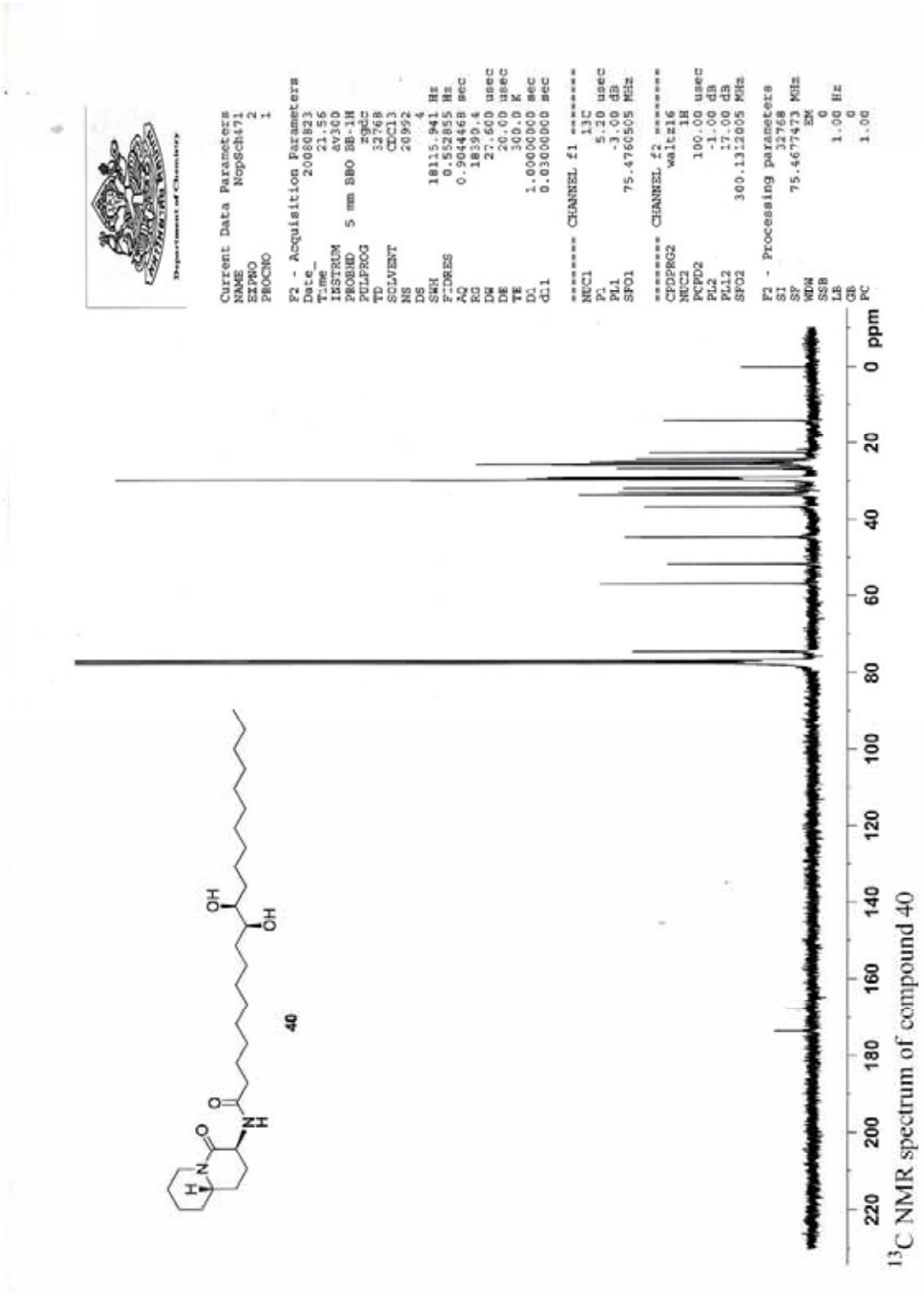
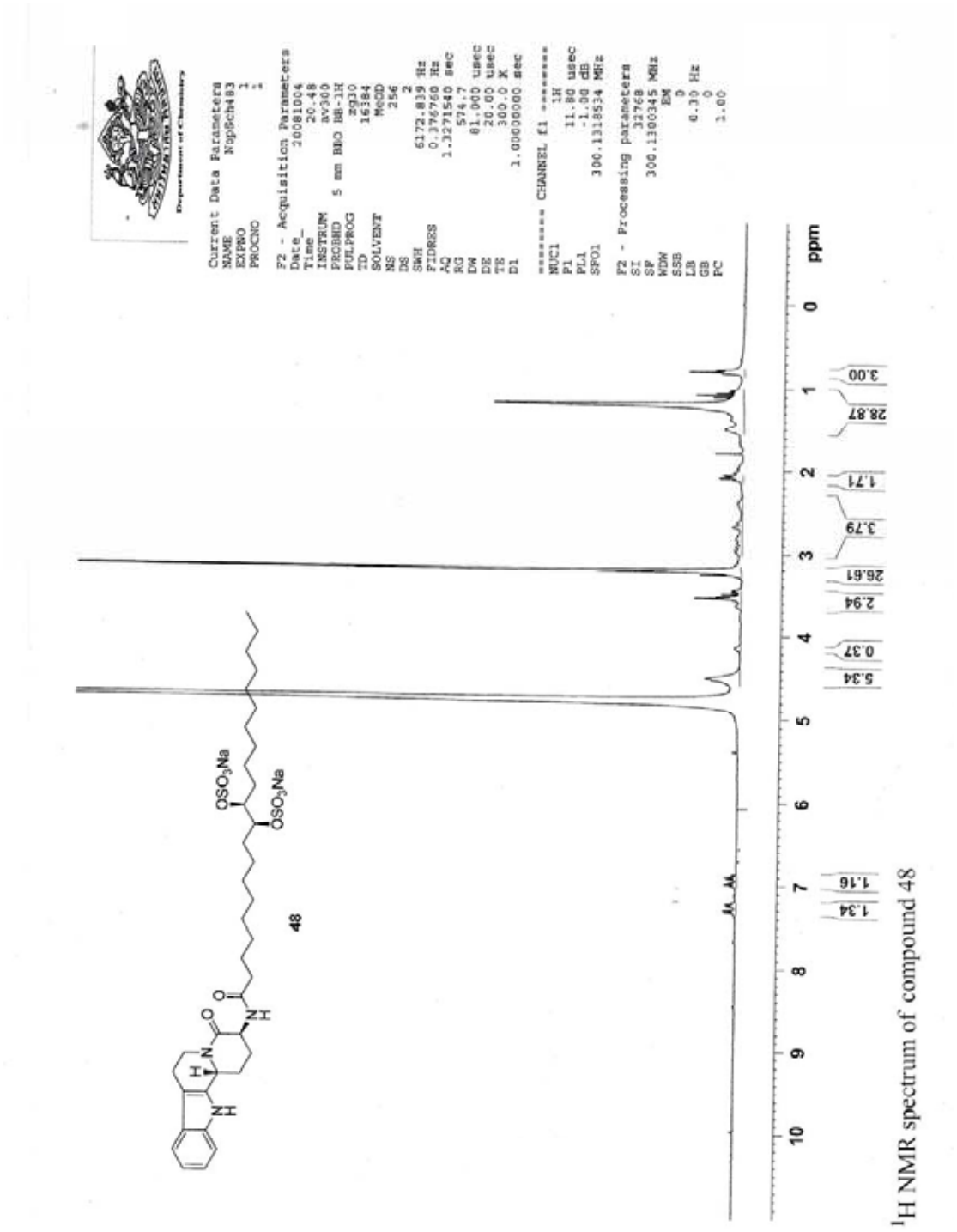
^{13}C NMR spectrum of compound 39



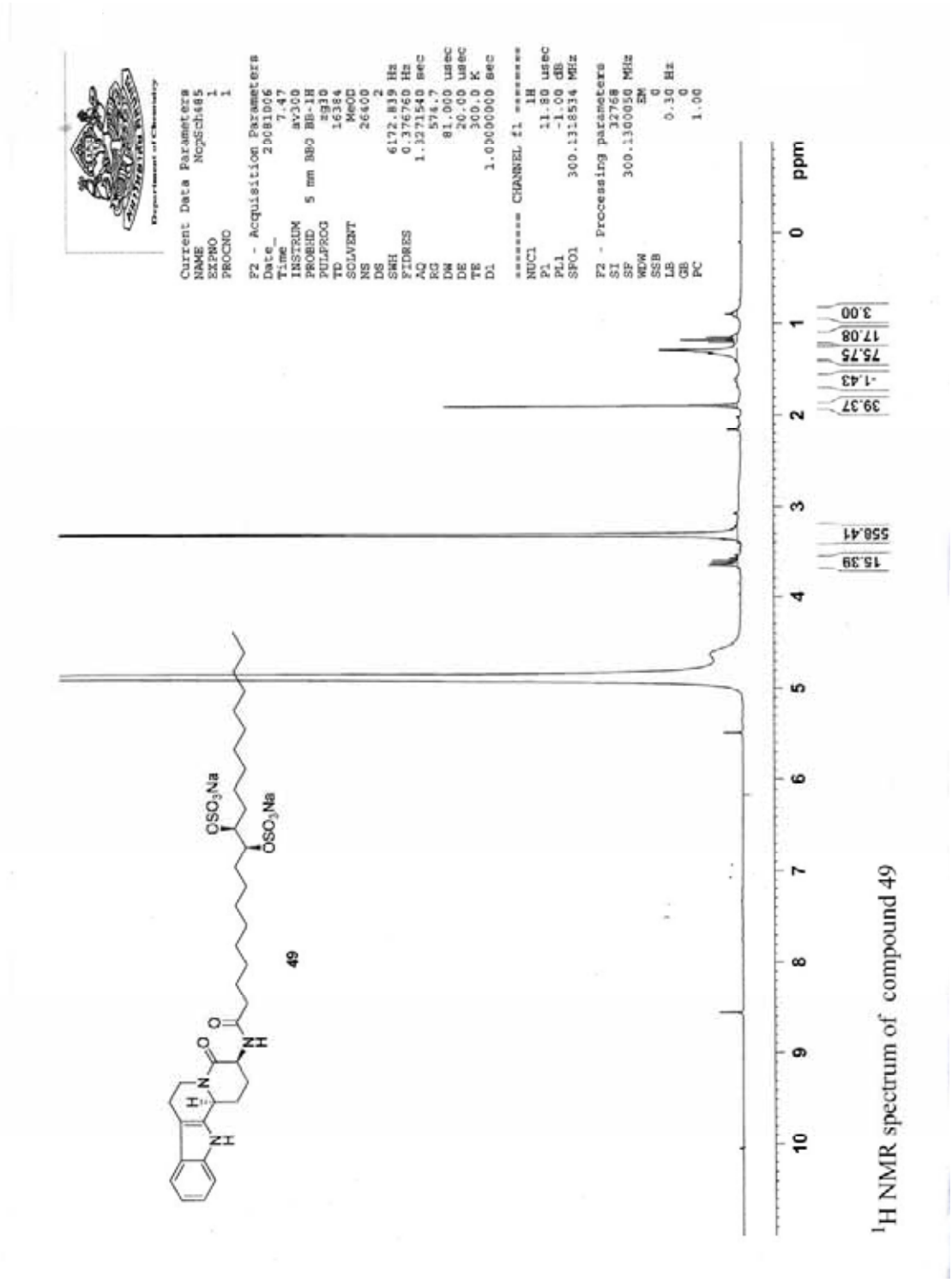
^{1}H NMR spectrum of compound 40



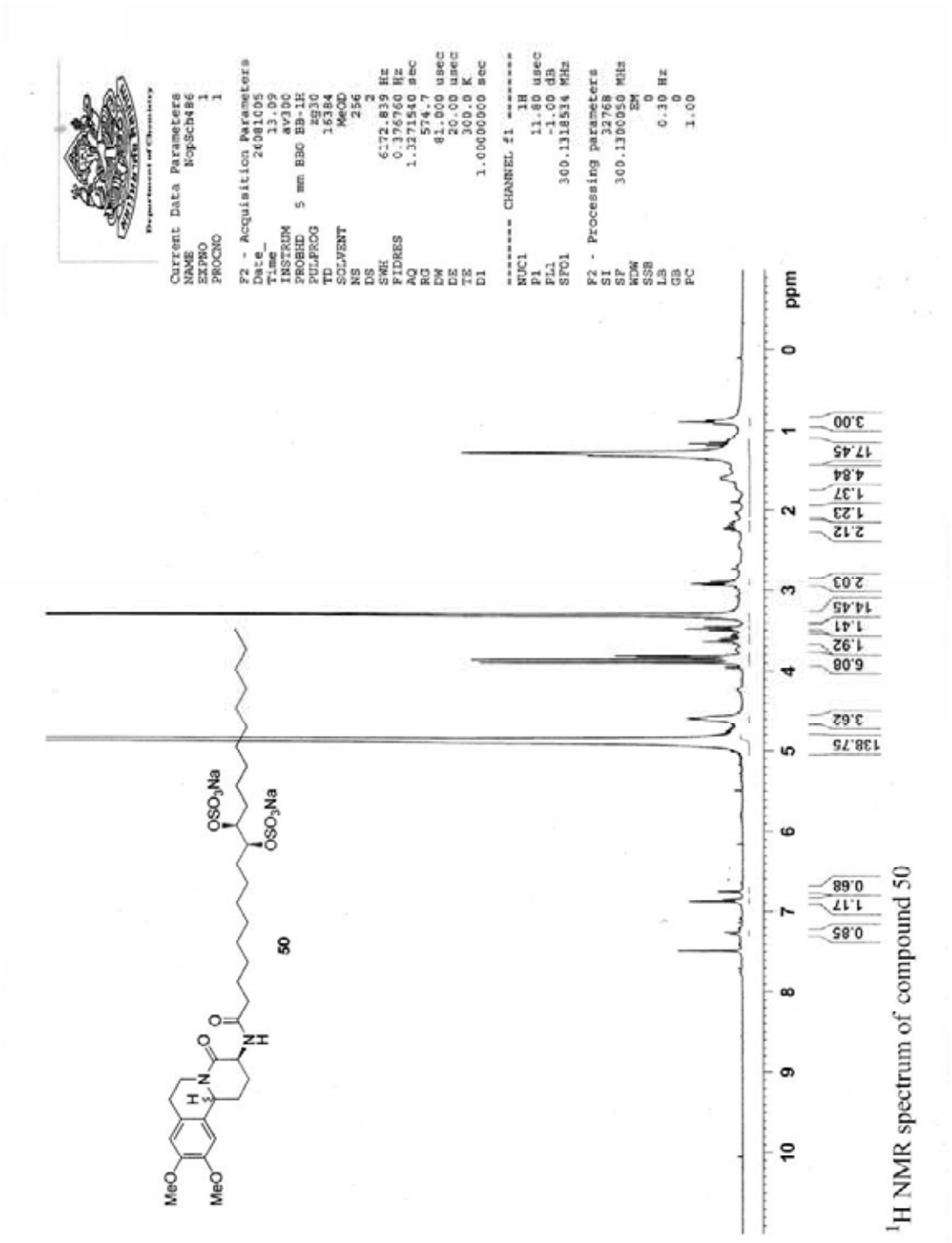
^{13}C NMR spectrum of compound 40



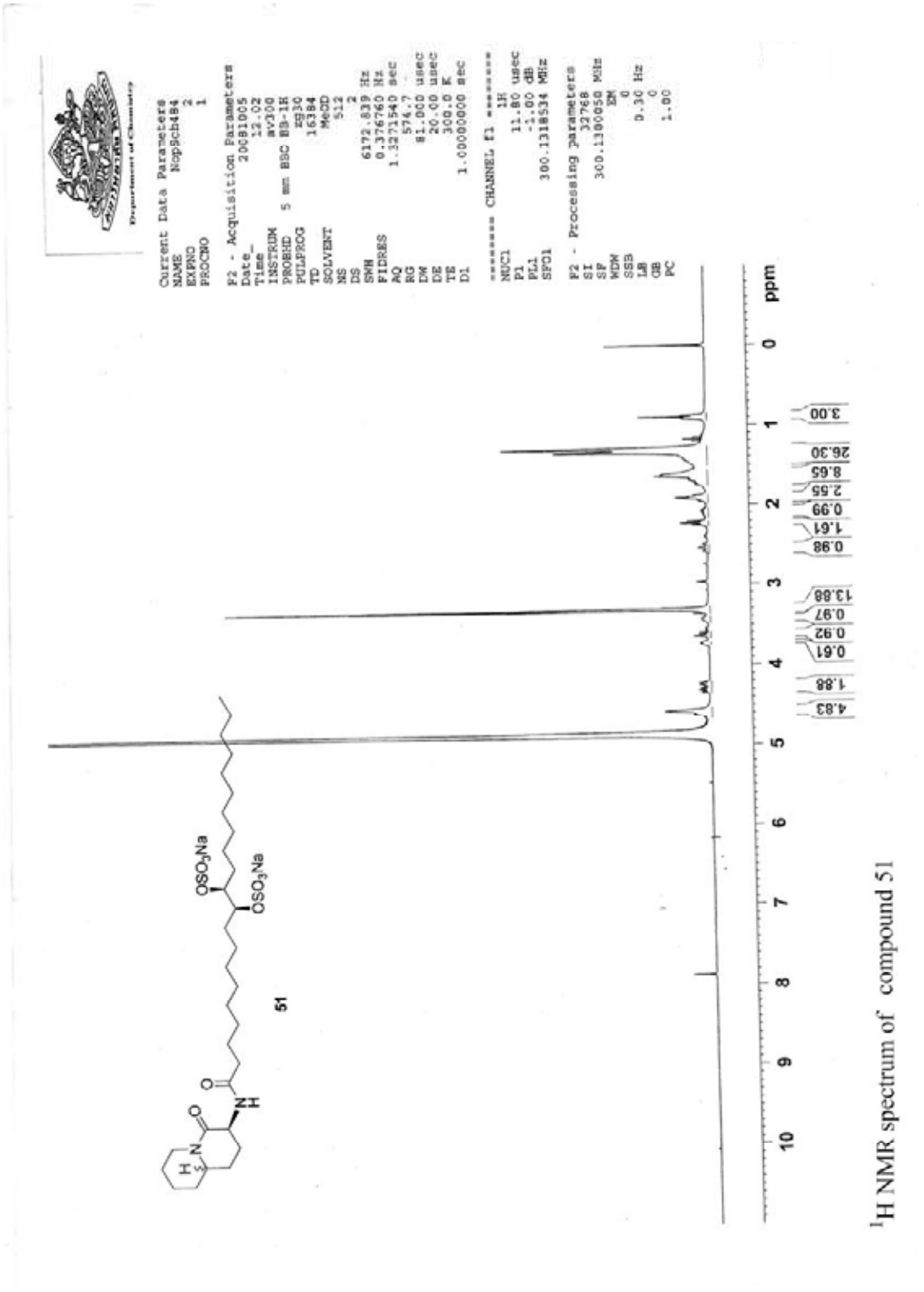
^{1}H NMR spectrum of compound 48



^{1}H NMR spectrum of compound 49



^{1}H NMR spectrum of compound 50



^{1}H NMR spectrum of compound 51

Biography

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