SYNTHETIC STUDIES TOWARD TOTAL SYNTHESES OF QUINOLIZIDINE ALKALOIDS, TETRABENAZINE, PROTOEMETINOL AND SYNTHESIS OF CRISPINE A ANALOGS

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

By

Duangkamon Namborisut

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

Master of Science Program in Organic Chemistry

Department of Chemistry

Graduate School, Silpakorn University

Academic Year 2016

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การศึกษาการสังเคราะห์อัลคาลอยด์ quinolizidine tetrabenazine protoemetinol และการสังเคราะห์สารที่มีโครงสร้างคล้าย crispine A

โดย

นางสาวดวงกมล น้ำบริสุทธิ์

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเคมีอินทรีย์
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Quinolizidine and indolizidine are important classes of alkaloids with various intriguing biological activities. Herein we report our synthetic studies toward selected quinolizidine alkaloids; tetrabenazine and protoemetinol. Tetrabenazine is a chiral synthetic drug used for treatment of chorea associated with the Huntington's disease. It is a pro-drug that is metabolized to the active drug dihydrotetrabenazine. Protoemetinol was isolated from *Alangium Salviifolium Lamarckii* and has been found to be a precursor for several other potent biologically active alkaloids with anticancer, anti-amoebic and emetic activities, etc. We used *N*-acyliminium ion to construct the tricyclic benzoquinolizidinone in two synthetic routes toward tetrabenazine and protoemetinol. In the first route, the tricyclic benzoquinolizidinone underwent Cope elimination to give the corresponding enamide which underwent Michael additions with methoxide and allylmagnesium bromide at the β-carbon to give the synthetic intermediate for tetrabenazine and protoemetinol, respectively. However the subsequent α-alkylations of the resulting lactam were not successful. In the second route, the chiral imide intermediate underwent aldol reaction prior to carbonyl reduction and *N*-acyliminium ion cyclization. Cope elimination of the resulting benzoquinolizidine gave β,γ-unsaturated lactam intermediate with the substituent on the α-carbon of the lactam. The remaining steps require functionalization at the β-carbon of the lactam. In this route diastereomeric product of the aldol reaction led to enantiomeric product of the Cope elimination. We use the same strategy to synthesize analogs of cytotoxic indolizidine alkaloids, crispine A and discovered that regioisomeric product of nucleophilic addition chiral succinimide led to enantiomeric product of the analogs of crispine A. Hence our finding can potentially lead to enantio-divergent synthetic route for quinolizidine and indolizidine alkaloids.

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คำสำคัญ : Tetrabenazine, protoemetinol, สารที่มีโครงสร้างคล้าย Crispine A, ปฏิกิริยาการปิดวงของ *N*-acyliminium ion

ดวงกมล น้ำบริสุทธิ์ : การศึกษาการสังเคราะห์อัลคาลอยด์ quinolizidine tetrabenazine, protoemetinol และการสังเคราะห์สารที่มีโครงสร้างคล้าย crispine A : อาจารย์ที่ปรึกษาวิทยานิพนธ์ : ผศ.ดร.พัลลภ คันธิยงค์. 123 หน้า.

ควิโนลิซิดีนและอินโดลิซิดีนเป็นกลุ่มที่สำคัญของอัลคาลอยด์ที่มีฤทธิ์ต่างๆทางชีวภาพที่น่าสนใจ ในวิทยานิพนธ์นี้จะรายงานการศึกษาการสังเคราะห์อัลคาลอยด์ควิโนลิซิดีน เตตระเบนาซีน และโปรโตเอเมติ-นอล เตตระเบนาซีนเป็นยาที่สังเคราะห์เพื่อใช้ในการรักษาอาการโคเรียในโรคฮันติงตันและยังเป็นโปรดรักที่เมื่อผ่านกระบวนการเมตาโบลิซึมจะกลายเป็นไดไฮโดรเตตระเบนาซีนที่ใช้เป็นยาได้ โปรโตเอเมตินอลสกัดได้จาก *Alangium Salviifolium Lamarckii* และพบว่าเป็นสารตั้งต้นสำหรับอัลคาลอยด์ที่มีฤทธิ์ทางชีวภาพหลายชนิดที่มีฤทธิ์ต้านมะเร็ง ต่อต้านแบคทีเรียที่ก่อโรคและอื่นๆ เราใช้ปฏิกิริยาการปิดวงของ *N*-acyliminium ion เพื่อสร้างเบนโซควิโนลิซิดิโนนในสองเส้นทางการสังเคราะห์เตตระเบนาซีนและโปรโตเอเมตินอล โดยในเส้นทางแรกเบนโซควิโนลิซิดิโนนทำปฏิกิริยา Cope elimination เพื่อให้ enamide ซึ่งจะเกิด Michael addition กับ methoxide และ allylmagnesium bromide ที่ β-carbon เพื่อให้ได้ intermediate สำหรับเตตระเบนาซีนและโปรโตเอเมตินอลตามลำดับ อย่างไรก็ตามเมื่อทำ α-alkylation ของ lactam ที่เกิดขึ้นพบว่าไม่ประสบความสำเร็จ ในเส้นทางที่สองchiral imide จะทำ aldol reaction carbonyl reduction และ ปฏิกิริยาการปิดวงของ *N*-acyliminium ion ตามด้วยปฏิกิริยา Cope elimination ของเบนโซควิโนลิซิดิโนนจะให้ β,γ-unsaturated lactam และมีหมู่แทนที่บน α-carbon ของ lactam โดยขั้นตอนที่เหลือคือการปรับเปลี่ยนหมู่ฟังก์ชันที่ตำแหน่ง β-carbon ของ lactam ในเส้นทางนี้ผลิตภัณฑ์ที่เป็น diastereomer จากปฏิกิริยา aldol นำไปสู่การได้ผลิตภัณฑ์ที่เป็น enantiomer จากปฏิกิริยา Cope elimination เราจึงใช้วิธีการเดียวกันนี้ในการสังเคราะห์สารที่มีโครงสร้างคล้ายคลึงของอัลคา-ลอยด์ อินโดลิซิดีนคือ คริสปีน เอ จากปฏิกิริยาการเติม nucleophile บน chiral succinimide พบว่าผลิตภัณฑ์ที่ได้เป็น regioisomer ซึ่งจะนำไปสู่ผลิตภัณฑ์ ที่เป็น enantiomer ของสารที่มีโครงสร้างคล้ายคริสปีน เอ ดังนั้นการค้นพบของเราอาจนำไปสู่เส้นทางสังเคราะห์แบบ enantio-divergent สำหรับอัลคาลอยด์ควิโนลิซิดีน และอินโดลิ-ซิดีน อื่นๆด้วย

ภาควิชาเคมี บัณฑิตวิยาลัยมหาวิทยาลัยศิลปากร

ลายมือชื่อนักศึกษา ..... ปีการศึกษา 2559

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Abbreviations

DCC	dicyclohexylcarbodiimide
DMAP	*N*,*N*-dimethylamino pyridine
LAH	lithium aluminium hydride
THF	tetrahydrofuran
LDA	lithium diisopropylamide
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
DIBALH	diisobutylaluminium hydride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
BF_3-OEt_2	boron trifluoride diethyl etherate
dr	diastereomeric ratio
m-CPBA	3-chloroperoxybenzoic acid
Et_2O	diethyl ether
Ac_2O	acetic anhydride
TLC	thin layer chromatography
NMR	nuclear magnetic resonance spectroscopy
rt	room temperature
UV	ultraviolet
IR	infrared

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CHAPTER 1

INTRODUCTION

Alkaloid is an important class of natural products. Alkaloids are organic compounds containing nitrogen within the molecule in the form of amine, amine oxide as well as amide and imide. The nitrogen in the alkaloids comes from the amino acids. Most alkaloids have medicinal properties. In nature, many alkaloids are found in multicellular plant species, such as leaves, flowers, seeds, roots and bark and are less common in various parts of unicellular plant, animal and microorganism. Tetrahydroisoquinoline is a major subclass of alkaloids with various intriguing biological activities and diversity in structures. Tetrahydroisoquinoline fused to other heterocyclic systems gives rise to the structural diversity. For examples, pyrrolidino-tetrahydroisoquinoline is called benzoindolizidine while piperidino-tetrahydroisoquinoline is also called benzoquinolizidine.

The most common reaction for synthesis of tetrahydroisoquinoline is Pictet-Spengler reaction[1] and its many variations (Scheme 1.1). Arylethylamine and aldehyde combine in acidic conditions to give iminium ion intermediate. This undergoes intramolecular cyclization to form tetrahydroisoquinoline.

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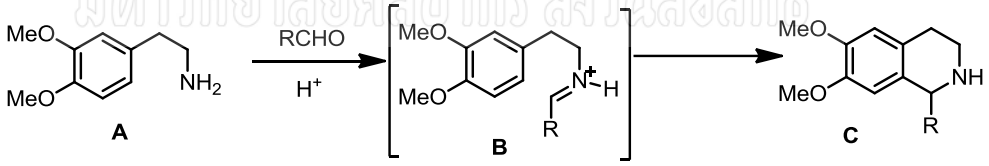
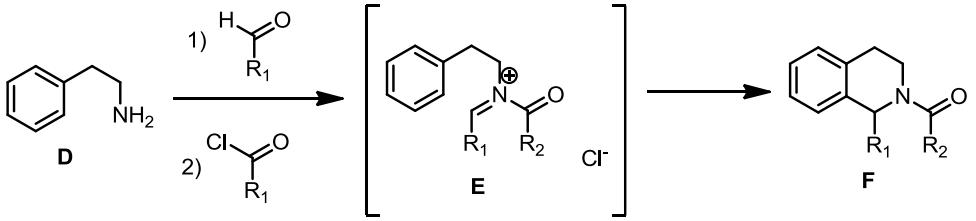
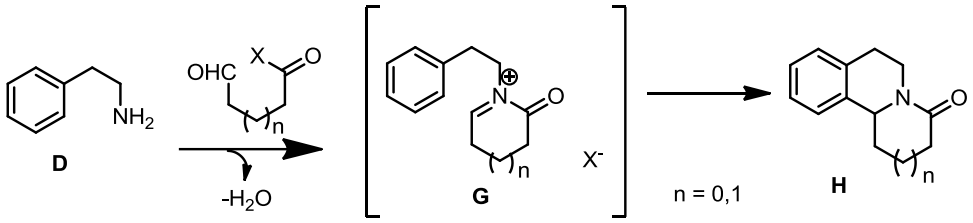


Scheme 1.1 Pictet-Spengler reaction

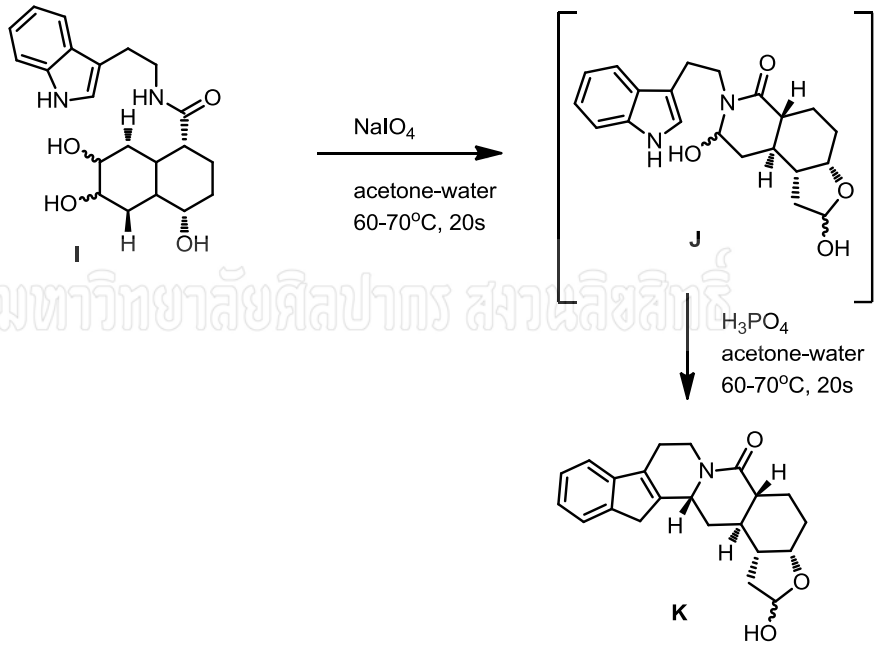
N-acyliminium ion cyclization[2] is another form of Pictet-Spengler reaction. ***N***-acyliminium ion is more reactive than iminium or *N*-alkyliminium ion in Pictet-Spengler reaction due to electron withdrawing ability of the acyl group. When the aldehyde and the acylating moiety are in the same molecule, it is possible to make 5- or 6-membered cyclic *N*-acyliminium ion which cyclizes to give benzoindolizidine or benzoquinolizidine, respectively (Scheme 1.2). Examples of *N*-acyliminium ion cyclizations in quinolizidines and indolizidine syntheses in recent literatures are shown below.





Scheme 1.2 ***N***-acyliminium ion cyclization

Indole alkaloids provide diverse platforms for application of *N*-acyliminium ion cyclization of arene π-nucleophiles in total synthesis. A classical application resulted in an early total synthesis of (±)-yohimbine by Van Tamelen and co-workers.[3,4] *N*-acyliminium ion J derived from a trapped dialdehyde from sodium metaperiodate oxidation of I, cyclized upon reaction with phosphoric acid to yield polycyclic lactam K (pseudoyohimbine configuration) in 60 % yield with high stereoselectivity (Scheme 1.3).



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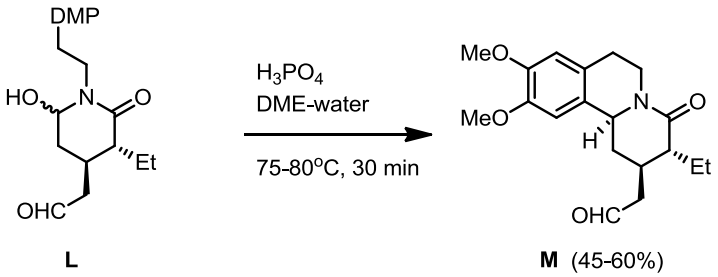
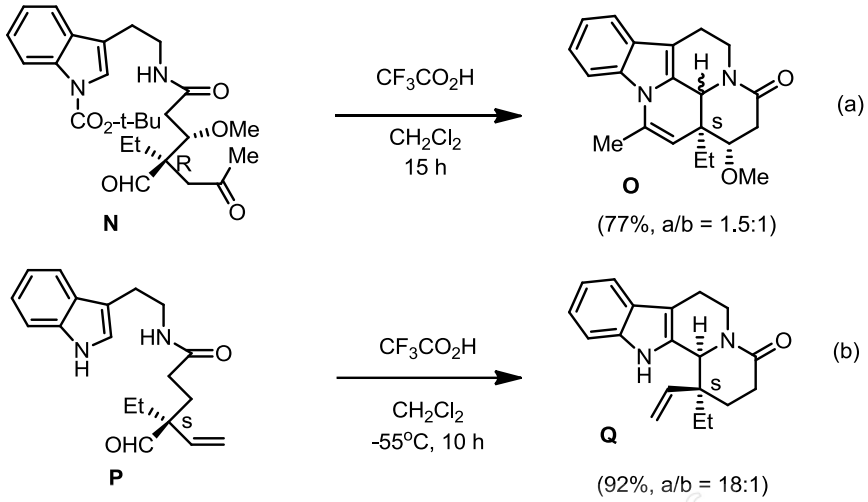
Scheme 1.3 *N*-acyliminium ion cyclization of indole

However, this type of reaction does not always yield high diastereoselectivity. For example, in an analogous cyclization en route to emeine, hydroxylactam **L** gave a mixture of three stereoisomers, including **M**. The difference in outcomes may relate to the greater reactivity of an indole group compared to a dimethoxyphenyl group[5] (Scheme 1.4).



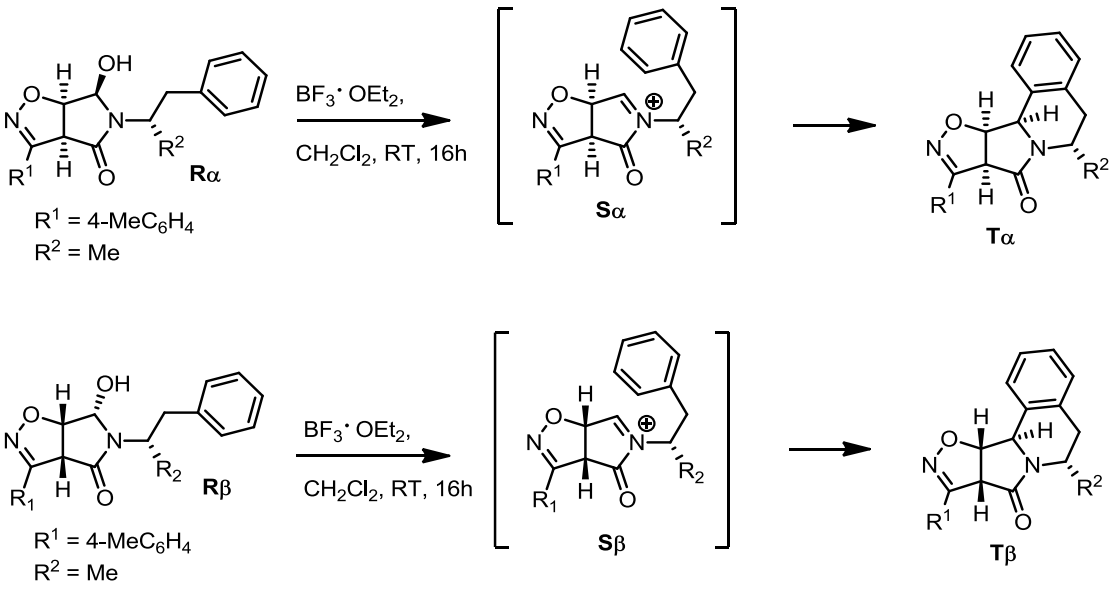
Scheme 1.4 *N*-acyliminium ion cyclization of benzene ring

In a formal total synthesis of (+)-vincamine by Schultz and co-workers, three new rings were constructed in the *N*-acyliminium ion cyclization, but the reaction gave just a 1.5:1 ratio of isomer(eq a).[6] However, in the analogous cyclization of **P**, diastereomeric ratio of 18:1 was obtained (eq b; 7 : 1 at 20ºC).[7] This high stereoselectivity may come from an electronic effect of the π-bond of the vinyl group, perhaps via a π–π interaction with the indole. In general, such indole-based cyclization with substituents on the stereogenic center α to the carbocation in a six-membered-ring- *N*-acyliminium ion deliver marginal diastereoselectivities, ca 1:1 (Scheme 1.5).



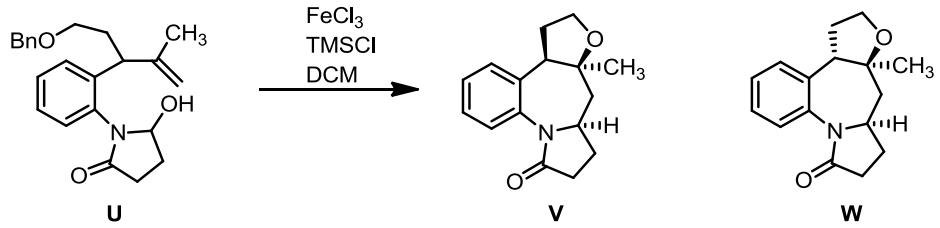
Scheme 1.5 Diastereoselectivity *in N*-acyliminium ion cyclization

The synthesis of substituted isoxazolopyrroloisoquinolines by Stepakov and co-workers [8] which is a major structural fragment of *Erythrina* and lamellarin alkaloids via diastereoselective *N*-acyliminium ion cyclization is shown below. This reaction gave tetracyclic product as a single diastereomer. The new stereogenic center assumed *R*-configuration regardless of the configurations at the isoxazole ring junction. This is due to the fact that the R_2 substituent prefers to be in the equatorial position of the 6-membered ring constructed in the *N*-Acyliminium ion cyclization (Scheme 1.6).



Scheme 1.6 Diastereoselective in *N*-acyliminium ion cyclization

Other than phenyl and indole derivatives, alkene and alkyne can serve as π-nucleophile in intramolecular *N*-acyliminium ion cyclization. In addition, when the carbocationic intermediate can be trapped intramolecularly by a second nucleophile, *i.e.* a heteroatom, the process becomes a tandem cyclization in which two rings are formed in one step. An interesting example is shown below. In synthetic study on tetrapetalones by Hong and co-workers[9], diastereoselective tandem cyclization of *N*-acyliminium ion derived from hydroxylactam **U** constructed substituted 1-benzazepines as mixture of diastereomers **V** and **W** (Scheme 1.7).

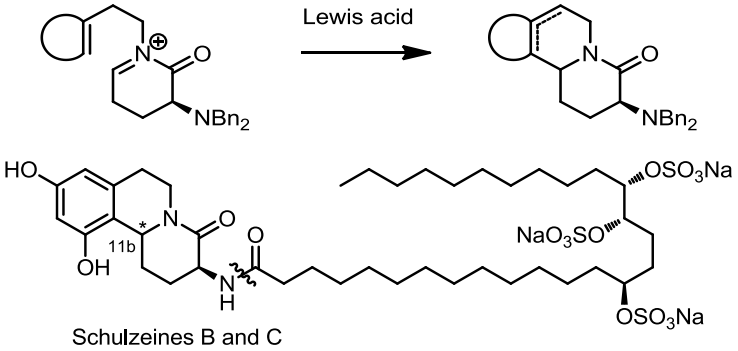


U **V** **W**

Scheme 1.7 Stereoselective cyclization of *N*-acyliminium ion to construct substituted 1-benzazepines

Our Previous work

Previously we reported advanced intermediate of α-glucosidase inhibitors schulzeines B and C[10] (a formal synthesis) via *N*-acyliminium ion cyclization. The *N*-acyliminium ion derived from protected 2-(3,5-dihydroxyphenyl)ethylamine and L-glutamic acid derivative underwent cyclization that gave diastereomeric benzoquinolizidinone products with the amino group substituted at the right position and configuration for schulzeines B and C (Scheme 1.8).



Schulzeines B and C

Scheme 1.8 Schulzeines B and C

Starting from indole, homoveratrylamine and 3-butenylamine we synthesized indoloquinolizidine, dimethoxybenzoquinolizidine and quinolizidine **b**, **d** and **f**[11], respectively. With these heterocyclic cores in hand we synthesized non-natural analogs **g**, **h**, and **i** of schulzeines and preliminary testing showed that they possessed anti-α-glucosidase activity (Figure 1.1).

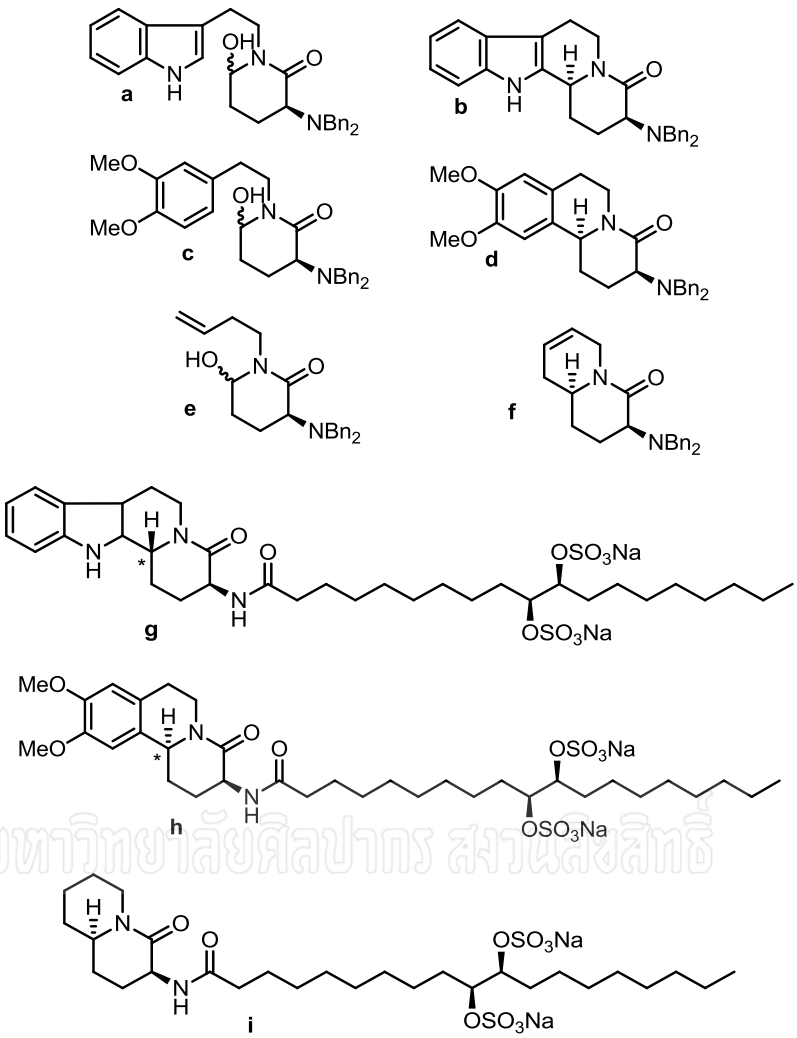


Figure 1.1 Indoloquinolizidine, dimethoxybenzoquinolizidine, quinolizidine and schulzeines analogs

Using L-aspartic acid derivative as starting material, chiral succinimide intermediates were synthesized and converted to hydroxylactam **j** and **l**. *N*-acyliminium ion cyclization from these hydroxylactams gave benzoindolizidine **k** and indolizidine **m**, respectively. This result gives us the starting point for synthetic studies of various indolizidine alkaloids (Scheme 1.10).

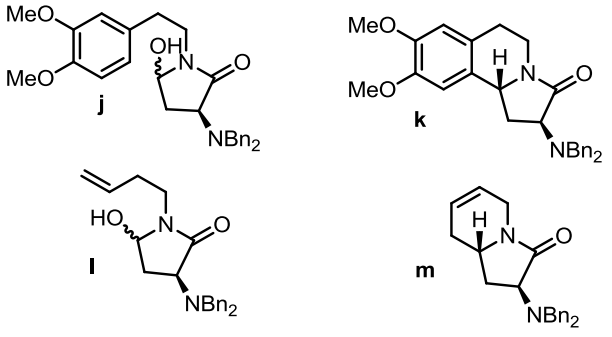


Figure 1.2 indolizidine alkaloids

In this thesis we discuss our effort to expand the scope of the key reaction, *N*-acyliminium ion cyclization, to synthesize the quinolizidine alkaloids; tetrabenazine, protoemetinol and analogs of cytotoxic indolizidine alkaloids crispine A.

Tetrabenazine[12] is a chiral synthetic drug used for treatment of motor dysfunction associated with the Huntington's disease. It is a pro-drug that is metabolized to the active drug dihydrotetrabenazine (Figure 1.3).

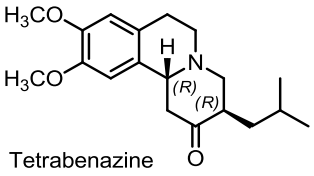
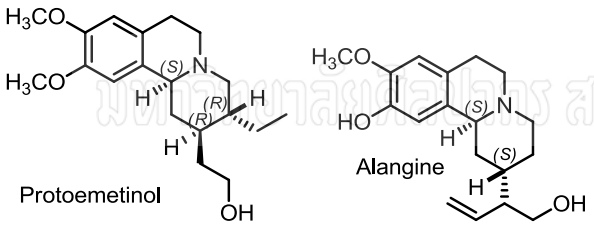


Figure 1.3 Structure of Tetrabenazine

Protoemetinol was isolated from the *Alangium Salviifolium Lamarckii*[13]. It has been found as precursor for several other alkaloids with intriguing biological activities such as anticancer, anti-amoebic, anti-HIV and emetic activities. We are also looking into another quinolizidine alkaloid, alangine which is a potential drug for hypertension, diabetes, epilepsy, cancer, inflammation, ulcer, etc (Figure 1.4).



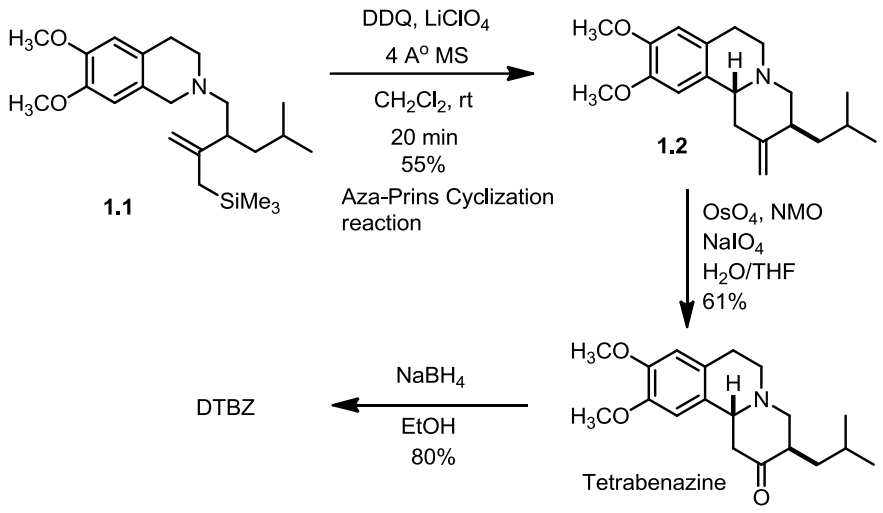
Alangium salviifolium Lamarckii

Figure 1.4 Structure of Protoemetinol, Alangine and *Alangium Salviifolium Lamarckii*

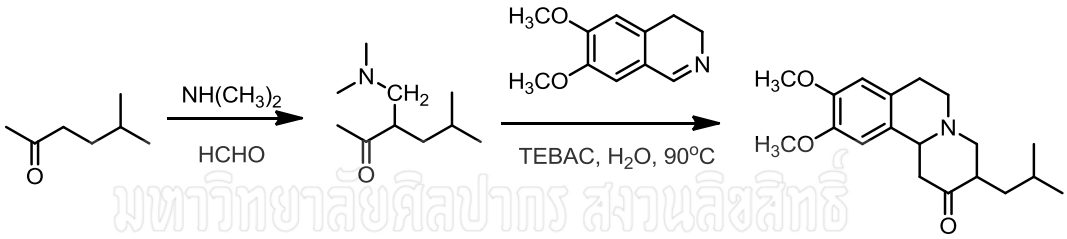
Related work and Literature Review

Previous synthesis of Dihydrotetrabenazine

Several previous syntheses of tetrabenazine have been reported as both racemic and asymmetric syntheses. For example, Yong Wook Son and co-workers[14] used intramolecular aza-Prins-type cyclization of amino allylsilane **1.1** to give the tricyclic core **1.2** with an exocyclic olefin in high diastereoselectivity, albeit as racemic mixture, as the key reaction. Oxidative cleavage of the olefin gave tetrabenazine and subsequent carbonyl reduction gave dihydrotetrabenazine (Scheme 1.9). Moreover, Xiaomin and co-workers[15], synthesis started from 3-dimethylaminomethyl-5-methyl-hexan-2-one which was synthesized from 5-methyl-2-hexanone via Mannich reaction. This compound reacted with 6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride and triethylbenzylammonium chloride (TEBAC) as catalyst to give tetrabenazine (scheme 10).



Scheme 1.9 Synthesis of dihydrotetrabenazine by Yong Wook Son and co-workers



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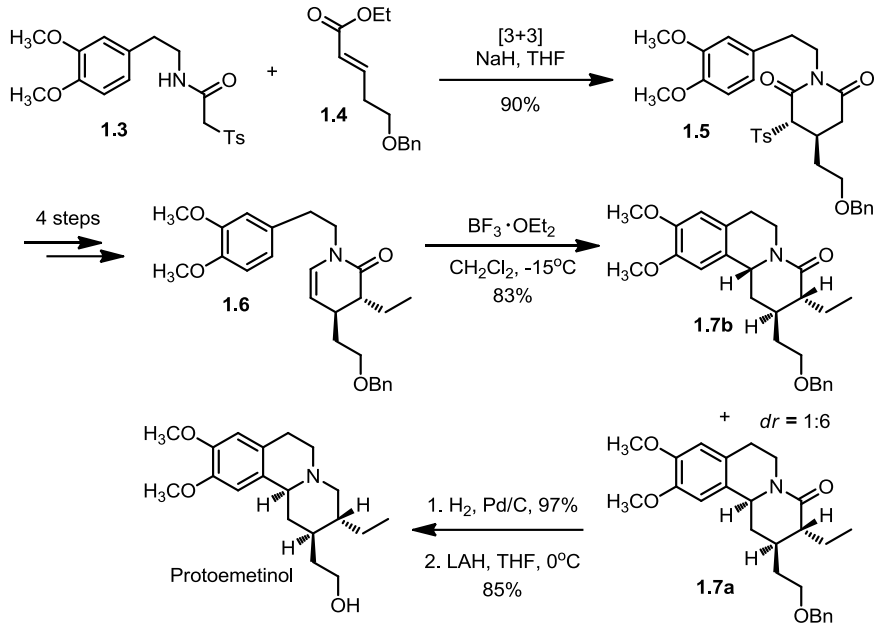
Scheme 1.10 Synthesis of dihydrotetrabenazine by Xiaomin and co-workers

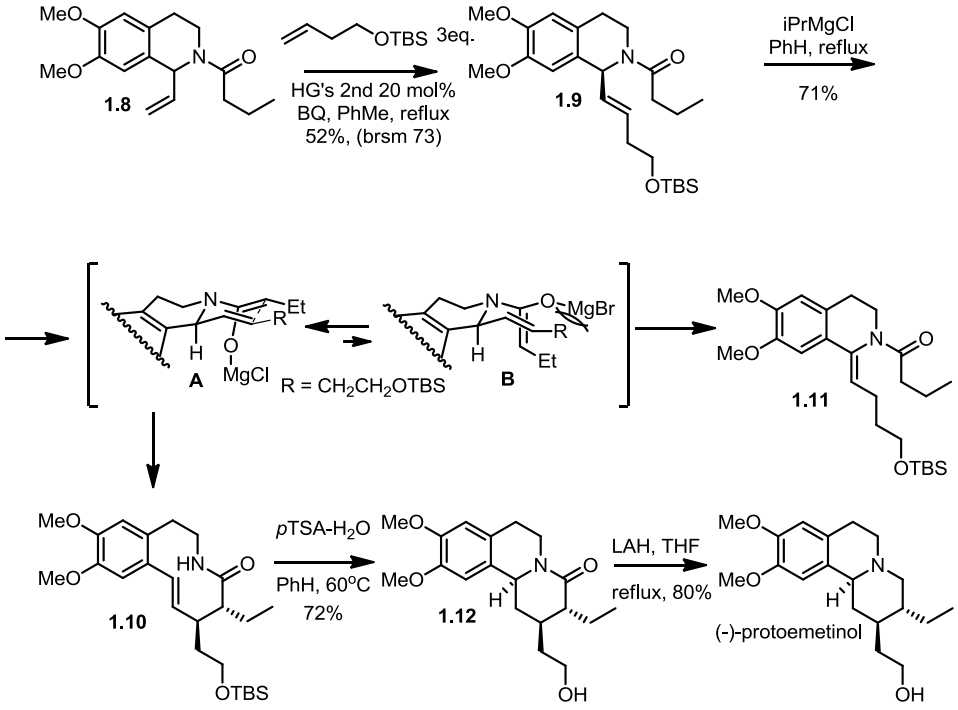
Previous synthesis of Protoemetinol

A racemic synthesis of (±)-protoemetinol by Chang and co-workers[16] in 2008 started from α-sulfonyl acetamide. They completed the recemic synthesis in 8 steps. The key transformations involved a formal [3+3] cycloaddition that formed imide **1.5** which underwent α-alkylation and elimination of the toluenesulfonyl group to give eneamide **1.6**. *N*-Acyliminium ion cyclization upon treatment with BF_3-OEt_2 gave the substituted benzoquinolizidine core. The major diastereomer **1.7a** was converted to protoemetinol in two additional steps (Scheme 1.11).



Scheme 1.11 Synthesis of (±)-protoemetinol by Chang and co-workers

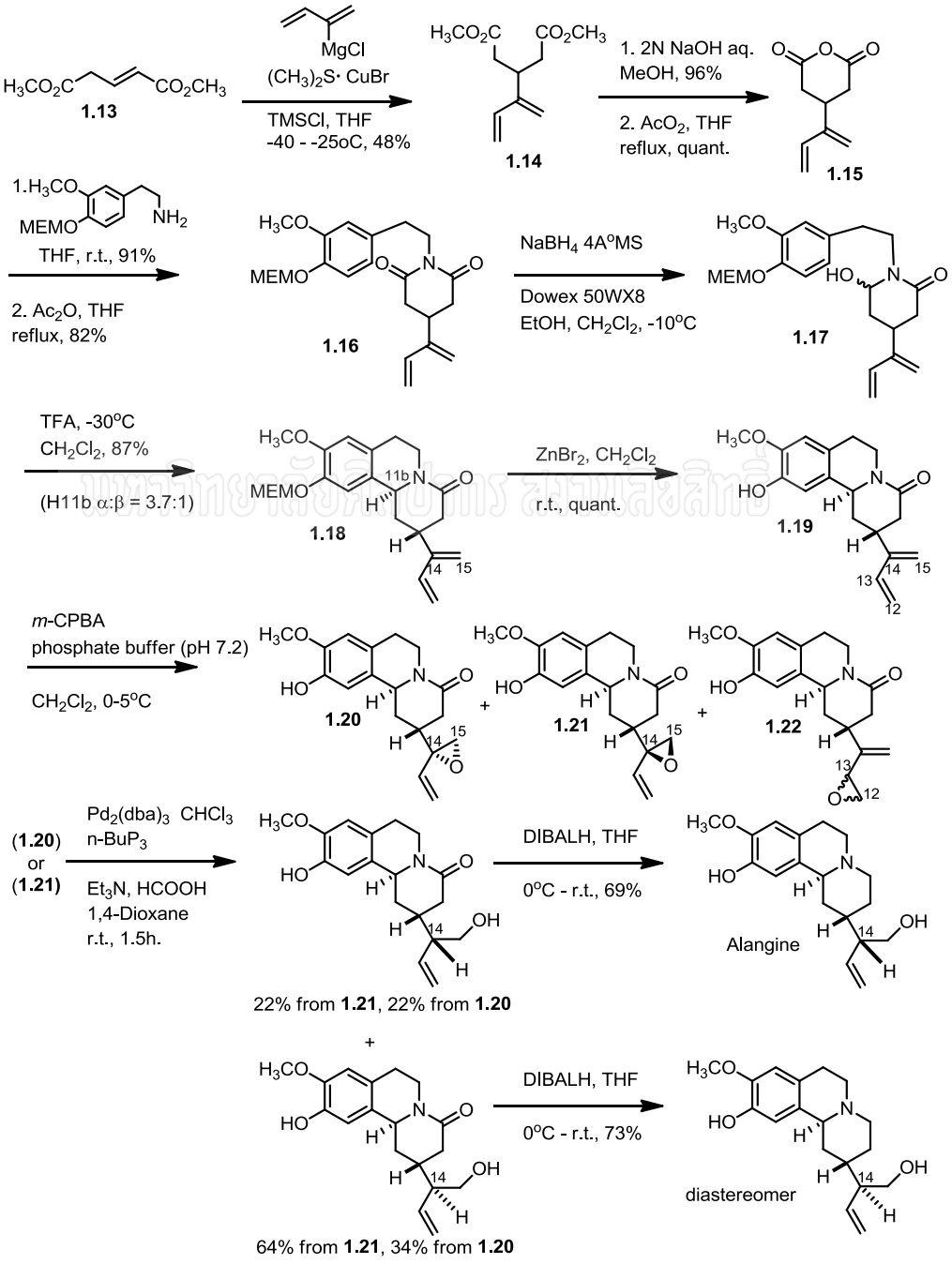
The stereoselective synthesis of (-)-protoemetinol by Suh and co-workers[17] was accomplished through nine steps from a known tetrahydroisoquinoline **1.8**. They used aza-Claisen rearrangement as a key step. Formation of benzo[α]quinolizine skeleton **1.12** and three stereogenic centers was accomplished via acid-catalyzed transannulation (Scheme 1.12).



Scheme 1.12 Synthesis of (-)-protoemetinol by Suh and co-workers

Previous synthesis of Alangine

Alangine is a related benzoquinolizine alkaloid lacking a substituent at C3 (α-carbon). Synthesis of (±)-alangine by Takayama and co-workers[18] was completed in 11 steps. The key imide intermediate with diene substituent was formed from dimethyl ester of glutaric acid and arylethylamine. Subsequent carbonyl reduction and *N*-acyliminium ion cyclization gave the desired tricyclic product with moderate diastereoselectivity. The remaining steps concerned conversion of the diene substituent into 3-buten-1-ol-2-yl substituent using epoxidation and Pd(II) catalyzed epoxide opening via π-allyl-Pd intermediate (Scheme 1.13).



Scheme 1.13 Synthesis of (±)-Alangine by Takayama and co-workers

We envision alangine could be synthesized using same strategy as tetrabenazine and protoemetinol. However, the starting arylethylamine foe alangine synthesis is anot commercially available and need to be synthesized in several steps. Therefore, we postponed the synthetic study of alangine to later occasion.

Indolizidine alkaloids[19] are another important class of natural products with a diversity of structural variations and intriguing biological activities. Polyhydroxylated indolizidines are exemplified in Fig 1.5 by natural toxin swainsonine (**1.22**) which is a potential chemotherapeutic drug for glioma, gastric and renal carcinoma and lentiginosine (**1.23**) which inhibits amyloglucosidase, ATPase and chaperones activity of Hsp90, therefore it is also a potential multi-target anti-cancer drug. Benzoindolizidine crispine A (**1.24**) is a highly cytotoxic alkaloid isolated from flowering plant *Carduus crispus.* Jamtine (**1.25**), isolated from climbing shrub of *Cocculu hirsutus*, exhibits anti-hyperglycemic activity. Alkaloids isolated from plants of the *Erythrina* genus such as erysotramidine (**1.26**) and erytraditinone (**1.27**) have a more complex spirotetracyclic system. *Erythrina* alkaloids possess many pharmaceutical properties and have been used as hypoglycemic, hypotensive, sedative antidiarrheal, antiasthma, CNS activity depressing, anticonvulsive and muscle relaxing agent (Figure 1.5).

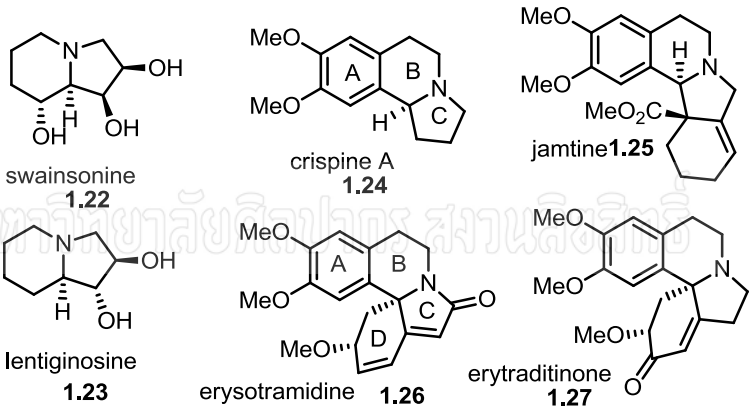


Figure 1.5 Benzoindolizidine, hydroxylated indolizidine alkaloids and *Erythrina* alkaloids

Crispine A[20] is an indolizidine alkaloids which was isolated from the Chinese plant *Carduus crispus*. It has been used as folk medicine for treatment of stomachache and rheumatism. Biological activity studies have also shown that it inhibits the growth of cancer (Figure 1.6).

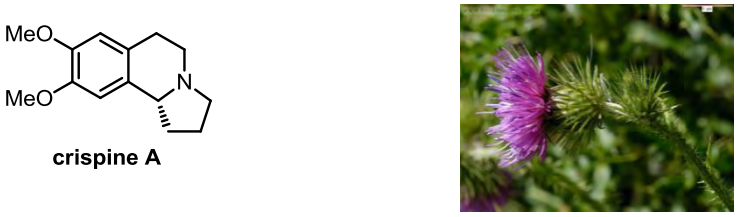
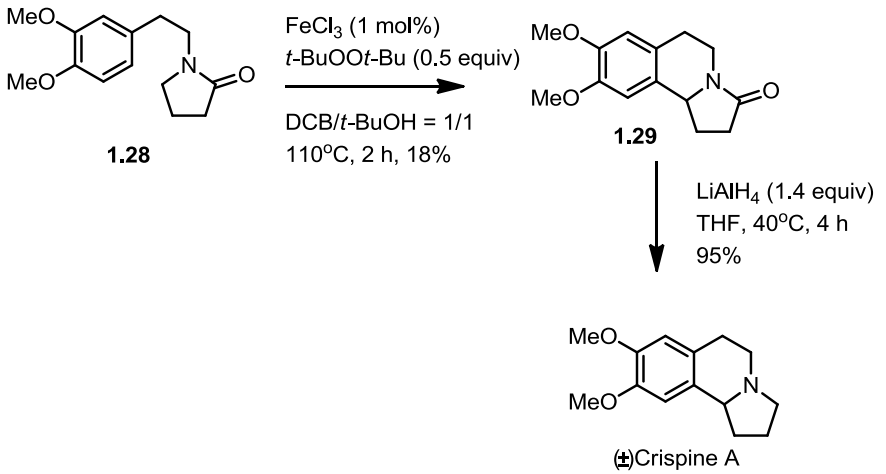


Figure 1.6 Structure of crispine A and *Carduus crispus*

Related work and Literature Review

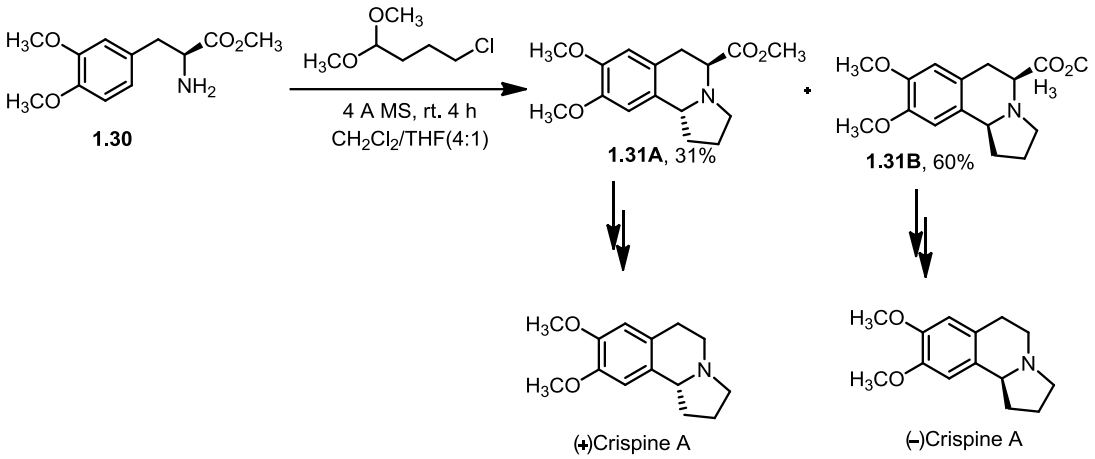
Synthesis of Crispine A

Several previous synthesis of Crispine A have been reported as racemic and asymmetric syntheses. For example a racemic synthesis by Shirakawa, Uchiyama and Hayashi[21] used tetrahydroisoquinoline ring formation via *N*-acyliminium ion cyclization as the key reaction. Then carbonyl group was removed by LAH reduction to give Crispine A in racemic form (Scheme 1.14).



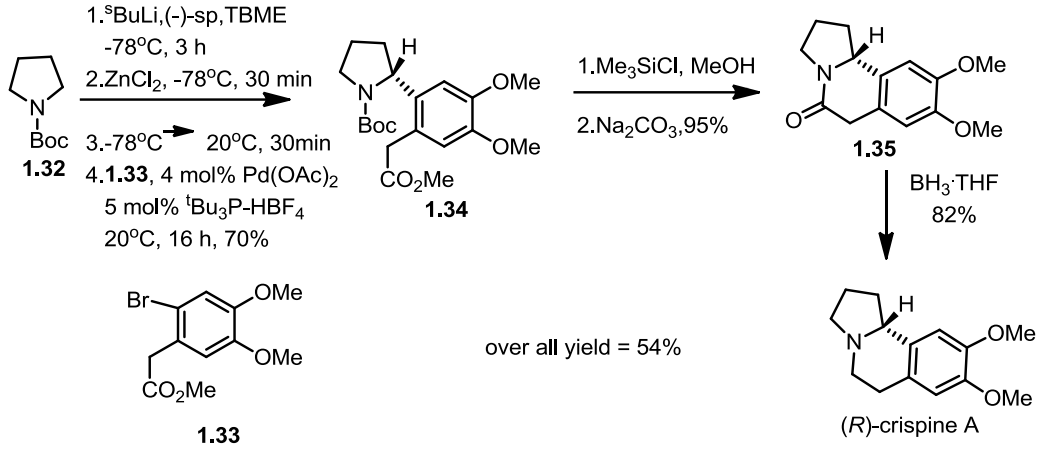
Scheme 1.14 Synthesis of crispine A by Shirakawa Uchiyama and Hayashi.

Asymmetric synthesis of crispine A by Herr and co-works[22] started from methyl ester of chiral amino acid. The generation of stereogenic center of the product was controlled by the stereogenic center of the substrate. The key reactions were nucleophilic substitution, Pictet-Spenler type reaction of amino acid and chlorodimethylketal. This reaction gave diastereomer **1.31B** in favor over **1.31A** in the ratio of 2:1. The major diastereomer was used for synthesis of (-)-crispine A whereas **1.31A** was converted to (+)-crispine A (Scheme 1.15).



Scheme 1.15 Synthesis of crispine A by Herr and co-workers.

An asymmetric synthesis by O'Brien and co-workers[23] used chiral sparteine for enantio-controlled coupling of organozinc species derived from *N*-Boc pyrrolidine **1.32** and aryl bromide **1.33** employing palladium catalysis. The resulting key intermediate **1.34** was changed to lactam **1.35**. Then reduction of lactam **1.35** gave *R*-Crispine A (Scheme 1.16).



Scheme 1.16 Synthesis of Crispine A by O'Brien and co-workers.

Syntheses of methyl analog **1.41** of crispine A have also been reported. Baskaran[24] (Scheme 1.17) used intramolecular Schmidt reaction of azido-indenone **1.36** as the key reaction and the product was obtained as a racemic mixture. Early enantioselective synthesis was reported by Meyers[25] (Scheme 1.18) featuring asymmetric quaternary alkylation based on chiral formamidine auxiliary. Sato[26] (Scheme 1.19) reported an enantioselective synthesis using asymmetric addition of chiral propionaldehyde titanium homoenolate equivalent to imine carbon of a dihydroisoquinoline.

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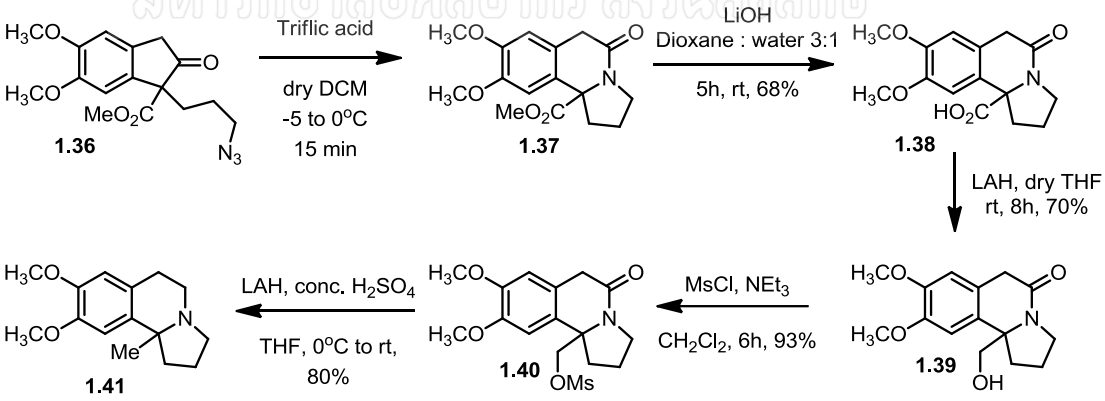
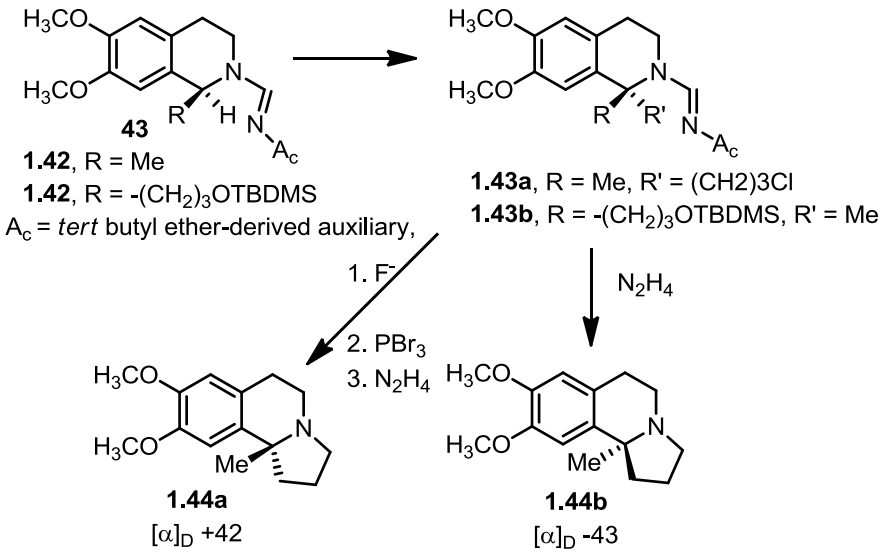
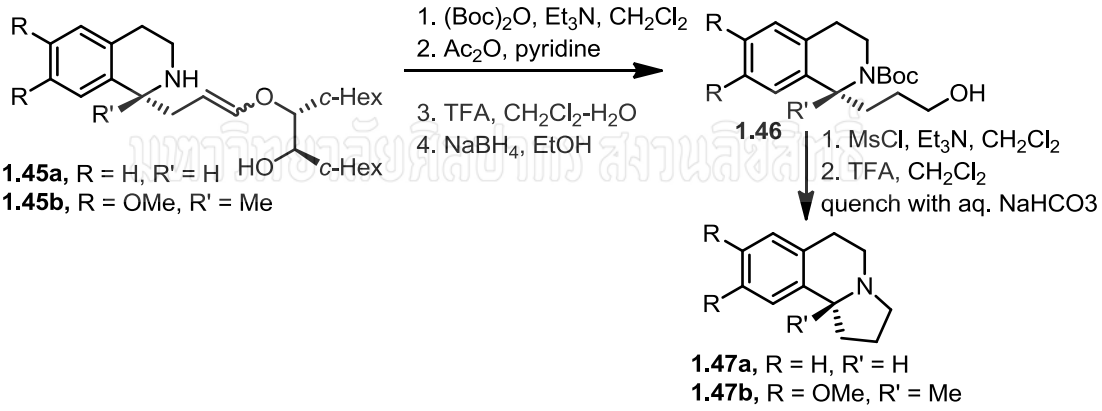


Scheme 1.17 Synthesis of methyl analog of crispine A by Baskaran and co-workers.



Scheme 1.18 Synthesis of methyl analog of crispine A by Meyers and co-workers.



Scheme 1.19 Synthesis of methyl analog of crispine A by Sato and co-workers.

We use *N*-acyliminium ion cyclization as the key reaction in synthetic studies of dihydrotetrabenazine, protoemetinol and analogs of crispine A. The stereocenter bearing the dibenzylamino (NBn_2) group served as the stereocontrol element of the key reaction. It would subsequently be removed via Cope elimination to give the C=C double bond which would be functionalized in later steps toward the target molecules. Our synthetic approach is intended to be distinct in design but comparable in terms of efficiency to the previously reported syntheses. Most of those syntheses of quinolizidine alkaloids used *N*-acyliminium ion cyclization of precursor with all or most substituents already installed making the synthetic approach target-specific. We aim to develop a synthetic route that can be divergent in terms of structural diversity as well as enantio-divergent.

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CHAPTER 2

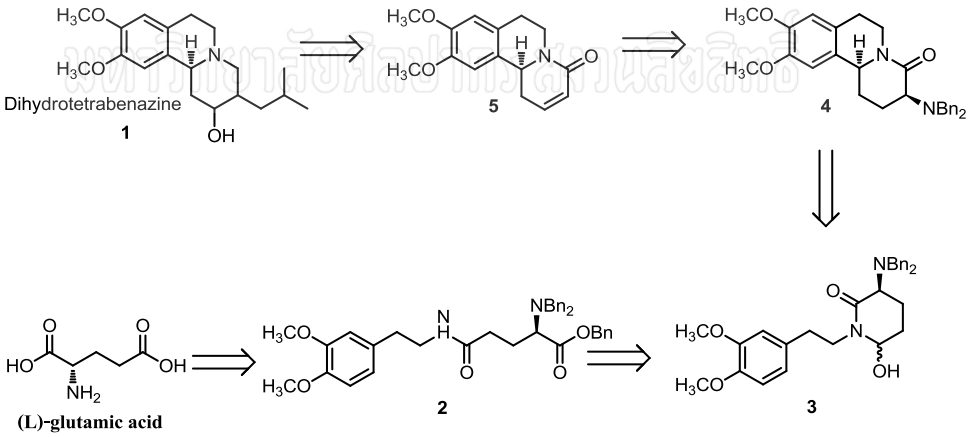
PART A : SYNTHETIC STUDY OF DIHYDROTETRABENAZINE

In this chapter we discuss synthetic Studies toward total syntheses of quinolizidine alkaloids, dihydrotetrabenazine, protoemetinol and analogs of cytotoxic indolizidine alkaloid crispine A featuring *N*-acyliminium ion cyclization as the key reaction and subsequent Cope elimination to provide the suitable functionality for the remaining steps of the synthesis.

First route: Formation of enamide for Michael addition

Retrosynthetic analysis

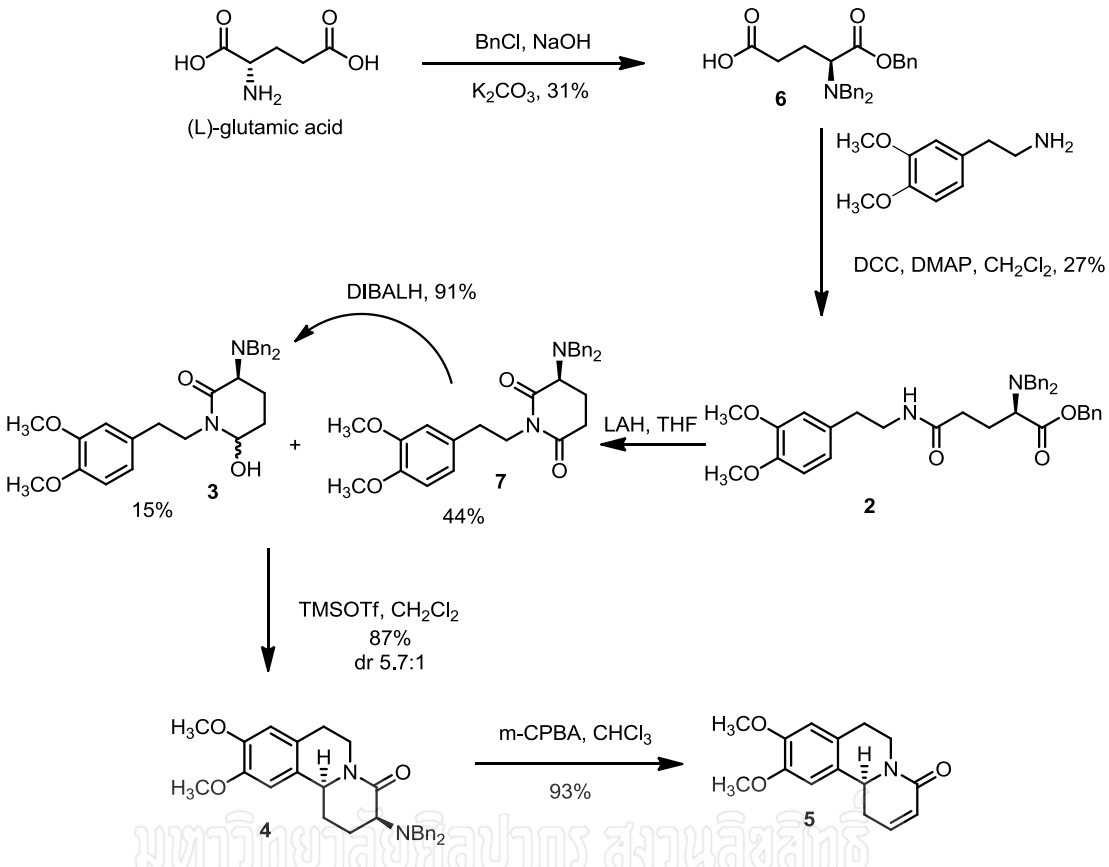
Our retrosynthetic analysis for dihydrotetrabenazine is shown in scheme 2.1. We envision dihydrotetrabenazine **1** to be obtained from tricyclic enamide **5**. The tricyclic enamide **5** could be synthesized by Cope elimination[1] of tricyclic benzoquinolizidinone **4** with *m*-CPBA. The benzoquinolizidinone **4** would be the product of *N*-acyliminium ion cyclization of hydroxylactam **3**. The hydroxylactam **3** could be prepared from reduction of amido-ester **2**. The amido-ester **2** would be derived from homoveratrylamine and L-glutamic acid.



Scheme 2.1 Retrosynthetic analysis of dihydrotetrabenazine

Synthetic of tricyclic enamide precursor 5

Synthesis of tricyclic enamide precursor **5** started from L-glutamic acid which was converted to tricyclic enamide **5** in 5 steps. First, benzylation of L-glutamic acid provided benzyl dibenzylamino glutamate **6** which reacted with homoveratrylamine to give amido-ester **2**. The amido-ester **2** was then treated with LAH to give hydroxylactam **3** along with imide **7**. Carbonyl reduction of the imide **7** with DIBALH gave hydroxylactam **3**. Then hydroxlactam **3** was treated with TMSOTf to give tricyclic benzoquinolizidinone **4** as a mixture of 2 diastereomers with diastereomeric ratio of 5.7 : 1 via *N*-acyliminium ion cyclization. Finally, Cope elimination of tricyclic benzoquinolizidinone **4** with *m*-CPBA gave tricyclic enamide precursor **5 (**Scheme 2.2)**.**



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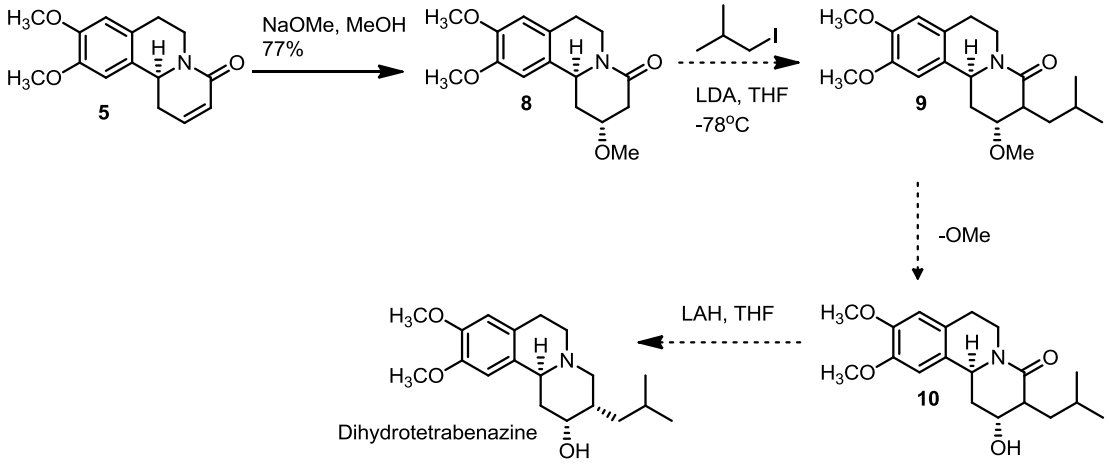
Scheme 2.2 Synthesis of tricyclic enamide precursor **5**

Michael addition of tricyclic enamide **5** with NaOMe gave methyl ether-lactam **8** as a single diastereomer. The remaining steps are alkylation, demethylation[2] and lactam reduction[3] respectively. However, alkylation reaction of lactam **8** with isobutyl iodide was not successful (Scheme 2.3).

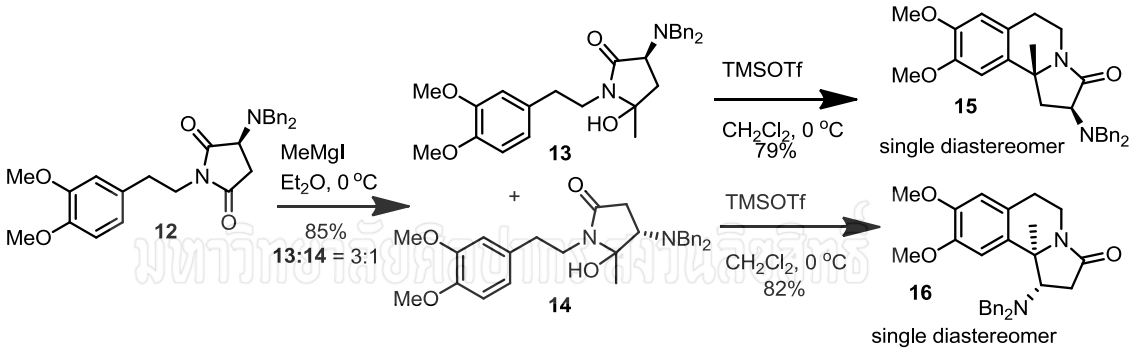


Scheme 2.3 Synthetic approach toward dihydrotetrabenazine from enamide **5**

PART B: SYNTHESIS OF ANALOGS OF CRISPINE A

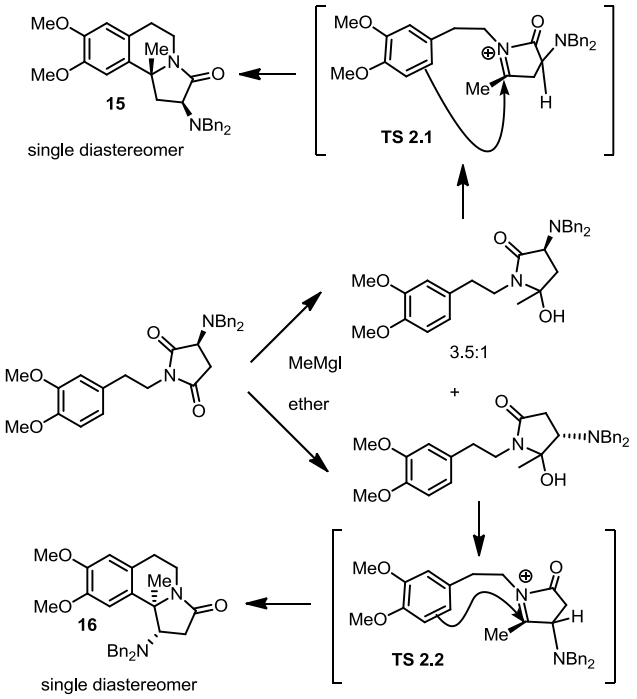
Tetrabenazine and protoemetinol are benzoquinolizidine alkaloids which can also be classified as piperidinotetrahydroquinoline alkaloids. We are also applying the same synthetic approach toward related benzoindolizidine alkaloids which can also be classified as pyrrololidinotetrahydroquinoline-alkaloids. We have conducted synthesis of analogs of a cytotoxic benzoindolizidine alkaloids, crispine A and the result is discussed below.

In our previous study, chiral *N*-arylethylsuccinimide **12** obtained from homoveratrylamine and a *N*,*N*-dibenzyl derivative of L-aspartic acid underwent reduction with DIBALH exclusively at the less hindered carbonyl to give the corresponding hydroxylactam. However, in this work, nucleophilic addition to the carbonyl of chiral *N*-arylethylsuccinimide **12** with methyl magnesium iodide gave two regioisomeric hydroxylactams **13** and **14** which were separated chromatographically (scheme 2.4).



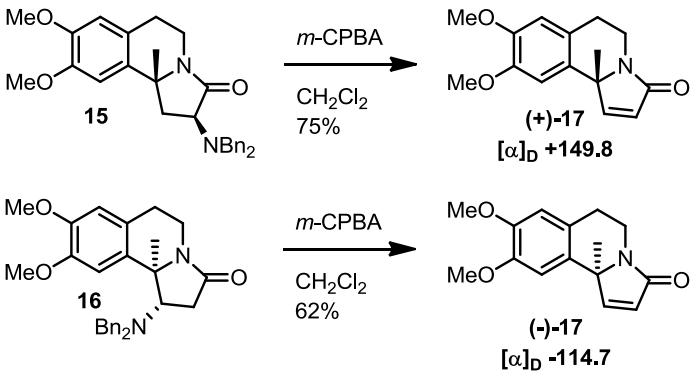
Scheme 2.4 Formation of benzoindolizidines **15** and **16**

We can rationalize the stereochemistry of the reaction with transition states shown in scheme 2.5. It can be seen that the nucleophile attacks the *N*-acyliminium ion on the opposite side of the *N*,*N*-dibenzylamino group due to its steric effect. If the reaction occurs through **TS 2.1** benzoindolizidine **15** is obtained while **TS 2.2** provided benzoindolizidine **16**.

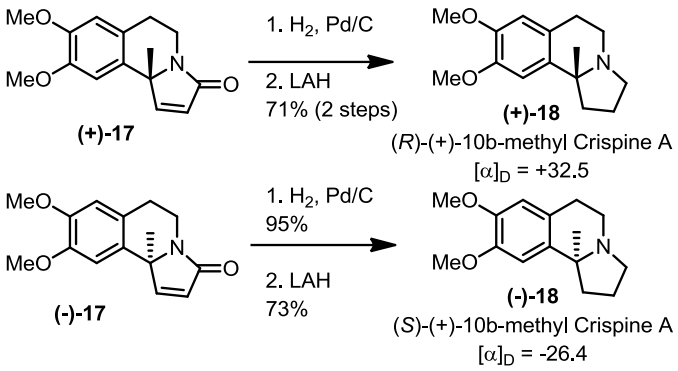


Scheme 2.5 Transition states for *N*-acyliminium ion cyclization giving benzoindolizidines **15** and **16**

Treatment of hydroxylactam **13** with TMSOTf gave tricyclic product **15** and hydroxylactam **14** gave **16** as single diastereomers setting up the quaternary stereogenic center. Cope elimination upon treatment of dibenzylamino lactams **15** and **16** gave cyclic enamides (+)-**17** and (-)-**17**, respectively (scheme 2.6). We could determine that the configurations of the stereogenic center at C10b of the regioisomeric cyclized products were opposite by comparing the optical rotation of tricyclic enamides **17**. Hydrogenation followed by lactam reduction of the cyclic enamides gave methyl analog of crispine A (+)-**18** and (-)-**18** (scheme 2.7).



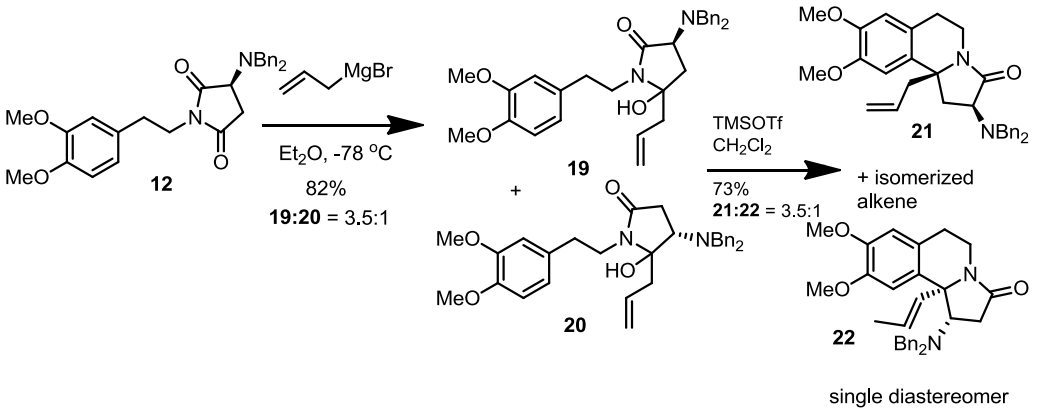
Scheme 2.6 Cope elimination



Scheme 2.7 Synthesis of crispine A analogs

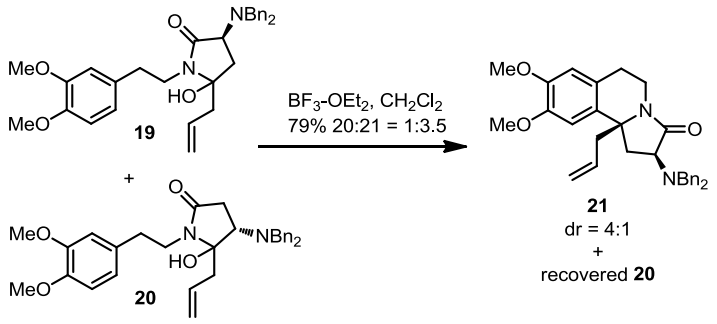
Comparison of their optical rotations with the reported values led us to the conclusion that **15** gave (+)-**17** with *R*-configuration while **16** gave (-)-**17** with *S*-configuration. The magnitudes of the optical rotation, however, were surprisingly lower than expected of a highly enantio-enriched products. This suggests a loss of enantiomeric excess via epimerization which appeared to occur at a larger extent with **16** during the synthetic route.

Our synthesis of 11b-n-propyl-3-oxocrispine A began with imide **12** which reacted with allyl magnesium bromide to give regioisomeric mixture of hydroxylactams **19** and **20**. Attempts at chromatographic separation of this mixture led to decomposition of **19**. Therefore this mixture was treated with TMSOTf in CH_2Cl_2 which resulted in a complex mixture. The cyclized products of hydroxylactam **19** consisted of benzoindolizidine **21** along with the olefin-isomerized product as a mixture of 2 diastereomers. The cyclized product **22** with an isomerized C=C double bond from hydroxylactam **20** was more polar and easily separated from the others (scheme 2.8).



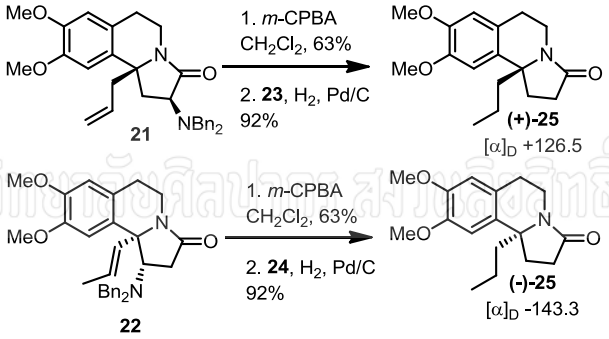
Scheme 2.8 Formation of C10b-allylbenzoindolizidines **21** and **22**

On contrary, treatment of imide allylation product mixture with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 resulted in *N*-acyliminium ion cyclization of hydroxylactam **19** to give the cyclized product **21** without isomerization of the C=C double bond, whereas the regioisomeric hydroxylactam **20** was recovered intact. The ratio of the product **21** and unreacted hydroxylactam **20** was 3.5:1 by weight. The diastereomeric ratio of benzoindolizidine **21** was determined to be 4:1 from analysis of ^{1}H NMR spectrum (scheme 2.9).



Scheme 2.9 $BF_3 \cdot OEt_2$ mediated *N*-acyliminium ion cyclization

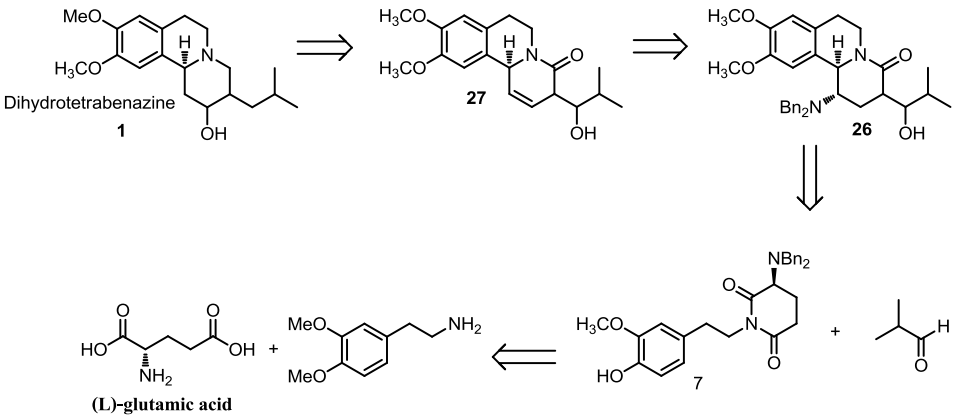
The configurations of the stereogenic center at C10b of the regioisomeric cyclized products were proven to be opposite by comparing the optical rotation of a common intermediate. Conversion of regioisomeric benzoindolizidines **21** and **22** into their corresponding tricyclic enamides **23** and **24**, respectively, was accomplished via Cope elimination. Hydrogenation of these enamides gave enantiomeric (+)-**25** and (-)-**25** proving that the dibenzylamino group exerted stereochemical control that enabled synthesis of both enantiomers of the heterocyclic compounds (scheme 2.10). [4]



Scheme 2.10 synthesis of tetracyclic core of 11b-propyl-3-oxocrispine A

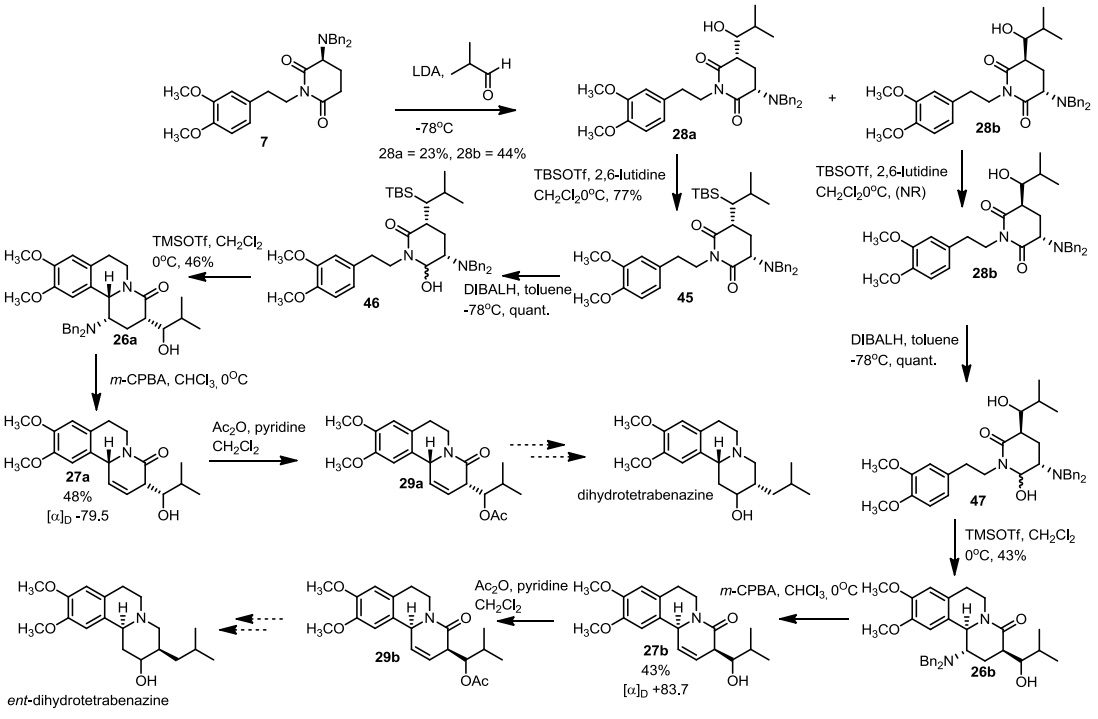
Second Route: Enantio-divergent route toward tricyclic quinolizidine

Facing the difficulty of adding the substituent at the α-position of the advanced intermediate and also intrigued by the possibility of making an enantio-divergent route, inspired by the results of synthesis of crispine A analogs, we redesigned the synthetic route toward dihydrotetrabenazine. Our second retrosynthetic analysis is shown in scheme 2.10. We envision dihydrotetrabenazine **1** to be obtained from unsaturated lactam **27** by reduction of lactam carbonyl, deoxygenation of the alcohol and hydration of the alkene. The tricyclic enamide **27** could be synthesized by Cope elimination of tricyclic benzoquinolizidine **26** with *m*-CPBA. The tricyclic **26** in turn could be prepared from aldol reaction of chiral imide **7** with isobutyraldehyde. Expecting that the aldol reaction could give diastereomeric products, we hypothesized that the opposite configurations of the aldol adduct could lead to opposite diastereomers during the *N*-acyliminium ion cyclization. The chiral imide **7** would be derived from homoveratrylamine and (L)-glutamic acid (Scheme 2.11).



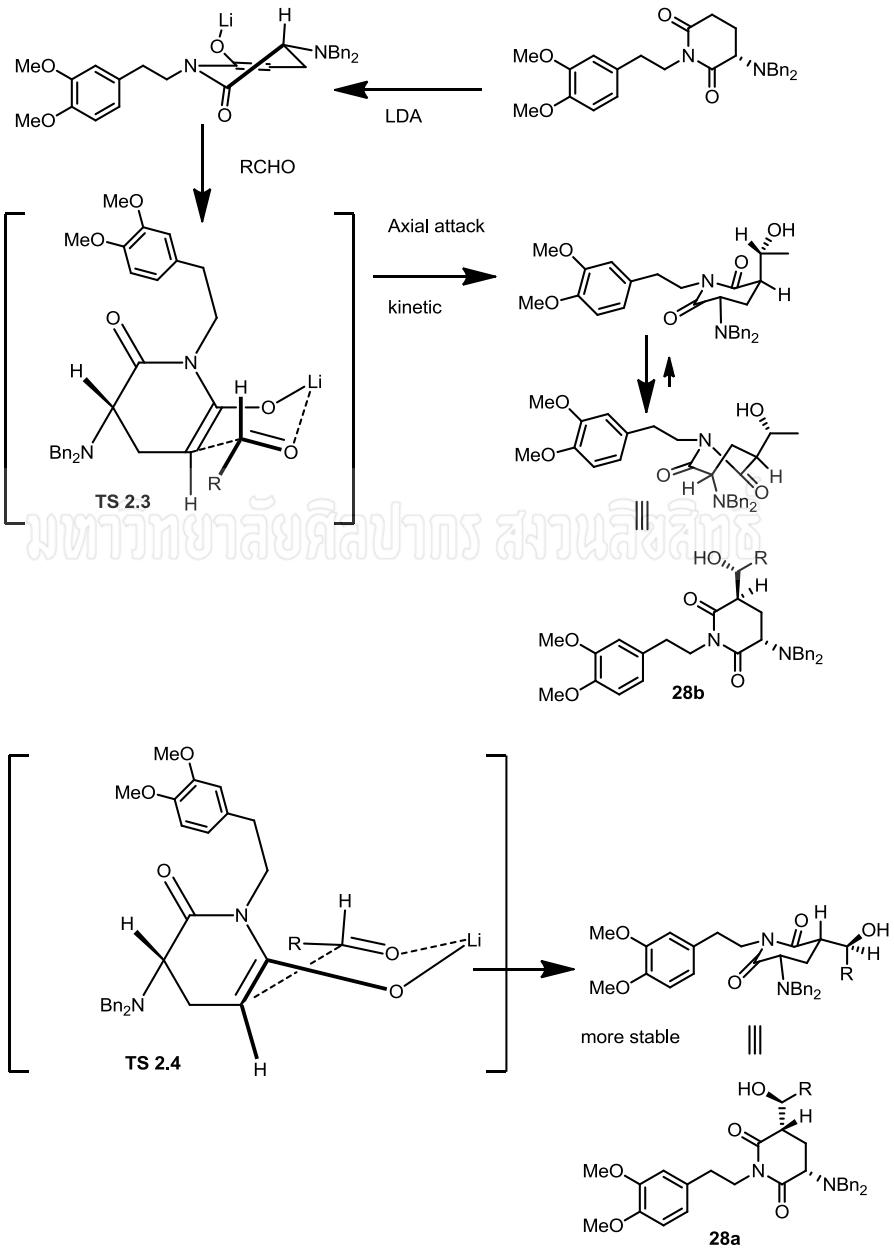
Scheme 2.11 second retrosynthetic analysis of dihydrotetrabenazine

Accordingly, the synthesis began with imide **7** which was reacted with isobutyraldehyde to obtain alcohols **28a** and **28b** which were separated by flash chromatography. The secondary alcohol was protected as a TBS ether. Interestingly, only **28a** could be converted to the corresponding TBS ether with TBSOTf, 2,6-lutidine in CH_2Cl_2, whereas **28b** failed to do so under the same conditions. DIBALH reduction occurred exclusively at the carbonyl adjacent to the stereocenter bearing the dibenzylamino group. Construction of the tricyclic system via *N*-acyliminiumion cyclization was accomplished by treatment with TMSOTf with concomitant removal of the silyl group to give tricyclic lactams **26a** and **26b**. The unsaturated lactam **27a** and **27b** was obtained from lactam **26a** and **26b**, respectively, by Cope elimination with *m*-CPBA with loss of *N*,*N*-dibenzyl group. These compounds were found to be enantiomeric with identical 1H and 13C NMR spectra and opposite sign of optical rotation with comparable magnitude. We assigned the configurations of **26a**-**28a** and **26b**-**28b** according to conformational analysis and the proposed transition states. The secondary alcohols were then converted to acetate **29a** and **29b** (Scheme 2.12).



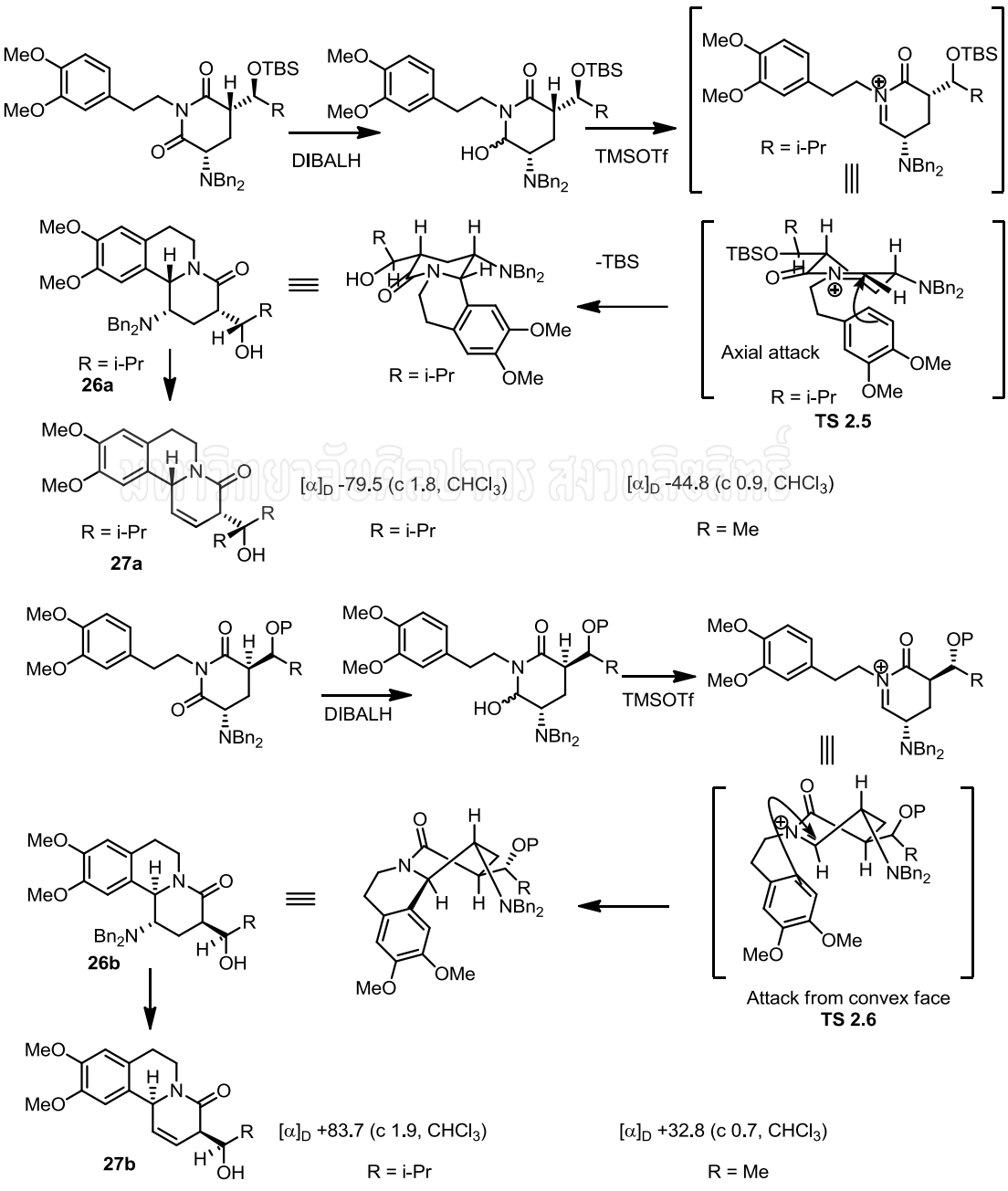
Scheme 2.12 Second synthetic approach toward dihydrotetrabenazine

Aldol reaction of lithium enolate occurs via six-membered chair transition state in which *E*-enolate gives anti aldol adduct. If the aldehyde approaches from the top face as in **TS 2.3**, it will be an axial attack to give the kinetic product which has the new substituent in axial position. It will equilibrate from chair to twist conformation of aldol adduct **28b**. If the aldehyde approaches from the back as in **TS 2.4** aldol adduct **28a** will be obtained. It has substituents in equatorial positions of the chair conformation thus **28a** is more stable than **28b** and we assume that **28a** is the thermodynamic product.



Scheme 2.13 Transition states for aldol reaction

The proposed transition states of *N*-acyliminium ion cyclizations of hydroxylactams **46** and **47** that explain the opposite configuration at C11b of **26a** and **26b** are shown in scheme 2.14. Upon treatment with TMSOTf, hydroxylactam **46** was converted to *N*-acyliminium ion **TS 2.5** which assumed half-chair conformation. The aryl ring underwent cyclization from the axial direction of **TS 2.5** leading to *S*-configuration at the newly generated C11b stereogenic center. *N*-acyliminium ion derived from hydroylactam **47**, on the other hand, assumed twist conformation **TS 2.6** which favored aryl-attack from the less hindered convex face leading to *R*-configuration at the newly generated C11b stereogenic center.



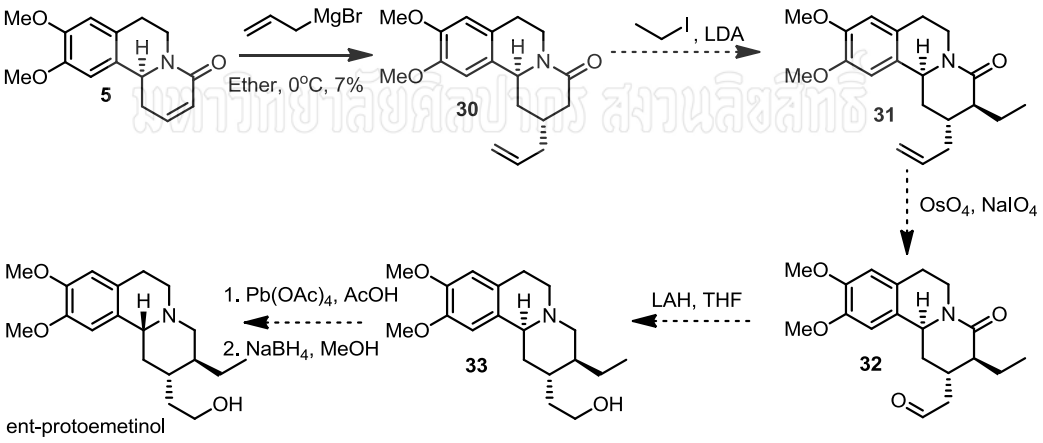
Scheme 2.14 Transition states for benzoquinolizidine *N*-acyliminium ion cyclization

The fact that **26a** and **26b** have the same relative configurations (anti) at the C11b and C3 positions was proven by their conversion to unsaturated lactams **27a** and **27b**, respectively. These lactams have identical 1H and 13C NMR spectra but opposite sign of optical rotation with comparable magnitudes. This suggests that they are pair of enantiomers. Along with the results from synthesis of crispine A analogs, we have developed synthetic routes that are potentially enantio-divergent toward benzoquinolizidine and benzoindolizidine starting from L-glutamic and L-aspartic acids, respectively.

PART C : SYNTHETIC STUDY OF PROTOEMETINOL

First Route: Michael addition of the enamide

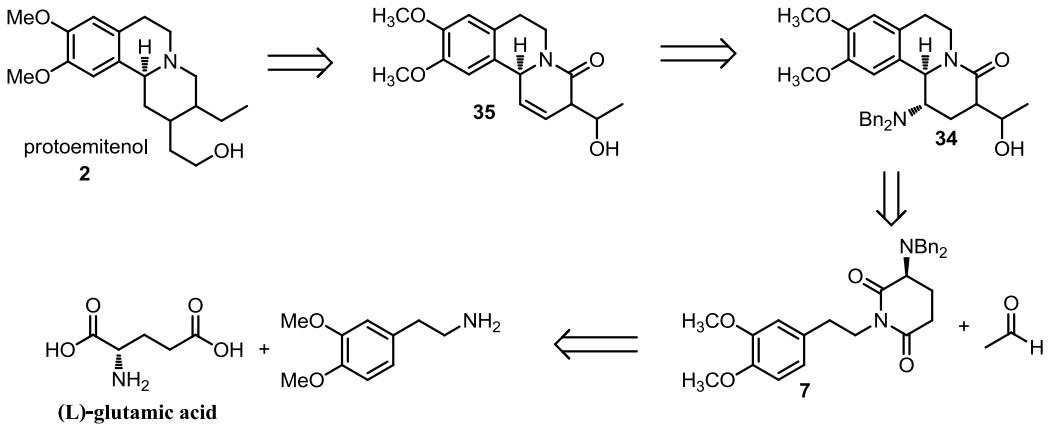
With tricyclic enamide **5** in hand, we performed Michael addition with AllylMgBr to obtain β-allyl tricyclic lactam **30** in low yield, perhaps due to the low reactivity of unsaturated lactam compared with other α, β- unsaturated carbonyl compounds. The remaining steps are a-alkylation, oxidative cleavage of C=C [5], carbonyl reduction, and C11b-epimerization via oxidation and reduction[6]. Due to the low yield of Michael addition and the finding of the results in PART A and B we turned our attention to the second synthetic route (Scheme 2.15).



Scheme 2.15 Synthesis of *ent*-protoemetinol

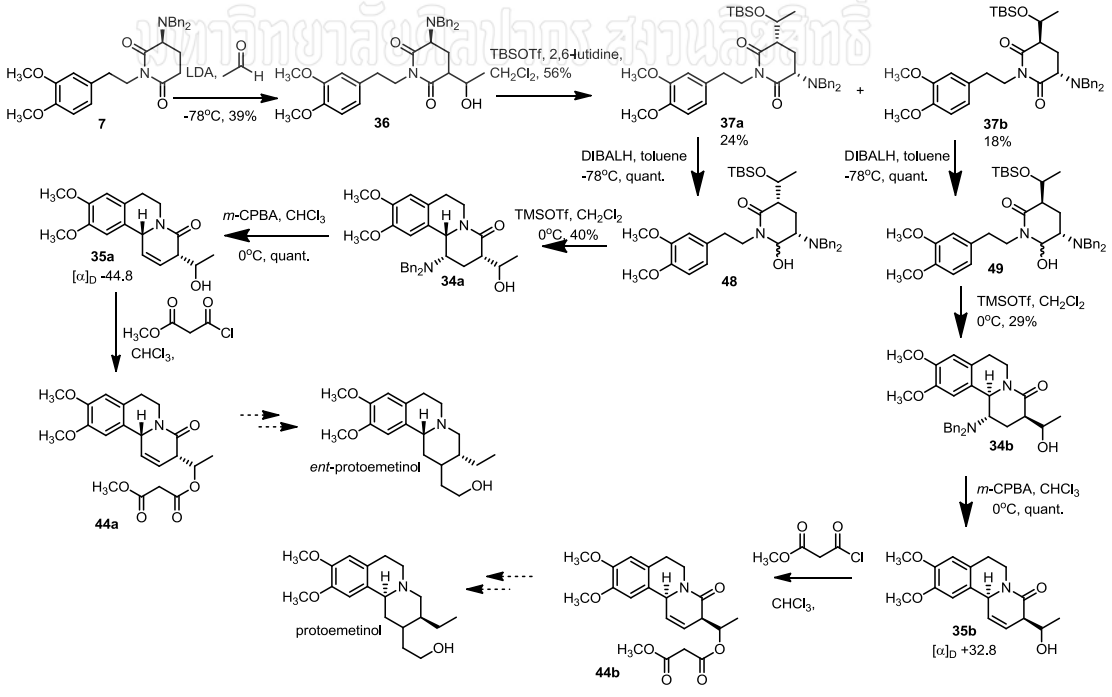
Second Route: Enantio-divergent approach toward tricyclic quinolizidine core

Our second retrosynthetic analysis for protoemetinol parallels that of tetrabenazine with the difference being the substituent on the piperidine ring and is shown in scheme 2.16. We envision protoemetinol **2** to be derived from unsaturated lactam **35**. The tricyclic enamide **35** could be synthesized by Cope elimination of dibenzylamino-lactam **34** with *m*-CPBA. The tricyclic **34** could be prepared from aldol reaction of chiral imide **7** with acetaldehyde. The chiral imide **7** would be derived from homoveratrylamine and (L)-glutamic acid.



Scheme 2.16 retrosynthetic analysis of protoemetinol

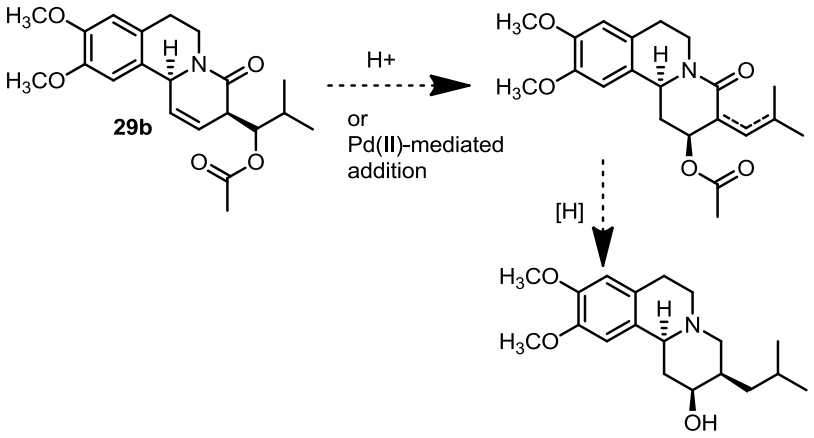
In the same way, imide **7** reacted acetaldehyde in the presence of LDA in THF at -78 °C via aldol reaction to give diastereomeric alcohol **36** which were protected as TBS silyl ether and the two diastereomers **37a** and **37b** were separated. DIBALH reduction and subsequent *N*-acyliminium ion cyclization gave tricyclic quinolizidine **34a** and **34b** with concomitant removal of TBS group. Cope elimination of **34a** and **34b** gave enantiomeric **35a** and **35b**, The secondary alcohol on the substituent of the tricyclic benzoquinolizidine **35b** reacted with malonate derivative to give **44a** and **44b** respectively. (Scheme 2.17). The remaining steps will be discussed in the FUTURE PLAN.



Scheme 2.17 Second synthetic route toward protoemetinol

FUTURE PLAN

Completion of Dihydrotetrabenazine



Scheme 2.18 Plan for completion of dihydrotetrabenazine

The acetate group on the ring substituent of unsaturated lactam **29b** situates at the right position for addition to the C=C in acidic conditions or Pd(II)-mediated or catalyzed process[7]. This should result in ring oxygenation and unsaturation on the isobutyl moiety. The remaining steps after this pivotal transformation will be trivial hydrogenation and reduction of the lactam ring (Scheme 2.18).

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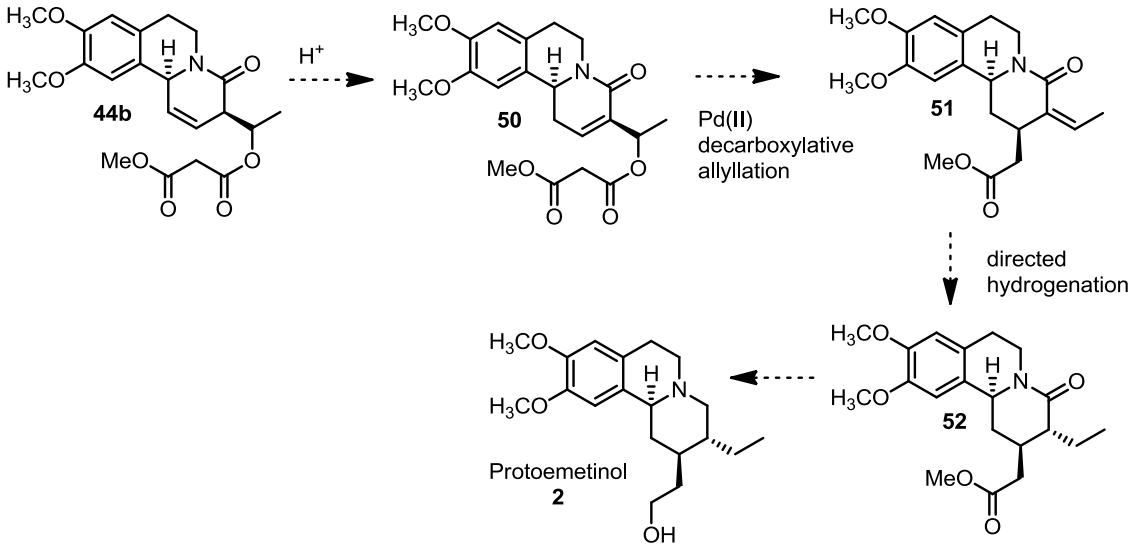
Completion of Protoemetinol



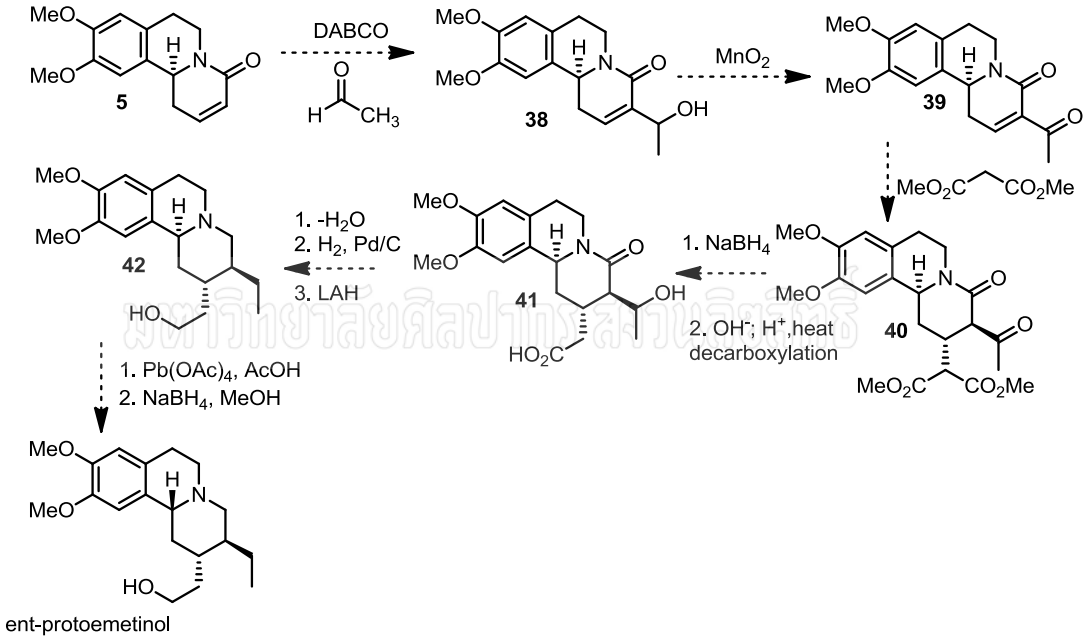
Scheme 2.19 Plan for completion of protoemetinol

The proposed route is more promising especially if the unsaturated lactam undergoes isomerization into conjugation where a few alternative approaches can be attempted. We are particularly interested in a Pd(II)-catalyzed decarboxylative allylation[8] and directed

hydrogenation[9] that would lead to the intermediate with the complete carbon skeleton of protoemetinol in efficient manner (Scheme 2.19).

The solution low reactivity of tricyclic unsaturated lactam

Attempts will also be made to cope with the low reactivity of the tricyclic unsaturated lactam intermediate in route 1. Activation of Michael acceptor by adding electron withdrawing group at alpha position is an interesting approach. We plan to use Baylis-Hilman reaction[10] of tricyclic enamide **5** with DABCO and acetaldehyde to obtain allylic alcohol **38**. Oxidation of allylic alcohol **38** should give methyl ketone **39**. Next, Michael addition with dimethyl malonate and decarboxylation would lead to the full carbon skeleton of protoemetinol. The remaining steps would involve functionalization via lactam reduction and formal deoxygenation. Finally, epimerization by oxidation and reduction should lead to *ent*-protoemetinol (Scheme 2.20).



Scheme 2.20 Baylis-Hilman approach toward protoemetinol

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CHAPTER 3

GENERAL CONCLUSIONS

The synthetic studies of tetrabenazine and protoemetinol have not been completed, however we have found useful information and synthesized advanced intermediates. We have experimented with two major synthetic routes toward benzoquinolizidine alkaloids. We have synthesized C11b-alkyl analogs of cytotoxic indolizidine alklaoids crispine A using the same approach which was *N*-acyliminium ion cyclization[1] followed by Cope elimination[2] to form C=C bond which would be used for further synthetic steps. The finding from these results have led us to an enantio-divergent synthesis of tricyclic indolizidine and quinolizidine cores for various alkaloids. The remaining task for completion of the quinolizidine alkaloids will allow us to experiment with more exciting chemistry such as Neighboring Group Participation in oxygenation of the unsaturated lactam ring in synthesis of dihydrotetrabenazine and Pd(II)-catalyzed decarboxylative allylation[3] in synthesis of protoemetinol. We aim to make our synthetic route distinct in design by making common intermediate for divergent alkaloid synthesis, in contrast to other reported syntheses which utilized highly functionalized precursor for *N*-acyliminium ion cyclization, therefore making the synthetic route target specific.

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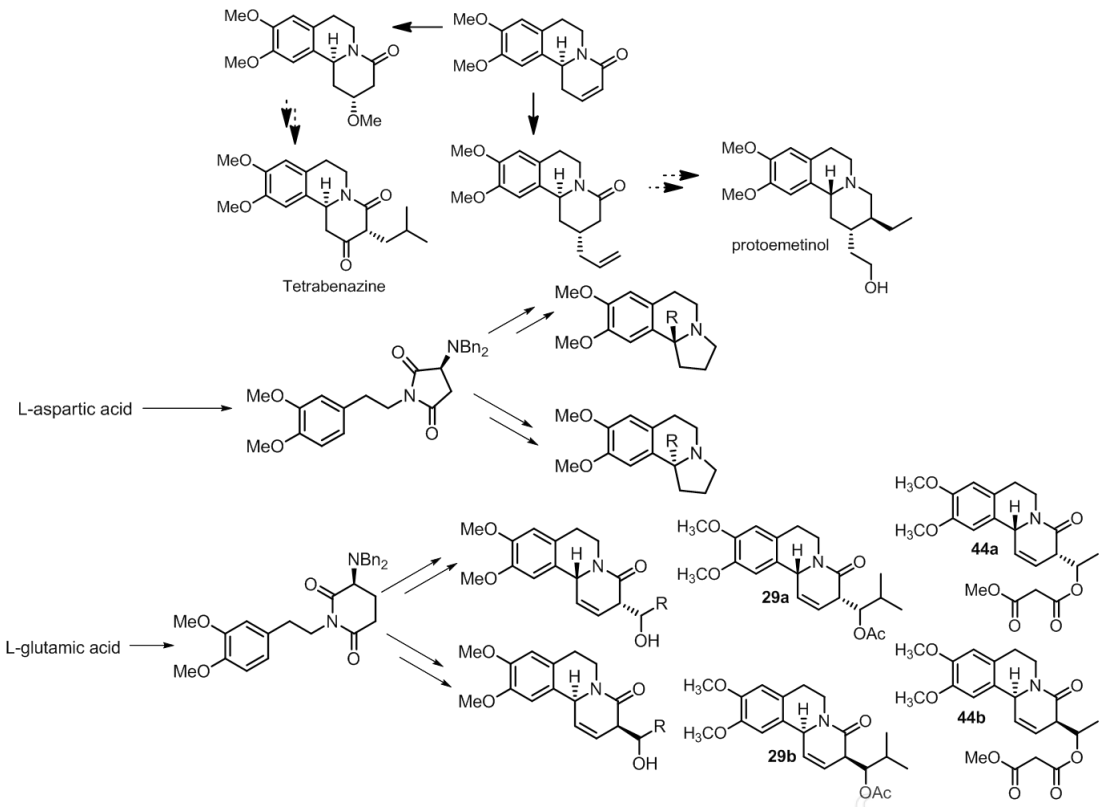

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Scheme 3.1 Conclusion of finding from this research

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CHAPTER 4

EXPERIMENTAL PROCEDURES

General methods

All commercially available reagents were used without purification. Moisture and air-sensitive compound were used under an argon atmosphere with oven-dried glasswares. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ on a 300 MHz Bruker spectrometer. Chemical shift are in δ (ppm) with trimethylsilane as an internal standard. Coupling constant are reported in Hertz (Hz). Absoption spectra were collected on a Hewett Packard 8453 spectrometer. Infrared spectra (IR) were recorded by Perkin Elmer spectrum GX FI-IR system. Major bands (ν_{max}) were recorded in wave number (cm^{-1}). Optical rotations were measured in chloroform solution with sodium D line (590 nm) on JASCO P-1010 Polarimeter. Thin layer chromatography (TLC) was performed on Fluka aluminum backed silics 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

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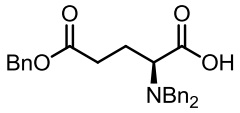
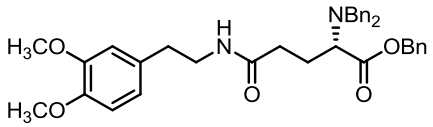
SYNTHESIS OF DIHYDROTETRABENAZINE

1-benzyl-*N*,*N*-dibenzyl glutamate



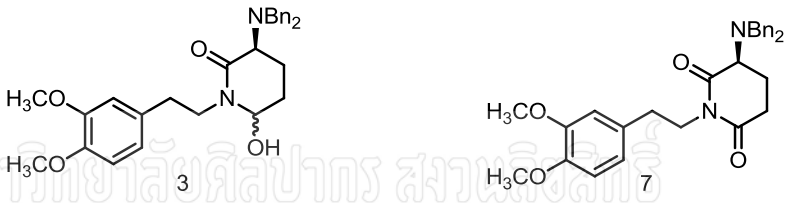
L-glutamic acid (5 g, 33.98 mmol) was dissolved in 100 mL of 1:1 MeOH:H_2O. To this solution was added benzyl chloride (15.6 mL, 118.9 mmol), NaOH (3.06 g, 79.60 mmol) and K_2CO_3 (10.56 g, 79.60 mol). The mixture was heated to reflux overnight. The reaction was quenched with 1M HCl (50 mL) and H_2O and the mixture was then extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were dried over anh.Na_2SO_4, filtered and concentrated to give the acid as a yellow oil. The crude product was purified by column chromatography (silica gel, 4:1 hexane/ethyl acetate) to give the benzyl glutamate (4.4 g, 31 %) as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.12 (m, 15H); 5.2 (dd, 2H, *J*=12.2 Hz, *J*=37.4 Hz); 3.9 (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 (75 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}

Amide 2



To a solution of glutamate (1.57 g, 3.76 mmol) in CH2Cl2 was added DMAP (55.1 mg) , homoveratrylamine (2.04 ml, 11.28 mmol) and DCC (1.16 g, 5.64 mmol) was stirred vigorously at room temperature overnight and the mixture was then filtered to remove urea by-product. The filtrate was concentrated under reduced pressure and the crude material was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give amide (582.3 mg, 27 %) as a yellow oil. ^{1}H NMR (300 MHz,$CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.10 (m, 15H), 6.81 (d, J = 8.5 Hz, 1H), 6.65-6.75 (m, 2H), 5.29 (d, J = 12.1 Hz, 1H), 5.19 (s, 1H), 5.18 (d, J = 12.1 Hz, 1H), 3.89 (d, J = 13.7 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.55 (d, J=13.7 Hz, 2H), 3.47-3.31 (m, 2H), 3.25 (ddd, J= 20.1, 13.1, 6.7 Hz, 1H), 2.65 (t, J= 7.1 Hz, 2H), 2.32-2.18 (m, 1H), 2.18-1.95 (m, 3H)

Hydroxylactam 3 and imide 7



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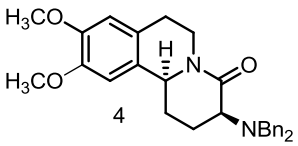
To a solution of amide **2** (316.2 mg, 0.55 mmol) in dry THF (5 mL) was added $LiAlH_4$ at 0 ºC under an argon atmosphere. The resulting suspension was stirred vigorously. Upon completion adjudged by TLC (30 min), the reaction was quenched by drop-wise addition of sat aq $NaHCO_3$ into the reaction. The mixture was extracted with EtOAc (3x30 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude material by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) produced hydroxylactam **3** (40.3 mg, 14 %) as a yellow oil and imide **7** (114.6 mg, 44%) as a yellow oil. hydroxylactam **3** ^{1}H NMR (300 MHz,CDCl3) δ 7.45-7.03 (m, 10H), 6.75 (brs, 2H), 6.70 (s, 1H), 4.59 (brs, 1H), 4.03 (d, J = 14.1 Hz, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73 (d, J = 14.1 Hz, 2H), 3.75-3.72 (m, 1H), 3.65-3.40 (m, 2H), 3.35-3.20 (m, 1H), 2.92-2.82 (m, 2H), 2.30-2.10 (m, 1H), 1.91-1.77 (m, 2H), 1.52-1.72 (m, 1H)

imide **7** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.12 (m, 10H), 6.88-6.65 (m, 3H), 4.10 (m, 2H), 3.93 (d, *J* = 13.0 Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 3.63 (d, *J* = 13.0 Hz, 2H), 3.42 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.75 (t, 2H), 2.70 (m, 1H), 2.41 (m, 1H), 1.96 (m, 2H)

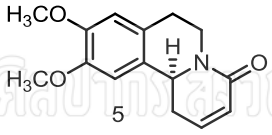
Benzoquinolizidine 4



4

To a solution of hydroxylactam **3** (49.8 mg, 0.11 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (0.06 mL., 0.32 mmol) at 0ºC under an argon atmosphere and strried for 3 hours. The reaction was quenched with sat aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 4:1 hexane/ethyl acetate) to give 2 inseperable diastereomers of the benzoquinolizidinone **4** (43.7 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.15 (m, 10H), 6.64 (s, 1H), 6.62 (s, 1H), 4.82 (dd, J = 9.7, 1.8 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 4.12 (d, J = 14.2 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.75 (d, J = 14.2 Hz, 2H), 3.46 (dd, J = 10.0, 6.6 Hz, 1H), 3.02-2.76 (m, 2H), 2.67 (d, J = 12.0 Hz, 1H), 2.24-1.80 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) 171.5, 147.9, 147.7, 140.7, 128.6, 128.5, 128.2, 127.8, 126.8, 111.8, 108.1, 57.7, 56.1, 55.9, 55.4, 55.1, 40.4, 28.7, 28.5, 23.9

Enamide 5



5

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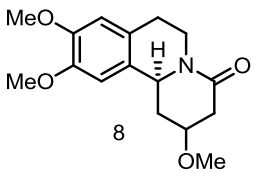
To a solution of tricyclic **4** (44.3 mg, 0.11 mmol) in $CHCl_3$ (5 mL) was added m-CPBA (0.06 mg, 0.32 mmol) at 0ºC and strried for 1 hours. The reaction was quenched with sat aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give tricyclic enamide **5** (24.0 mg, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70-6.60 (m, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.10 (dd, J = 9.8, 2.9 Hz, 1H), 4.91-4.58 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.08-2.55 (m, 4H), 2.31 (dddd, J = 16.7, 14.0, 2.3, 2.3 Hz, 1H)

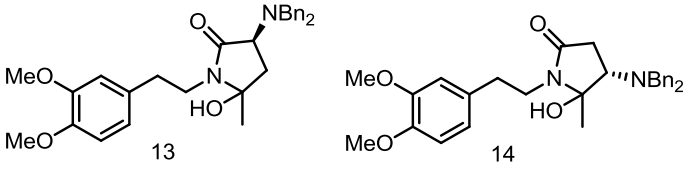
β-OMe-lactam 8



8

To a solution of tricyclic enamide (24 mg, 0.093 mmol) in MeOH (3 mL) was added NaOMe (2.13 mg, 0.093 mmol) at room temperature under an argon atmosphere and strried overnight. The reaction was quenched with 1 MHCl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh Na_2SO_4, filtered and evaporated under reduced pressure to give product (20.8 mg, 77%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70-6.60 (m, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 4.91-4.58 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 3.08-2.55 (m, 4H), 2.31 (dddd, J = 16.7, 14.0, 2.3, 2.3 Hz, 1H)

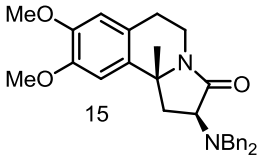
Hydroxylactams 13 and 14



To a solution of imide **12** (602 mg, 1.32 mmol) in Et_2O (10 mL) was added freshly prepared MeMgI (MeI 0.57 mL, 9.2 mmol, Mg 1.10 g, 45.8 mmol) at 0 °C and the mixture was stirred for 1h. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give a mixture of regioisomeric hydroxylactams **13** (401 mg, 64%) and **14** (133 mg, 21%) as colorless oils after separation with flash chromatography (silica gel, 2:1 hexane/EtOAc); Hydroxylactam **13**; R_f (2:1 hexane/EtOAc) 0.29; ^{1}H (300 MHz, $CDCl_3$) 7.50-7.13 (m, 10H), 6.88-6.62 (m, 3H), 3.91 (d, *J* = 13.8 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.67 (d, *J* = 13.8 Hz, 2H), 3.62-3.48 (m, 2H), 3.34-3.20 (m, 1H), 2.95 (ddd, *J* = 13.3, 9.4, 6.3 Hz, 1H), 2.80 (ddd, *J* = 13.5, 9.4, 5.8 Hz, 1H), 2.28 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.94 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.27 (s, 3H) ; ^{13}C (75 MHz, $CDCl_3$) 172.7, 148.9, 147.7, 139.3 (2C), 131.7, 128.8 (4C), 128.3 (4C), 127.1 (2C), 120.9, 112.2, 111.2, 87.0, 59.3 (2C), 55.9 (2C), 54.9, 40.9, 40.2, 34.5, 25.8; $[\alpha]_{25}^{D}$ –38.5 (c 1.1, CH_2Cl_2); νmax (film) 3347, 2935, 2836, 1663, 1516, 1263, 1156, 738, 700 cm^{-1}; ESI-HRMS calculated for $C_{29}H_{35}N_2O_4$ $[M+H]^+$ 475.2591, found 475.2592.

Hydroxylactam **14**; R_f (2:1 hexane/EtOAc) 0.16; ^{1}H (300 MHz, $CDCl_3$) 7.50-7.21 (m, 10H), 6.79 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.00 (brs, 1H), 3.85 (s, 3H), 3.83 (d, *J* = 13.4 Hz, 2H), 3.77 (s, 3H), 3.75-3.59 (m, 1H), 3.45 (d, J = 13.4 Hz, 2H), 3.77 (s, 3H), 3.75-3.59 (m, 1H), 3.45 (d, *J* = 13.4 Hz, 2H), 3.41-3.26 (m, 2H), 3.20-2.84 (m, 2H), 2.65 (d, *J* =17.7 Hz, 1H), 2.48 (dd, *J* = 17.8, 8.1 Hz, 1H), 1.20 (s, 3H) ; ^{13}C (75 MHz, $CDCl_3$) 171.6, 148.8, 147.4, 137.5 (2C), 131.7, 128.7 (4C), 128.6 (4C), 127.6 (2C), 120.8, 112.0, 111.1, 88.5, 61.1, 55.8, 55.7, 54.8 (2C), 41.0, 34.8, 29.6, 25.6 ; $[\alpha]_{25}^{D}$ +18.6 (c 1.0, CH_2Cl_2); νmax (film) 3356, 2935, 2835, 1668, 1516, 1263, 1150, 1029, 700 cm^{-1}; ESI-HRMS calculated for $C_{29}H_{34}N_2O_4Na$ $[M+Na]^+$ 497.2411, found 497.2407.

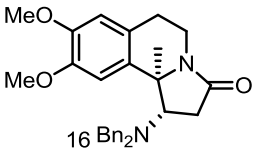
Benzoindolizidine 15



To a solution of hydroxylactam **13** (371 mg, 0.781 mmol) in CH_2Cl_2 (10 mL) at 0 □C was added TMSOTf (0.24 mL, 1.2 mmol) via syringe. The mixture was stirred at this temperature for 3 h. CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give benzoindolizidine 10 (282 mg, 79%) as a colorless oil; Rf (2:1 hexane/EtOAc) 0.48; ^{1}H (300 MHz, CDCl3) 7.46 (d, JJ = 7.3 Hz, 4H), 7.39-7.16 (m, 6H), 6.59 (s, 1H), 6.49 (s, 1H), 4.36 (dd, JJ = 13.1, 6.7 Hz, 1H), 3.99 (d, JJ = 13.8 Hz, 2H), 3.88

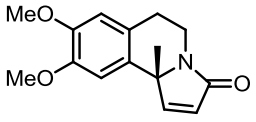
(s, 3H), 3.83 (s, 3H), 3.75 (d, JJ = 13.7 Hz, 2H), 3.63 (t, JJ = 8.3 Hz, 1H), 3.22 (ddd, JJ = 12.7, 12.5, 4.8 Hz, 1H), 2.95 (ddd, JJ = 16.2, 12.2, 6.9 Hz, 1H), 2.64 (dd, JJ = 13.5, 10.7 Hz, 1H), 2.55 (dd, JJ = 16.5, 4.6 Hz, 1H), 2.23 (dd, JJ = 13.6, 8.1 Hz, 1H), 1.63 (s, 3H); ^{13}C (75 MHz, CDCl3) 173.6, 148.0, 147.8, 139.6 (2C), 134.3, 128.7 (4C), 128.3 (4C), 127.0 (2C), 125.1, 111.7, 108.3, 59.6, 58.5, 56.1, 55.9, 54.7, 37.7, 34.9, 31.8, 27.3; $[\alpha]_{25}^{D}$ +85.9 (c 1.1, CH2Cl23); νmax (film) 2933, 2843, 1685, 1514, 1262, 1217, 746, 699 cm-1; ESI-HRMS calculated for $C_{29}H_{32}N_2O_3Na$ [M+Na]+ 479.2305, found 479.2307.

Benzoindolizidine 16



To a solution of hydroxylactam **14** (101 mg, 0.213 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TMSOTf (82 µL, 0.426 mmol) via syringe. The mixture was stirred at this temperature for 3 h. CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to provide benzoindolizidine **16** (80 mg, 82%) as a colorless oil; Rf (1:1 hexane/EtOAc) 0.63; δH (300 MHz, $CDCl_3$) 7.44 (d, *J* = 7.1 Hz, 4H), 7.37 (t, *J* = 7.1 Hz, 4H), 7.27 (t, *J* = 7.1 Hz, 2H), 6.78 (s, 1H), 6.50 (s, 1H), 4.30 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.97 (d, *J* = 14.2 Hz, 2H), 3.83 (s, 3H), 3.77 (dd, *J* = 8.4, 7.0 Hz, 1H), 3.66 (s, 3H), 3.57 (d, *J* = 14.2 Hz, 2H), 3.10 (ddd, *J* = 12.5, 12.2, 4.0 Hz, 1H), 2.95 (ddd, *J* = 15.6, 12.2, 6.5 Hz, 1H), 2.64 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.54 (dd, *J* = 15.9, 3.7 Hz, 1H), 2.13 (dd, *J* = 17.0, 8.5 Hz, 1H), 1.69 (s, 3H); δC (75 MHz, $CDCl_3$) 173.2, 147.7, 147.6, 138.6 (2C), 134.6, 128.7 (4C), 128.6 (4C), 127.3 (2C), 124.4, 111.6, 107.8, 64.9, 63.7, 55.8 (2C), 55.8, 55.3, 34.7, 30.1, 27.4, 24.1; $[\alpha]_{25}^{D}$ +18.8 (c 2.4, $CHCl_3$); νmax (film) 2930, 2852, 1693, 1513, 1455, 1260, 1213, 749, 700 cm^{-1}; ESI-HRMS calculated for $C_{29}H_{32}N_2O_3Na$ $[M+Na]^+$ 479.2305, found 479.2308.

Enamide (+)-17

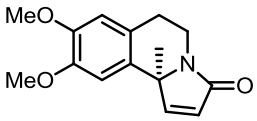


(+)-17

To a solution of benzoindolizidine **15** (260 mg, 0.569 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *m*-CPBA (210 mg, 0.854 mmol) and the mixture was stirred for 1 h. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give enamide **(+)-17** (111 mg, 75%) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.15; δH (300 MHz, $CDCl_3$); 7.36 (d, *J* = 5.8 Hz, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 6.12 (d, *J* = 5.8 Hz, 1H), 4.44 (dd, *J* = 13.3, 6.4 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.25 (ddd, *J* = 13.2, 12.0, 4.4 Hz, 1H), 2.95 (ddd, *J* = 16.1, 11.9, 6.5 Hz, 1H), 2.67 (dd, *J* = 15.9, 4.0 Hz, 1H), 1.61 (s, 3H); δC (75 MHz, $CDCl_3$); 170.2, 153.2, 148.2,

147.8, 129.3, 125.3, 125.1, 112.1, 109.1, 65.6, 56.2, 55.9, 34.6, 29.2, 26.8 $[\alpha]_{25}^{D}$ +149.8 (c 1.3, $CHCl_3$); νmax (film) 3056, 2931, 1712, 1686, 1269, 1262, 754, 704 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{17}NO_3Na$ $[M+Na]^+$ 282.1101, found 282.1101.

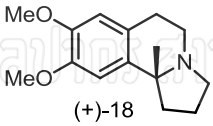
Enamide (-)-17



(-)-17

To a solution of benzoindolizidine **16** (62 mg, 0.136 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added *m*-CPBA (168 mg, 0.680 mmol) and the mixture was stirred for 1 h. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give enamide (-)-**17** (22 mg, 62%) as a colorless oil; $[\alpha]_{25}^{D}$ -114.7 (c 0.7, $CHCl_3$). All spectral data are identical with those of (+)-**17**.

Methyl analog of crispine A (+)-18



(+)-18

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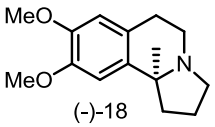
A mixture of enamide **(+)-17** (95 mg, 0.366 mmol) and Palladium on activated carbon (10%, 9.5 mg) in methanol under an atmosphere of hydrogen gas (balloon) was stirred for 1 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give the corresponding lactam (96 mg, quantitative) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.40; δH (300 MHz, $CDCl_3$) 6.58 (s, 1H), 6.57 (s, 1H), 4.29 (ddd, *J* = 13.1, 6.4, 1.1 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.07 (dddd, *J* = 13.1, 12.1, 4.6, 1.0 Hz, 1H), 2.87 (ddd, *J* = 15.9, 12.1, 6.5 Hz, 1H), 2.67 (dd, *J* = 16.3, 3.9 Hz, 1H), 2.66-2.54 (m, 1H), 2.48-2.31 (2, 2H), 2.09 (dd, *J* = 21.9, 11.0 Hz, 1H), 1.50 (s, 3H); δC (75 MHz, $CDCl_3$) 172.3, 148.1, 147.8, 134.7, 124.5, 111.6, 107.9, 61.0, 56.1, 55.9, 34.7, 34.1, 30.7, 28.1, 27.3; $[\alpha]_{25}^{D}$ +111.4 (c 4.6, $CHCl_3$); νmax (film) 2966, 2936, 1721, 1682, 1515, 1241, 1213, 856 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{19}NO_3Na$ $[M+Na]^+$ 284.1257, found 284.1257. The lactam (85 mg, 0.325 mmol) was dissolved in THF (7 mL) and $LiAlH_4$ (37 mg, 0.975 mmol) was added. The mixture was heated to reflux under argon atmosphere for 6 h. To the reaction mixture were added sat. aq. $NaHCO_3$ (5 mL) and EtOAc (10.0 mL) and phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give methyl analog of crispine A **(+)-18** (57 mg, 71%) as a colorless oil; R_f (10:1 CH_2Cl_2/MeOH) 0.43; δH (300 MHz, $CDCl_3$) 6.64 (s, 1H), 6.54 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.25 (ddd, *J* = 13.2, 11.0, 4.5 Hz, 1H), 3.17-3.05 (m, 2H), 2.97 (ddd, *J* = 16.4, 10.9, 5.6 Hz, 1H), 2.89 (dd, *J* = 17.2, 8.1 Hz, 1H), 2.51 (ddd, *J* = 16.3, 3.6, 3.1 Hz, 1H), 2.21-2.07 (m, 2H), 1.88 (dddd, *J* = 15.6, 12.2, 7.8, 7.8 Hz, 1H), 1.75-1.62 (m, 1H), 1.48 (s, 3H); δC (75 MHz, $CDCl_3$) 147.8, 147.3, 135.1, 125.5, 111.2,

109.6, 63.1, 56.2, 55.9, 50.4, 43.0, 40.2, 29.8, 23.4, 22.2; $[\alpha]_{25}^{D}$ +32.5 (c 2.0, $CHCl_3$); νmax (film) 2962, 1518, 1227, 1073, 873 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1648.

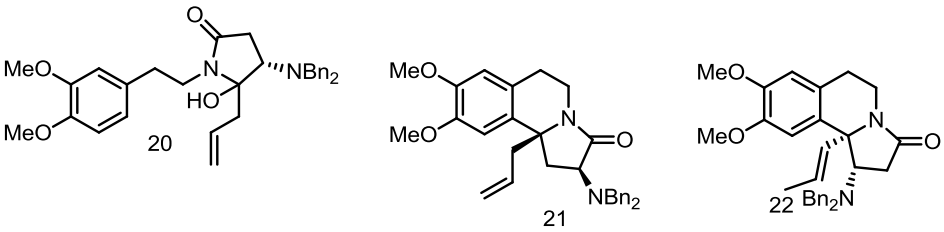
Methyl analog of crispine A (-)-18



(-)-18

A mixture of enamide **(-)-17** (12 mg, 46 mol) and Palladium on activated carbon (10%, 1.2 mg) in methanol under an atmosphere of hydrogen gas (balloon) was stirred for 1 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give the corresponding lactam (12 mg, 95%) as a colorless oil. The spectral data of this lactam are identical with those of the lactam derived from (+)-**17**. The Lactam (11 mg, 42 mol) was dissolved in THF (3 mL) and $LiAlH_4$ (4 mg, 0.105 mmol) was added. The mixture was heated to reflux under argon atmosphere for 6 h. To the reaction mixture were added sat. aq. $NaHCO_3$ (5 mL) and EtOAc (10.0 mL) and phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give methyl analog of crispine A (-)-**18** (8 mg, 73%) as a colorless oil; $[\alpha]_{25}^{D}$ -26.4 (c 0.8, $CHCl_3$). All spectral data of (-)-**18** are identical to those of (+)-**18**.

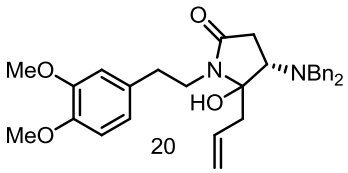
Hydroxylactams 20, C10b-allyl benzoindolizidines 21 and 22



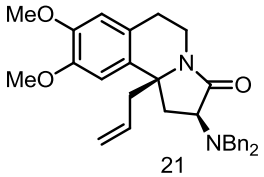
To a solution of imide **12** (417 mg, 0.909 mmol) in Et_2O (10 mL) was added freshly prepared AllylMgBr (Allyl bromide 0.23 mL, 2.73 mmol, Mg 199 mg, 8.29 mmol) at -78 °C and the mixture was stirred for 1h. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give a mixture of hydroxylactams **19** and **20** (373 mg, 82%) as a colorless oil. To a solution of this mixture of hydroxylactams **19** and **20** in CH_2Cl_2 (10 mL) at 0°C was added TMSOTf (0.24 mL, 1.24 mmol) via syringe. The mixture was stirred at this temperature for 3 h. CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to provide C10b-allyl benzoindolizidine **21** along with its isomerized alkene (249 mg, 57%) as a colorless oils and benzoindolizidine **22** (70 mg, 16%)

C10b-allyl benzoindolizidines **21**; R_f (2:1 hexane/EtOAc) 0.20; δH (300 MHz, $CDCl_3$) 7.42 (s, 1H), 7.40-7.19 (m, 10H), 6.56 (s, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.37 (dq, *J* = 15.5, 6.5 Hz, 1H), 4.27 (ddd, *J* = 13.0, 5.1, 1.1 Hz, 1H), 4.10 (d, *J* = 14.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (dd, *J* = 9.5, 8.3 Hz, 1H), 3.57 (d, *J* = 14.2 Hz, 2H), 3.00 (ddd, *J* = 12.2, 12.0, 4.1 Hz, 1H), 2.90 (ddd, *J* = 13.0, 11.9, 6.0 Hz, 1H), 2.69-2.55 (m, 1H), 2.54 (dd, *J* = 16.4, 9.8 Hz, 1H), 2.05 (dd, *J* = 16.5, 8.0 Hz, 1H), 1.62 (d, *J* = 6.5 Hz, 3H); δC (75 MHz, $CDCl_3$) 172.3, 147.8, 147.6, 138.4 (2C), 131.9, 131.2, 128.8 (4C), 128.4 (4C), 127.3 (2C), 126.1, 125.0, 111.6, 108.7, 67.4, 67.0, 56.0, 55.8, 55.1 (2C), 34.6, 30.3, 28.0, 17.8; $[\alpha]_{25}^{D}$ +26.8 (c 3.6, $CHCl_3$); νmax (film) 2933, 2853, 1694, 1514, 1258, 1108, 750, 700 cm^{-1}; $C_{31}H_{34}N_2O_3Na$ $[M+Na]^+$ 505.2462, found 505.2461.

Hydroxylactam 20 and C10b-allyl benzoindolizidines 21



20



21

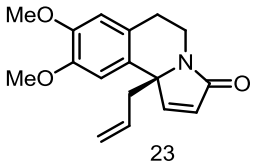
To a solution of this mixture of hydroxylactams **19** and **20** (230 mg, 0.459 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.11 mL, 0.92 mmol) via syringe. The mixture was stirred at this temperature for 3 h. CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (5 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to provide C10b-allyl benzoindolizidine **21** (137 mg, dr = 4:1, 62%) as a colorless oils and unreacted hydroxylactam **20** (40 mg, 17%) as a colorless oils.

Hydroxylactam **20**; R_f (2:1 hexane/EtOAc) 0.21; δH (300 MHz, $CDCl_3$) 7.50-7.21 (m, 10H), 6.79 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.30 (brs, 1H), 5.22 (ddd, *J* = 16.0, 10.9, 7.2 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.82 (d, *J* = 13.2 Hz, 2H), 3.77 (s, 3H), 3.69 (ddd, *J* = 13.2, 8.6, 5.4 Hz, 1H), 3.48 (d, *J* = 8.3 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 2H), 3.05-2.82 (m, 2H), 2.62 (d, *J* = 17.9 Hz, 1H), 2.41 (dd, *J* = 18.1, 8.3 Hz, 1H), 2.35-2.15 (m, 2H); δC (75 MHz, $CDCl_3$) 171.9, 148.8, 147.5, 137.4 (2C), 131.6, 128.9 (4C), 127.7 (2C), 127.5, 120.8, 119.3, 112.0, 111.1, 89.6, 64.0, 57.9, 55.9 (2C), 55.8, 54.8, 42.8, 41.2, 34.9, 29.7; $[\alpha]_{25}^{D}$ +12.5 (c 3.0, $CHCl_3$); νmax (film) 3331, 3029, 2937, 2834, 1687, 1516, 1263, 1144, 1029, 700 cm^{-1}; ESI-HRMS calculated for $C_{31}H_{36}N_2O_4Na$ $[M+Na]^+$ 523.2567, found 523.2563.

C10b-allyl benzoindolizidine **21**; R_f (2:1 hexane/EtOAc) 0.33; δH (300 MHz, $CDCl_3$) 7.46 (d, *J* = 7.1 Hz, 4H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.23 (t, *J* = 7.1 Hz, 2H), 6.61 (s, 1H), 6.53 (s, 1H), 5.75 (dddd, *J* = 14.9, 8.8, 6.0, 6.0 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 5.14 (d, *J* = 14.9 Hz, 1H), 4.37 (dd, *J* = 13.2, 6.9 Hz, 1H), 4.01 (d, *J* = 13.9 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.77 (d, *J* = 13.9 Hz, 2H), 3.59 (t, *J* = 9.6 Hz, 1H), 3.24 (ddd, *J* = 12.8, 12.2, 5.0 Hz, 1H), 2.99 (ddd, *J* = 16.4, 12.1, 7.3 Hz, 1H), 2.67 (dd, *J* = 14.4, 5.7 Hz, 1H), 2.56 (dd, *J* = 16.3, 4.6 Hz, 1H), 2.57-2.35 (m, 3H); δC (75 MHz, $CDCl_3$) 174.5, 148.1, 147.5, 139.8 (2C), 133.3, 132.2, 128.7 (4C), 128.3 (4C), 126.9 (2C), 125.5, 119.9, 111.8, 108.5, 60.6, 59.4, 56.2, 55.9, 54.9 (2C), 46.7, 35.0, 33.0, 26.9; $[\alpha]_{25}^{D}$ +48.7 (c 1.2, $CHCl_3$); νmax (film) 2929, 2853, 1683, 1516,

1455, 1259, 747, 700 cm^{-1}; ESI-HRMS calculated for $C_{31}H_{34}N_2O_3Na$ $[M+Na]^+$ 505.2462, found 505.2461.

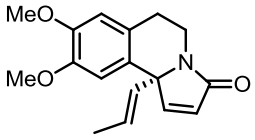
Enamide 23



23

To a solution of C10b-allyl benzoindolizidine **21** (83 mg, 0.173 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *m*-CPBA (45 mg, 0.259 mmol) and the mixture was stirred for 1 h. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give enamide **23** (31 mg, 63%) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.29; δH (300 MHz, $CDCl_3$) 7.28 (d, *J* = 5.7 Hz, 1H), 6.73 (s, 1H), 6.18 (d, *J* = 5.8 Hz, 1H), 5.54 (dddd, *J* = 16.9, 9.6, 7.2, 7.2 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 5.09 (d, *J* = 11.8 Hz, 1H), 4.45 (dd, *J* = 13.4, 6.5 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.26 (ddd, *J* = 13.2, 11.9, 4.6 Hz, 1H), 2.96 (ddd, *J* = 16.2, 11.7, 6.7 Hz, 1H), 2.79-2.64 (m, 3H); δC (75 MHz, $CDCl_3$) 170.7, 151.5, 148.3, 147.6, 131.2, 128.4, 126.3, 125.6, 119.1, 112.1, 109.2, 68.0, 56.2, 55.9, 43.3, 34.8, 29.0; $[\alpha]_{25}^{D}$ +150.3 (c 1.6, $CHCl_3$); νmax (film) 2938, 1685, 1516, 1257, 1228, 810 cm^{-1}; ESI-HRMS calculated for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$ 308.1257, found 308.1266.

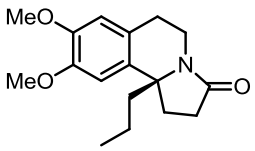
Enamide 24



24

To a solution of C10b-allyl benzoindolizidine **22** (206 mg, 0.428 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added *m*-CPBA (738 mg, 4.28 mmol) and the mixture was stirred for 36 h. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give enamide **24** (66 mg, 55%) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.25; δH (300 MHz, $CDCl_3$) 7.33 (d, *J* = 5.7 Hz, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.14 (d, *J* = 5.8 Hz, 1H), 5.50-5.40 (m, 2H), 4.33 (ddd, *J* = 13.2, 6.7, 1.2 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.21 (ddd, *J* = 13.1, 11.5, 4.8 Hz, 1H), 2.95 (ddd, *J* = 16.4, 11.3, 6.5 Hz, 1H), 2.67 (ddd, *J* = 16.0, 4.7, 1.5 Hz, 1H), 1.70 (d, *J* = 4.8 Hz, 3H); δC (75 MHz, $CDCl_3$) 170.1, 151.5, 148.4, 147.4, 131.1, 129.1, 126.5, 126.4, 125.3, 112.0, 110.4, 69.4, 56.2, 55.9, 34.6, 29.0, 17.7 ; $[\alpha]_{25}^{D}$ -76.4 (c 0.6, $CHCl_3$); νmax (film) 2938, 1686, 1516, 1265, 735 cm^{-1}; ESI-HRMS calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1438, found 286.1431.

(+)-(*R*)-10b-propyl-3-oxocrispine A (+)-25



(+)-25

A mixture of enamide **23** (20 mg, 70.1 mol) and Palladium on activated carbon (10%, 2 mg) in methanol under an atmosphere of hydrogen gas (balloon) was stirred for 1 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give (+)-(R)-10b-propyl-3-oxocrispine A **(+)-25** (19 mg, 92%) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.15; δH (300 MHz, $CDCl_3$) 7.28 (s, 2H), 4.31 (ddd, *J* = 13.1, 6.8, 1.4 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.09 (ddd, *J* = 13.0, 11.9, 4.8 Hz, 1H), 2.91 (ddd, *J* = 15.9, 12.0, 6.8 Hz, 1H), 2.67 (dd, *J* = 16.1, 3.8 Hz, 1H), 2.59 (dd, *J* = 16.8, 9.1 Hz, 1H), 2.51-2.41 (m, 1H), 2.39 (ddd, *J* =12.0, 10.4, 2.2 Hz, 1H), 2.25-2.10 (m, 2H), 1.91-1.72 (m, 2H), 1.50-1.20 (m, 2H), 0.91 (t, *J* =7.2 Hz, 1H); δC (75 MHz, $CDCl_3$) 173.2, 147.9, 147.8, 135.0, 124.6, 111.6, 108.1, 63.9, 56.2, 55.9, 44.4, 34.5, 32.1, 31.3, 27.7, 17.5, 14.3; $[\alpha]_{25}^{D}$ +126.5 (c 1.8, $CHCl_3$); νmax (film) 2960, 2934, 1682, 1515, 1259, 1022, 800 cm^{-1}; ESI-HRMS calculated for $C_{17}H_{23}NO_3Na$ $[M+Na]^+$ 312.1570, found 312.1573.

(-)-(*S*)-10b-propylyl-3-oxocrispine A (-)-25

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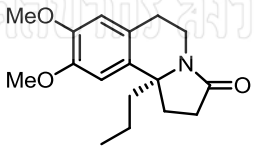
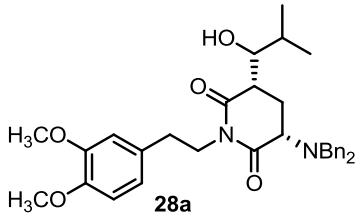


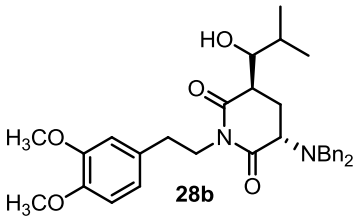
(-)-25

A mixture of enamide **24** (20 mg, 70.1 μmol) and Palladium on activated carbon (10%, 2 mg) in methanol under an atmosphere of hydrogen gas (balloon) was stirred for 1 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give (-)-(S)-10b-propylyl-3-oxocrispine A **(-)-25** (19 mg, 95%) as a colorless oil; $[\alpha]_{25}^{D}$ -143.3 (c 1.6, $CHCl_3$). All spectral data of (-)-**25** are identical to those of (+)-**25**.

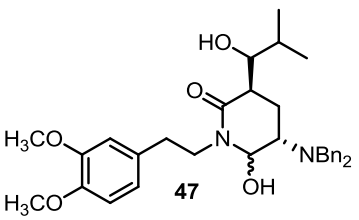
(3S)-3-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)-5-(1-hydroxy-2-methylpropyl)piperidine-2,6-dione 28a and 28b, hydroxylactam 47



28a



28b



47

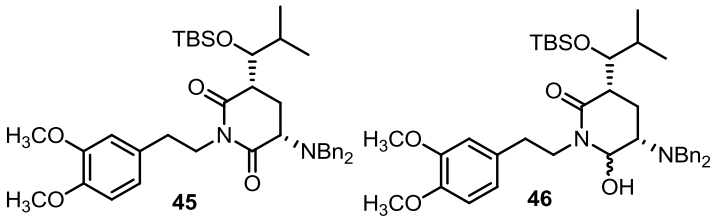
To a solution of imide **7** (1.0528g, 2.228 mmol) in dry THF (5 mL) was added LDA (3.34 mL, 6.68 mmol) at -78 ºC under an argon atmosphere and stirred for 15 min. The mixture was added isobutyraldehyde (0.30mL, 3.34mmol) and stired for 1 hour. The reaction

was quenched by sat aq NH_4Cl into the reaction. The mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude material by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) produced imide isobutyl (**28a** = 277.3mg, 23%, **28b** = 530.8mg, 44%) as a yellow oil. To a solution of imide **28b** (530.8 mg, 0.97 mmol) in dry toluene (5 mL) was added DIBALH (1.95mL, 1M in toluene, 1.95 mmol) under an argon atmosphere at -78ºC. Upon completion adjudged by TLC (1 h). The reaction quenched with MeOH. The resulting mixture was allowed to warm to room temperature and sat. aq. $NaHCO_3$ was added. The mixture was extracted with EtOAc (3x5 mL) and the combined organic layer were dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give hydroxylactam **47** (quantitative yield) as a light yellow oil.

28a ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.20 (m, 10H), 6.82-6.69 (m, 3H), 4.08 (m, 2H), 3.90 (m, 5H), 3.78 (s, 3H), 3.70-3.52 (m, 3H), 3.45 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.36 (m, 1H), 1.96 (m, 2H), 1.75 (dd, *J* = 7.0, 3.0 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H) : ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.90, 172.72, 148.89, 147.77, 139.33, 130.60, 129.88, 128.70, 128.48, 128.41, 127.24, 121.08, 120.62, 116.18, 113.90, 112.36, 111.03, 59.01, 55.89, 55.76, 55.59, 55.51, 53.08, 44.69, 41.00, 33.54, 30.94, 30.73, 29.83, 29.68, 25.62, 18.78, 14.94

28b ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.18 (m, 10H), 6.80-6.70 (m, 3H), 4.07-3.82 (m, 2H), 3.90-3.80 (m, 6H), 3,75 (s, 3H), 3.68-3.52 (m, 3H), 3.15 (m, 1H), 2.79 (t, 2H), 2.40 (d, 1H), 2.12 (td, 1H), 1.79 (td, 1H), 1.47 (m, 1H), 0.85 (m, 6H) : ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.33, 173.00, 148.82, 147.70, 139.56, 139.32, 130.83, 130.73, 129.13, 128.66, 128.55, 128.52, 128.38, 128.26, 127.24, 121.11, 112.39, 111.65, 110.98, 75.81, 55.88, 55.78, 55.13, 44.73, 40.68, 33.36, 30.85, 30.24, 26.30, 19.75, 18.69, 14.81

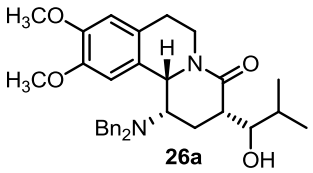
(5*S*)-3-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-5-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)piperidine-2,6-dione



To a solution of alcohol **28a** (191mg, 0.35 mmol) in dry CH_2Cl_2 (5 mL) was added 2,6-lutidine(0.05mL, 0.42mmol) and TBSOTf (0.10mL, 0.42 mmol) at 0ºC under an argon atmosphere and stired for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10:1 hexane/ethyl acetate) to give silyl ether **45** (177.65mg, 77%) as a yellow oil. To a solution of silyl ether **45** (176.5 mg, 0.27 mmol) in dry toluene (5 mL) was added DIBALH (0.54 mL, 1M in toluene, 0.54mmol) under an argon atmosphere at -78ºC. Upon completion adjudged by TLC (1 h). The reaction quenched with MeOH. The resulting mixture was allowed to warm to room temperature and sat. aq. $NaHCO_3$ was added. The mixture was extracted with EtOAc (3x5 mL) and the combined organic layer were dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give hydroxylactam **46** (quantitative yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.20 (m, 10H), 6.86-6.70 (m, 3H), 4.18 (m, 2H), 4.10-3.95 (m, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.73 (d, *J* = 13.0 Hz, 2H), 3.44 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.79 (t, 2H), 2.45 (m, 1H), 2.26 (m,

1H), 1.90 (dd, *J* = 7.0, 3.0 Hz, 1H), 1.65 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.10 (s, 3H), 0.05 (s, 3H)

Benzoquinolizidine 26a



26a

To a solution of hydroxylactam **46** (186.8 mg, 0.28 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (0.15mL , 0.85mmol) at 0ºC under an argon atmosphere and strried for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 2:1 hexane/ethyl acetate) to give benzoquinolizidinone **26a** (69.3 mg, 46%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.12 (m, 10H), 7.06 (s, 1H), 6.58 (s, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.50 (m, 1H), 4.10 (d, *J* = 13.0 Hz, 2H), 3.92-3.80 (m, 8H), 3.53 (dd, *J* = 7.0, 3.0 Hz, 1H), 3.20-3.00 (m, 3H), 2.65 (m, 1H), 2.43 (m, 1H), 2.00 (m, 2H), 1.78 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.43, 147.87, 146.86, 140.52, 131.82, 128.48, 128.16, 127.83, 126.71, 111.44, 110.23, 80.12, 57.83, 57.71, 55.94, 55.32, 42.80, 40.41, 29.99, 29.19, 27.30, 20.51, 14.61

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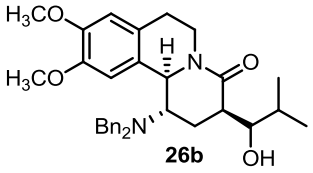
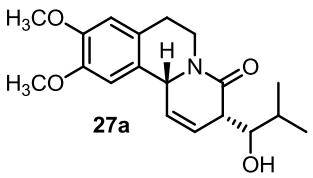
Benzoquinolizidine 26b



26b

To a solution of hydroxylactam **47** (532.4 mg, 0.97 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (0.53mL, 2.92mmol) at 0ºC under an argon atmosphere and strried for 3 hours. The reaction was quenched with sat aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 2:1 hexane/ethyl acetate) to give benzoquinolizidinone **26b** (221.8mg, 43%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.15 (m, 10H), 6.69 (s, 1H), 6.60 (s, 1H), 4.85 (m, 1H), 3.98 (d, *J*=13.0 Hz, 2H), 3.48 (d, 1H), 3.20 (dd, 1H), 3.10 (m, 1H), 2.85 (td, 1H), 2.65 (dd, 1H), 2.36 (m, 1H), 1.80 (td, 1H), 1.70 (m, 1H), 0.86 (d, *J*=7.0 Hz, 3H), 0.70 (d, *J*=7.0 Hz, 3H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.06, 148.13, 147.46, 140.46, 129.50, 129.22, 129.15, 128.80, 128.65, 128.63, 128.60, 128.57, 128.17, 128.10, 127.37, 126.84, 126.77, 112.42, 107.56, 73.72, 58.54, 56.35, 55.84, 55.29, 54.30, 53.70, 42.67, 39.21, 28.87, 28.61, 25.57, 20.37, 13.20

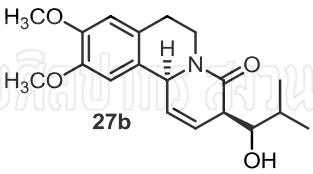
Tricyclic enamide 27a



27a

To a solution of tricyclic **26a** (69.3 mg, 0.13 mmol) in $CHCl_3$ (5 mL) was added m-CPBA (96.9 mg, 0.39 mmol) at 0ºC and strried for 1 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 40 : 1 CH_2Cl_2/MeOH) to give unsaturated lactam **27a** (20.5 mg, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.63 (s, 1H), 6.42 (dd, 1H), 5.90 (d, 1H), 5.08 (s, 1H), 4.67 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.78 (m, 1H), 3.30-3.08 (m, 2H), 3.03 (m, 1H), 2.65 (m, 1H), 1.95 (m, 1H), 1.73 (brs, 1H), 1.06 (d, J = 7.0 Hz, 6H) : ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.40, 148.24, 147.03, 138.30, 129.22, 128.61, 125.69, 112.67, 107.56, 75.97, 57.09, 56.40, 55.92, 43.23, 40.15, 29.70, 27.08, 20.42, 14.47; $[\alpha]_{25}^{D}$ -79.5 (c 1.8, $CHCl_3$)

Tricyclic enamide 27b



27b

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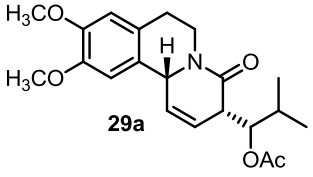
To a solution of tricyclic **26b** (221.8mg, 0.42 mmol) in $CHCl_3$ (5 mL) was added m-CPBA (310.3 mg, 1.26mmol) at 0ºC and strried for 1 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 40 : 1 CH_2Cl_2/MeOH) to give unsaturated lactam **27b** (60.3 mg, 43%) as a colorless oil. All spectral data are identical with those of **27a**; $[\alpha]_{25}^{D}$ +83.7 (c 1.9, $CHCl_3$)

1-((11b*S*)-9,10-dimethoxy-4-oxo-4,6,7,11b-tetrahydro-3H-pyrido[2,1-a]isoquinolin-3-yl)-2-methylpropyl acetate 29a

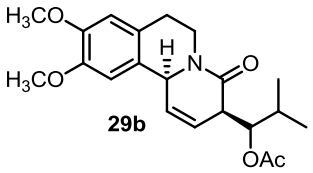


29a

To a solution of tricyclic enamide **27a** (46.5 mg, 0.14 mmol) in dry CH_2Cl_2 (1 mL) was added pyridine (1 drop) under an argon atmosphere The mixture reaction was added excess Ac_2O (0.50mL) and strried for overnight. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure to give crude product **29a** (quantitative yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.62 (s, 1H),

6.40 (dd, 1H), 5.95 (d, 1H), 5.18 (dd, 1H), 4.68 (dd, 1H), 4.50 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.20 (m, 2H), 3.05 (td, 1H), 2.65 (m, 1H), 2.12 (s, 3H), 2.05 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 2H), 0.98 (d, *J* = 7.0 Hz, 2H)

Acetate 29b



29b

To a solution of tricyclic enamide **27b** (20.2 mg, 0.06 mmol) in dry CH_2Cl_2 (1 mL) was added pyridine (1 drop) under an argon atmosphere The mixture reaction was added excess Ac_2O (0.50mL) and strried for overnight. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure to give crude product **29b** (quantitative yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.62 (s, 1H), 6.42 (dd, 1H), 5.96 (d, 1H), 5.18 (dd, 1H), 4.70 (dd, 1H), 4.58 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.20 (m, 2H), 3.08 (td, 1H), 2.65 (dt, 1H), 2.10 (s, 3H), 2.05 (m, 1H)

SYNTHESIS OF PROTOEMETINOL

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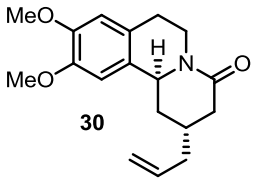
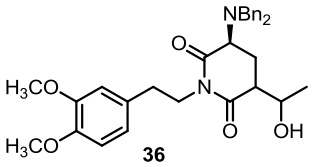
(2*R*,11b*S*)-2-allyl-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one 30



30

To a solution of tricyclic enamide (41.9mg, 0.16mmol) in dry ether (3 mL) was added allylMgBr which it was prepared freshly by mixing Mg(34.9mg, 1.46mmol) and allylBr (0.04mL, 0.48mmol) in dry Et_2O at room temperature under an argon atmosphere and strried overnight. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (1:1 hexane/ethyl acetate) to give product (9.0 mg, 7%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (m, 2H), 5.90 – 5.70 (m, 1H), 5.13 (m, 2H), 4.85 (m, 1H), 4.70 (m, 1H), 3.90 (s, 6H), 3.06-2.80 (m, 2H), 2.67 (m, 1H), 2.51 (dd, 1H), 2.37-2.08 (m, 6H)

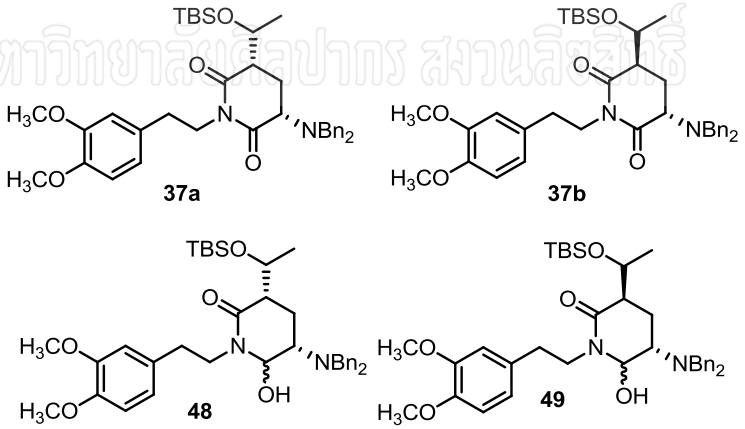
(3*S*)-3-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)-5-(1-hydroxyethyl)piperidine-2,6-dione 36



36

To a solution of imide **7** (787.2 mg, 1.66 mmol) in dry THF (5 mL) was added LDA (2.50 mL, 4.99 mmol) at -78 ºC under an argon atmosphere and stirred for 15 min. The mixture was added acetaldehyde (0.94 mL, 16.64 mmol)and stired for 1 hour. The reaction was quenched by sat. aq. NH_4Cl into the reaction. The mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude material by flash column chromatography (silica gel, 6:1 hexane/ethyl acetate) produced imide isobutyl **36** (334.7, 39 % yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.12 (m, 10H), 6.85-6.61 (m, 3H), 4.25-4.05 (m, 2H), 3.95-3.89 (d, *J* = 13.0 Hz, 2H), 3.88-3.79 (s, 6H), 3.69-3.61 (d, *J* = 13.0 Hz, 2H), 3.53-3.41 (d, *J* = 7.0, 3.0 Hz, 1H), 2.85-2.71 (t, 2H), 2.52-2.36 (m, 1H), 2.35-2.21 (m, 1H), 1.75-1.59 (m, 1H)

Silyl enol ethers 37a and 37b, hydroxylactams 48 and 49

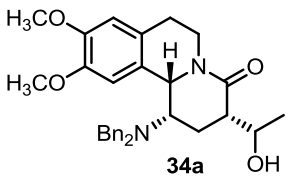


To a solution of alcohol **36** (196.6mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL) was added 2,6-lutidine (0.05mL, 0.46mmol) and TBSOTf (0.11mL, 0.46 mmol) at 0ºC under an argon atmosphere and stired for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 4:1 hexane/EtOAc) to give silyl ether (**37a** = 56.5 mg, 24%, **37b** = 42.6 mg, 18%) as a yellow oil. To a solution of imide **37a** (56.5mg, 0.09 mmol) in dry toluene (5 mL) was added DIBALH (0.18 mL, 1M in toluene, 0.18 mmol) under an argon atmosphere at -78ºC. Upon completion adjudged by TLC (1 h). The reaction quenched with MeOH. The resulting mixture was allowed to warm to room temperature and sat. aq. $NaHCO_3$ was added. The mixture was extracted with EtOAc (3x5 mL) and the combined organic layer were dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give hydroxylactam **48** (quantitative yield) as a yellow oil. To a solution of imide **37b** (42.6 mg, 0.07mmol) in dry toluene (5 mL) was added DIBALH (0.14mL, 1M in toluene, 0.14 mmol) under an argon atmosphere at -78ºC. Upon completion adjudged by TLC (1 h). The reaction

quenched with MeOH. The resulting mixture was allowed to warm to room temperature and sat. aq. $NaHCO_3$ was added. The mixture was extracted with EtOAc (3x5 mL) and the combined organic layer were dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give hydroxylactam **49** (quantitative yield) as a yellow oil. **37a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.19 (m, 10H), 6.81-6.64 (m, 3H), 3.96-3.88 (m, 4H), 3.85 (s, 6H), 3.68-3.56 (d, *J*=13.0 Hz, 2H), 3.48-3.38 (dd, *J*=7.0 Hz, 1H), 2.79-2.69 (t, 2H), 2.51-2.38 (dt, 1H), 2.28-2.18 (m, 1H), 1.85-1.68 (dd, 1H), 1.05 (d, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H)

37b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.15 (m, 10H), 6.84-6.68 (m, 3H), 4.80-4.54 (m, 1H), 4.15-3.89 (m, 4H), 3.85 (s, 6H), 3.78 (d, *J* = 13.0 Hz, 2H), 3.49-3.37 (m, 1H), 2.81-2.63 (t, 2H), 2.26-2.10 (m, 1H), 1.89-1.69 (m, 1H), 2.10-1.90 (m, 1H), 1.28-0.96 (m, 3H), 0.90-0.70 (m, 9H), 0.11- (-0.09) (m, 6H)

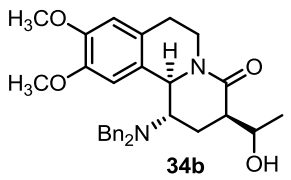
Benzoquinolizidine 34a



34a

To a solution of hydroxylactam **48** (63.9 mg, 0.10 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (0.05mL, 0.30 mmol) at 0ºC under an argon atmosphere and strried for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 1:1 hexane/EtOAc) to give benzoquinolizidinone **34a** (18.1 mg, 40%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.16 (m, 10H), 6.89 (s, 1H), 6.68 (s, 1H), 4.26-4.20 (d, *J* = 7.0 Hz, 1H), 4.16-4.04 (m, 1H), 3.89-3.79 (m, 6H), 3.89-3.71 (m, 2H), 3.39-3.28 (m, 1H), 3.28-3.18 (dd, 1H), 3.08-2.91 (m, 1H), 2.80-2.68 (m, 1H), 2.42-2.30 (m, 1H), 1.94-1.75 (m, 2H), 1.34-1.24 (d, *J* = 7.0 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.71, 148.29, 147.24, 140.55, 130.13, 129.36, 128.74, 128.59, 128.19, 126.74, 111.39, 109.44, 108.93, 69.63, 57.96, 56.61, 56.27, 56.13, 55.99, 55.42, 43.72, 43.17, 42.52, 41.86, 28.25, 27.55, 26.54, 24.14, 21.70, 20.01; $[\alpha]_{25}^{D}$ -14.3 (c 0.9, $CHCl_3$)

Benzoquinolizidine 34b

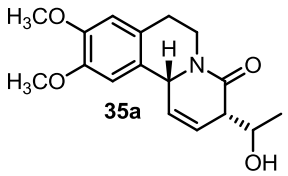


34b

To a solution of hydroxylactam **49** (45.0 mg, 0.07 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (0.04mL, 0.21mmol) at 0ºC under an argon atmosphere and strired for 3 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 1:1 hexane/EtOAc) to give benzoquinolizidinone **34b** (9.3 mg, 29%) as a yellow oil. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.50-7.13 (m, 10H), 6.67 (s, 1H), 6.58 (s, 1H), 4.82 (m, 1H), 4.00 (d, J=13.0 Hz, 2H), 3.92-3.73 (m, 8H), 3.58 (d, J=13.0 Hz, 2H), 3.25 (dd, 1H), 3.12 (m, 1H), 2.88 (td, 1H), 2.65 (dt, 1H), 2.25 (m, 1H), 1.80 (m, 2H), 1.02 (d, J=7.0 Hz, 3H) : ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.01, 148.08, 147.47, 140.52, 140.34, 130.06, 129.22, 129.10, 128.74, 128.65, 128.53, 128.20, 128.14, 126.82, 112.38, 107.28, 76.60, 58.01, 56.62, 56.23, 55.96, 55.44, 55.25, 53.73, 42.63, 41.84, 29.70, 28.87, 28.25, 25.94, 21.34;$[\alpha]_{25}^{D}$ -74.7 (c 0.8, $CHCl_3$)

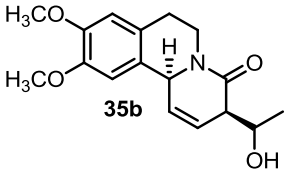
Tricyclic enamide 35a



35a

To a solution of tricyclic **34a** (18.1 mg, 0.04 mmol) in $CHCl_3$ (5 mL) was added m-CPBA (26.7 mg, 0.11mmol) at 0ºC and stired for 1 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 20:1 CH_2Cl_2/MeOH) to give unsaturated lactam **35a** (12.1mg, quantitative yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.82 (s, 1H), 6.51-6.42 (dd, 1H), 6.01-5.91 (d, *J* = 7.0 Hz, 1H), 4.96 (s, 1H), 4.70-4.60 (m, 1H), 4.11-4.01 (p, 1H), 3.85 (s, 6H), 3.22-3.12 (m, 1H), 3.12-2.98 (m, 1H), 2.94-2.85 (m, 1H), 2.70-2.56 (m, 1H), 1.75-1.60 (brs, 1H), 1.41-1.33 (d, *J* = 7.0 Hz, 3H): ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.62, 145.82, 144.73, 136.06, 126.30, 126.16, 123.27, 110.10, 105.22, 66.21, 54.43, 53.88, 53.51, 42.19, 40.22, 25.10, 18.78; $[\alpha]_{25}^{D}$ -44.8 (c 0.9, $CHCl_3$)

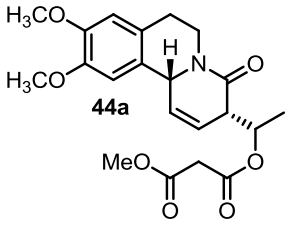
Tricyclic enamide 35b



35b

To a solution of tricyclic **34b** (9.3 mg, 0.02 mmol) in $CHCl_3$ (5 mL) was added *m*-CPBA (14.8 mg, 0.06 mmol) at 0ºC and stired for 1 hours. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by Thin layer chromatography (silica gel, 20:1 CH_2Cl_2/MeOH) to give unsaturated lactam **35b** (4.3 mg, 71%) as a colorless oil. All spectral data are identical with those of **35a**; $[\alpha]_{25}^{D}$ +32.8 (c 0.7, $CHCl_3$)

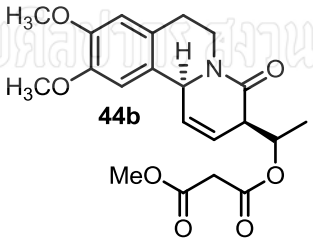
(R)-1-((3S,11bR)-9,10-dimethoxy-4-oxo-4,6,7,11b-tetrahydro-3H-pyrido[2,1-a]isoquinolin-3-yl)ethyl methyl malonate 44a



Malonic acid was dissolved in HCl/MeOH, then it was concentrated under reduced pressure. To this mixture (95.6 mg, 0.81 mmol) was added pyridine (0.07 mL) in $CHCl_3$(1 mL) at 0°C was added dropwise thionyl chloride (0.07 mL, 0.98 mmol) to give malonate derivative. To a solution of unsaturated lactam **35a** (12.1 mg, 0.04 mmol) in $CHCl_3$ was added malonate derivative (1mL) and stired overnight. The reaction was quenched with solution of 5N HCl (25 mL) and washed with 5N HCl (3x25mL), water (2x25mL), 10% Na_2CO_3 (3x25mL), water (2x25mL) and brine The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give crude product **44a** (24.9 mg, 67%) as a brown oil. All spectral data are identical with those of **44b**

(*S*)-1-((3*R*,11b*S*)-9,10-dimethoxy-4-oxo-4,6,7,11b-tetrahydro-3H-pyrido[2,1-a]isoquinolin-3-yl)ethyl methyl malonate 44b

มหาวิทยาลัยหลักการ ฝ่ายลิขสิทธิ์



Malonic acid was dissolved in HCl/MeOH, then it was concentrated under reduced pressure. To this mixture (95.6 mg, 0.81 mmol) was added pyridine (0.07 mL) in $CHCl_3$(1 mL) at 0°C was added dropwise thionyl chloride (0.07 mL, 0.98 mmol) to give malonate derivative. To a solution of unsaturated lactam **35b** (4.3 mg, 0.01 mmol) in $CHCl_3$ was added malonate derivative (1mL) and stired overnight. The reaction was quenched with solution of 5N HCl (25 mL) and washed with 5N HCl (3x25mL), water (2x25mL), 10% Na_2CO_3 (3x25mL), water (2x25mL) and brine The combined organic phase was dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give crude product **44b** (5 mg, 88%)as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (s, 1H), 6.64 (s, 1H), 6.44 (dd, 1H), 6.06 (d, J = 7.0 Hz, 1H), 5.24 (t, 1H), 4.66 (m,1H), 4.60 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.71 (s, 3H), 3.42 (s, 2H), 3.25 (m, 1H), 3.06 (m, 2H), 2.66 (m, 1H), 1.39 (d, J = 7.0 Hz, 3H): ^{13}C NMR (75 MHz, CDCl3): δ 166.86, 165.84, 163.32, 148.30, 147.46, 136.66, 128.54, 127.95, 126.16, 112.34, 107.55, 72.81, 56.72, 56.34, 55.94, 52.62, 42.27, 41.93, 41.51, 27.67, 16.64

Appendix

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Compound 19 ^{1}H NMR spectrum…… 80

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Compound 21 ^{1}H NMR spectrum…… 82

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Compound 22 ^{1}H NMR spectrum…… 84

^{13}C NMR spectrum…… 85

Compound 23 ^{1}H NMR spectrum…… 86

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Compound 24 ^{1}H NMR spectrum…… 88

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Compound 27a ^{1}H NMR spectrum..... 101

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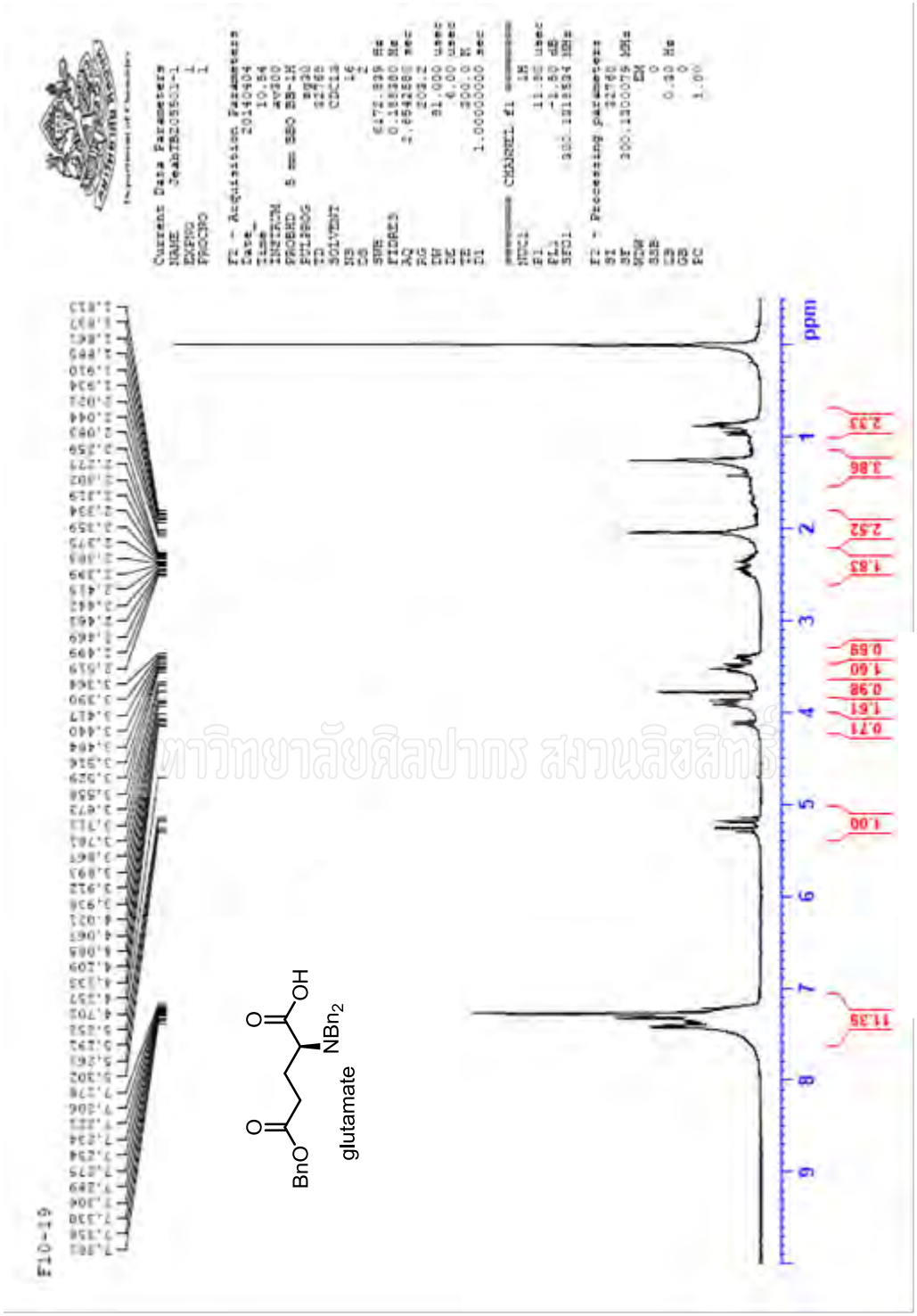
^{13C} NMR spectrum…… 120

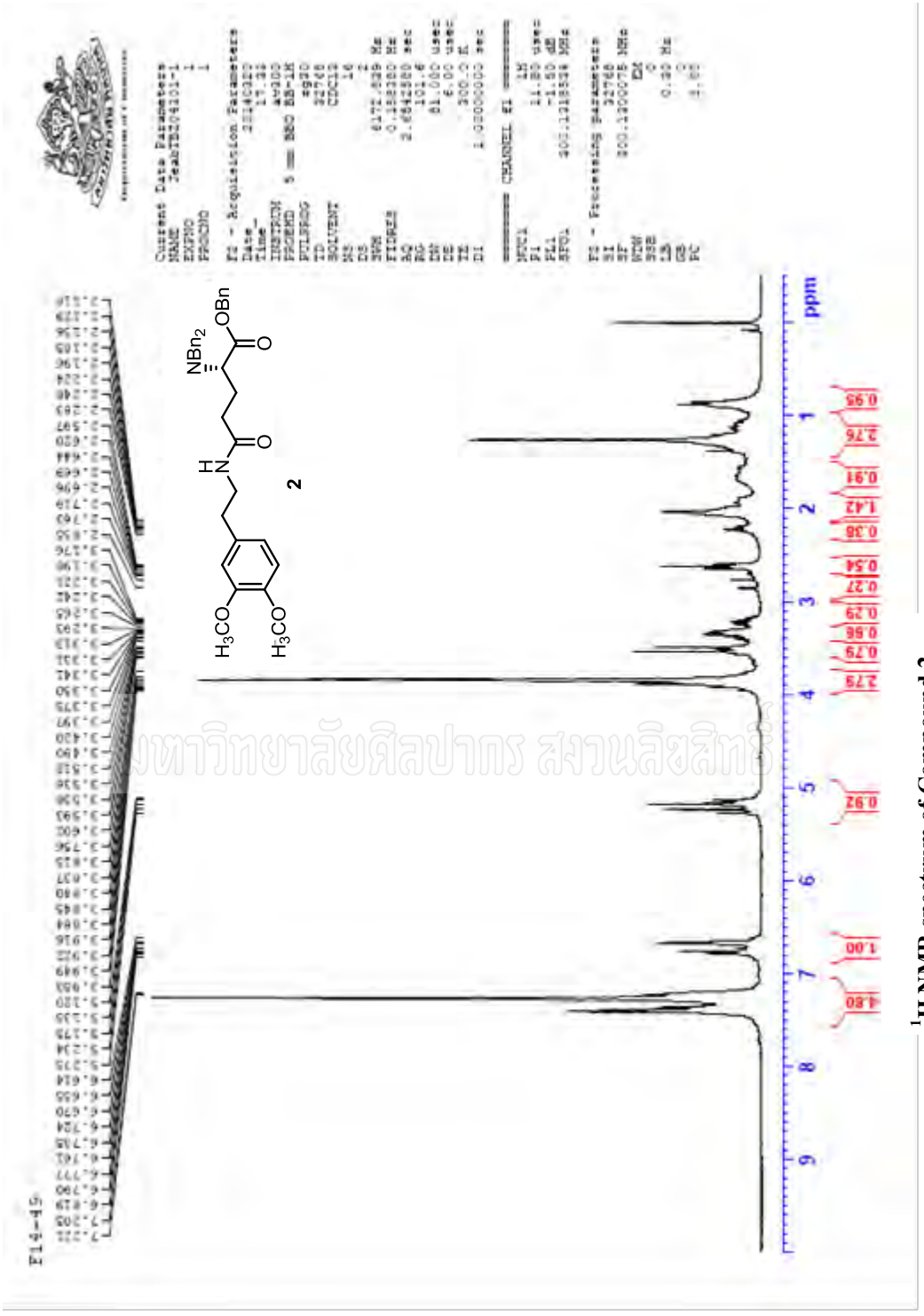
Compound 44b ^{1}H NMR spectrum…… 121

^{13C} NMR spectrum…… 122

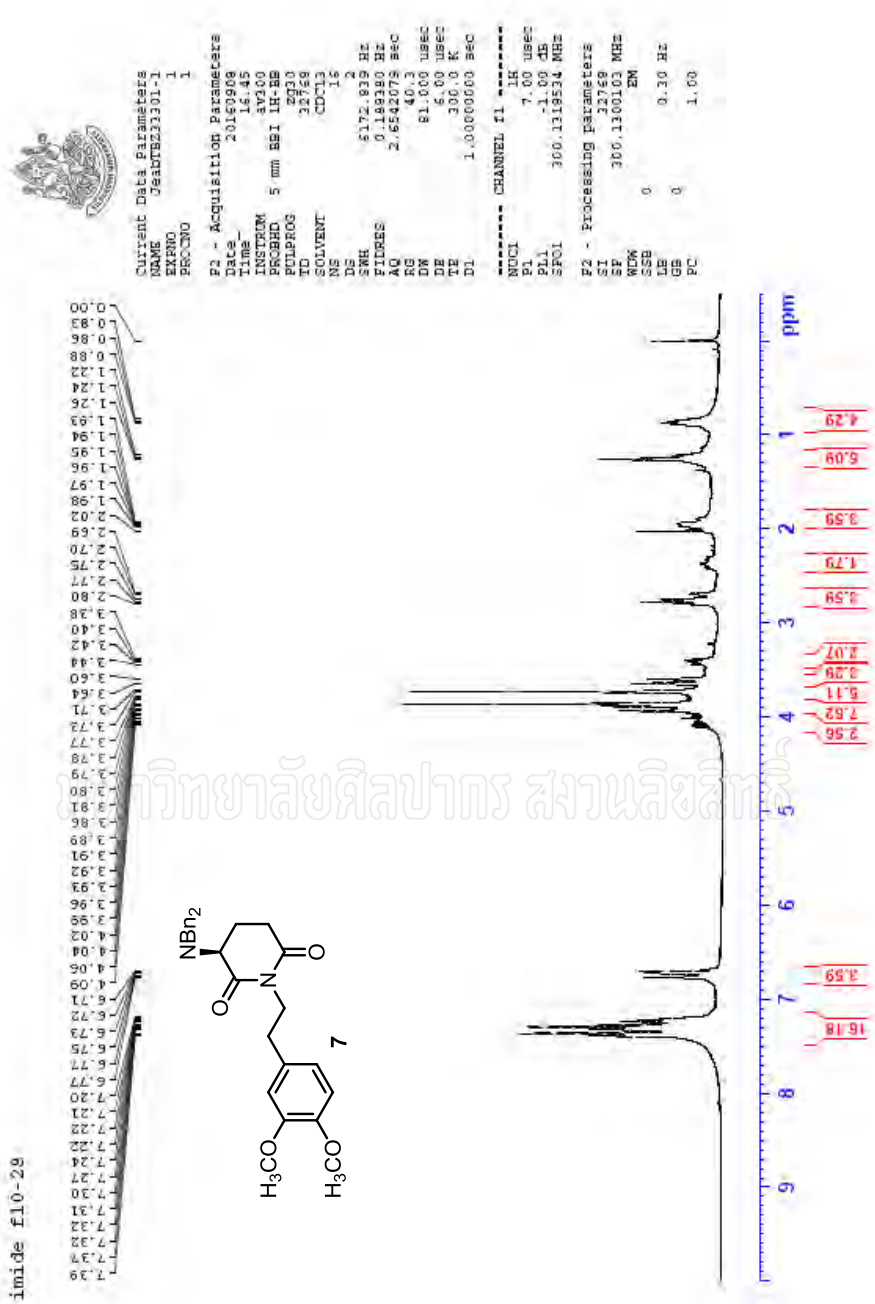
มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



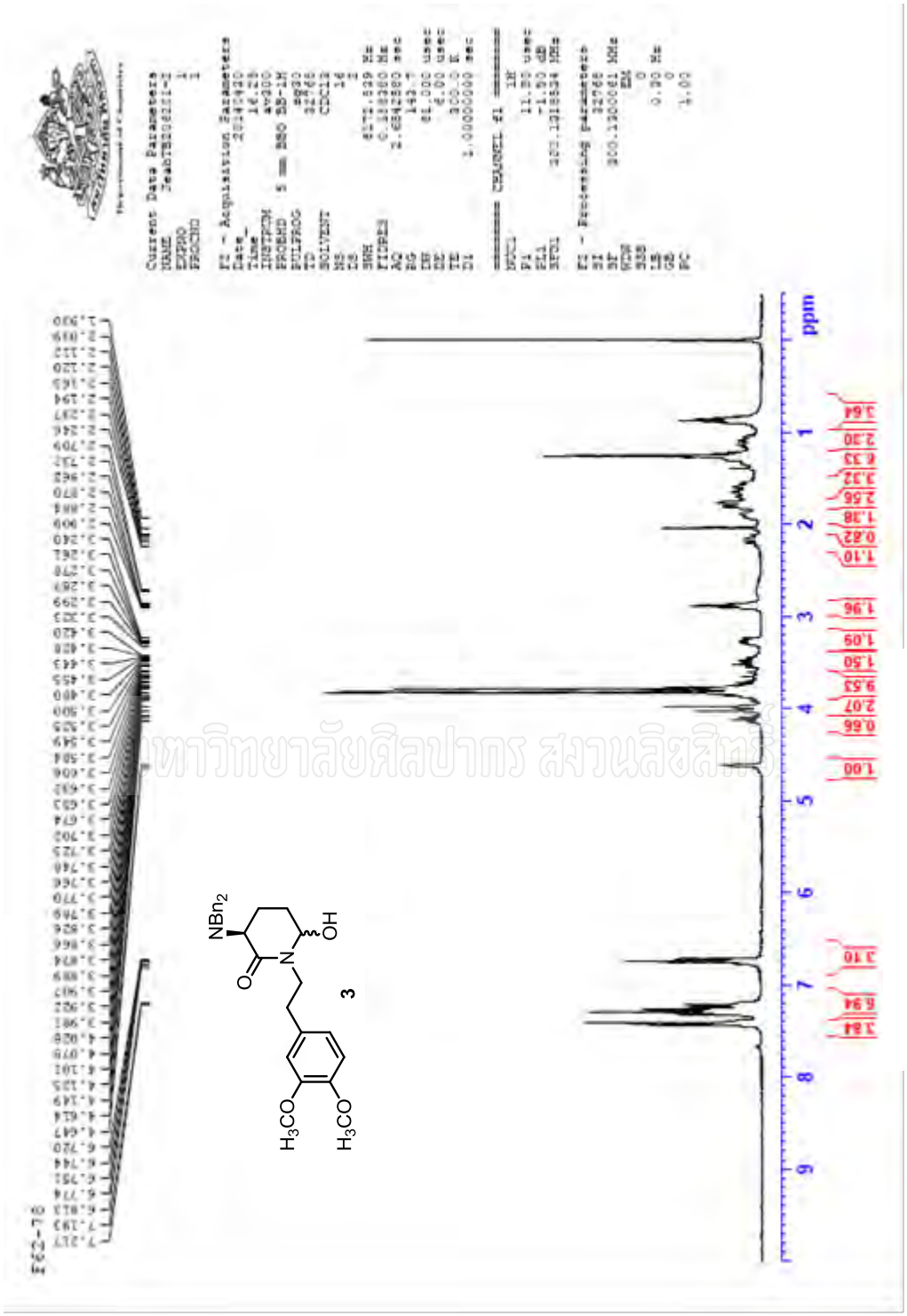
^{1}H NMR spectrum of Glutamate



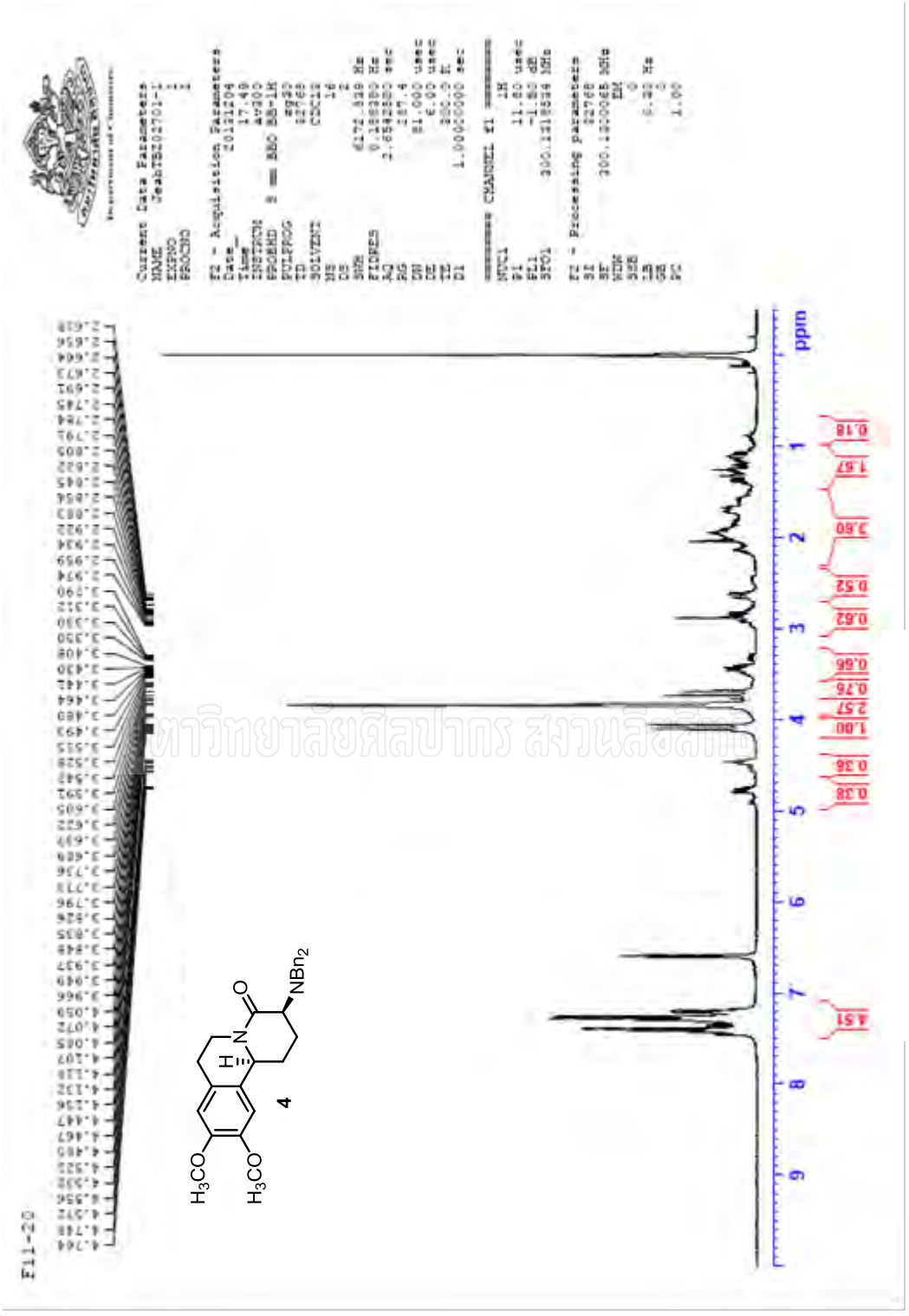
^{1}H NMR spectrum of Compound 2



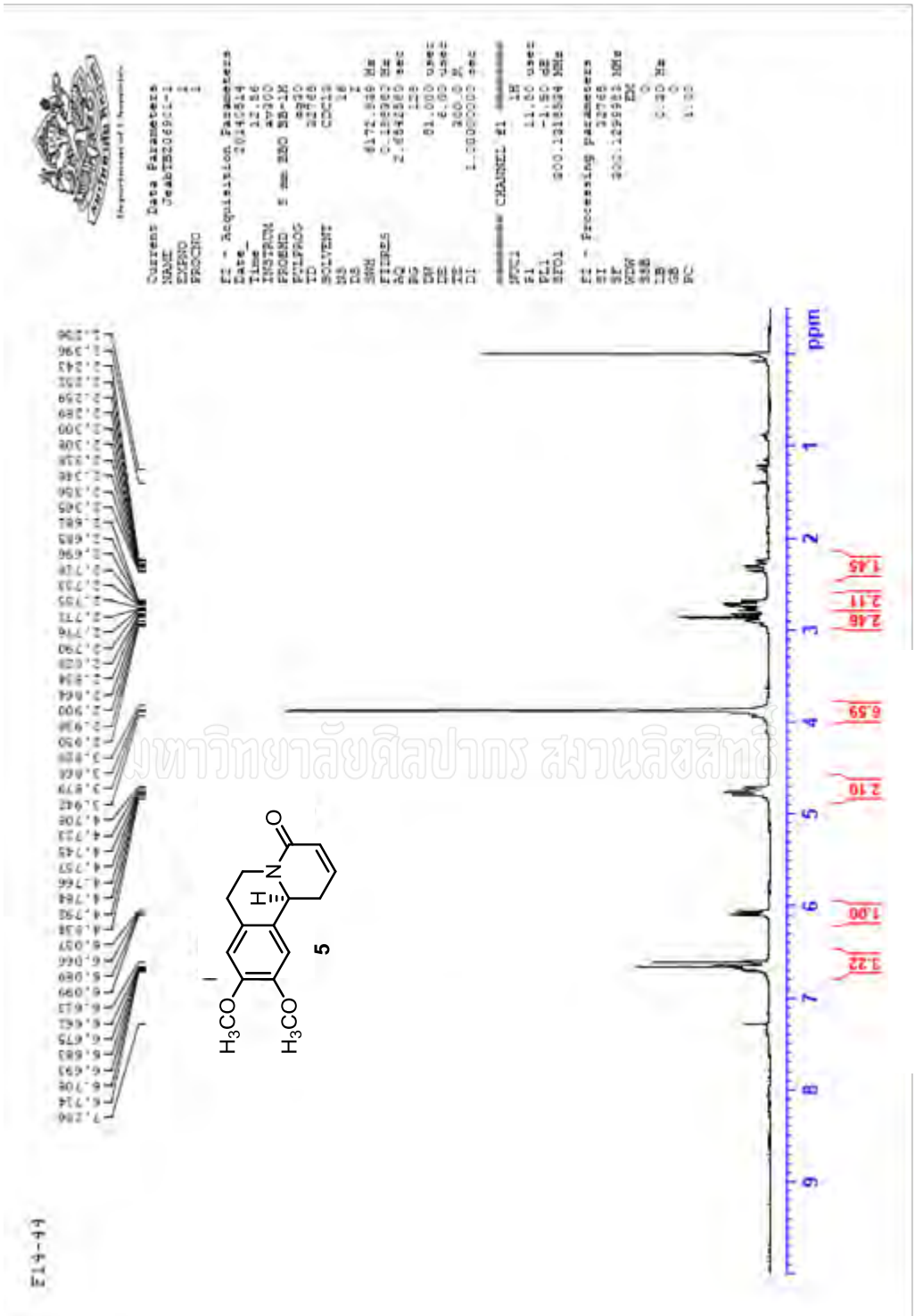
^{1}H NMR spectrum of Compound 7



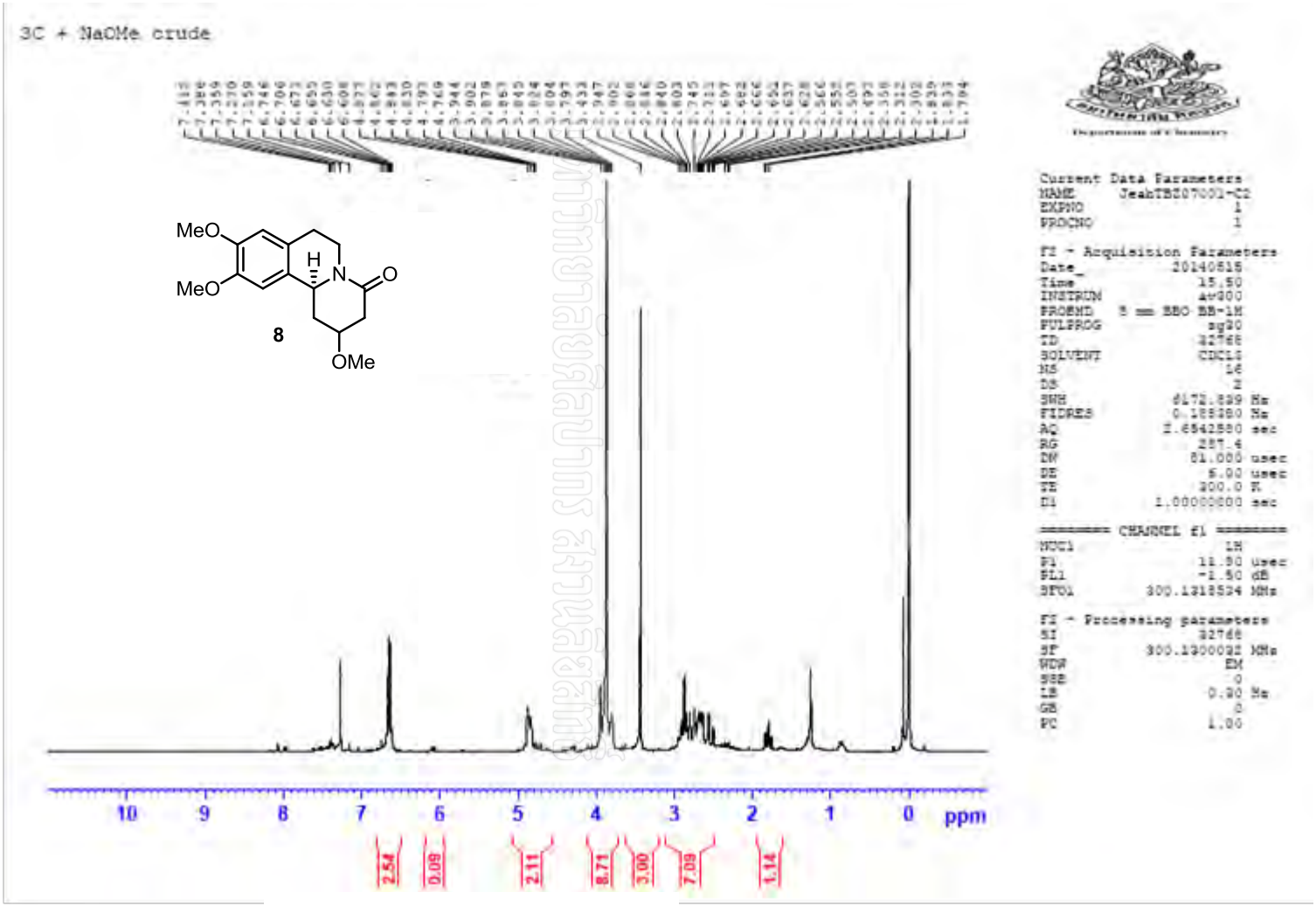
^{1}H NMR spectrum of Compound 3



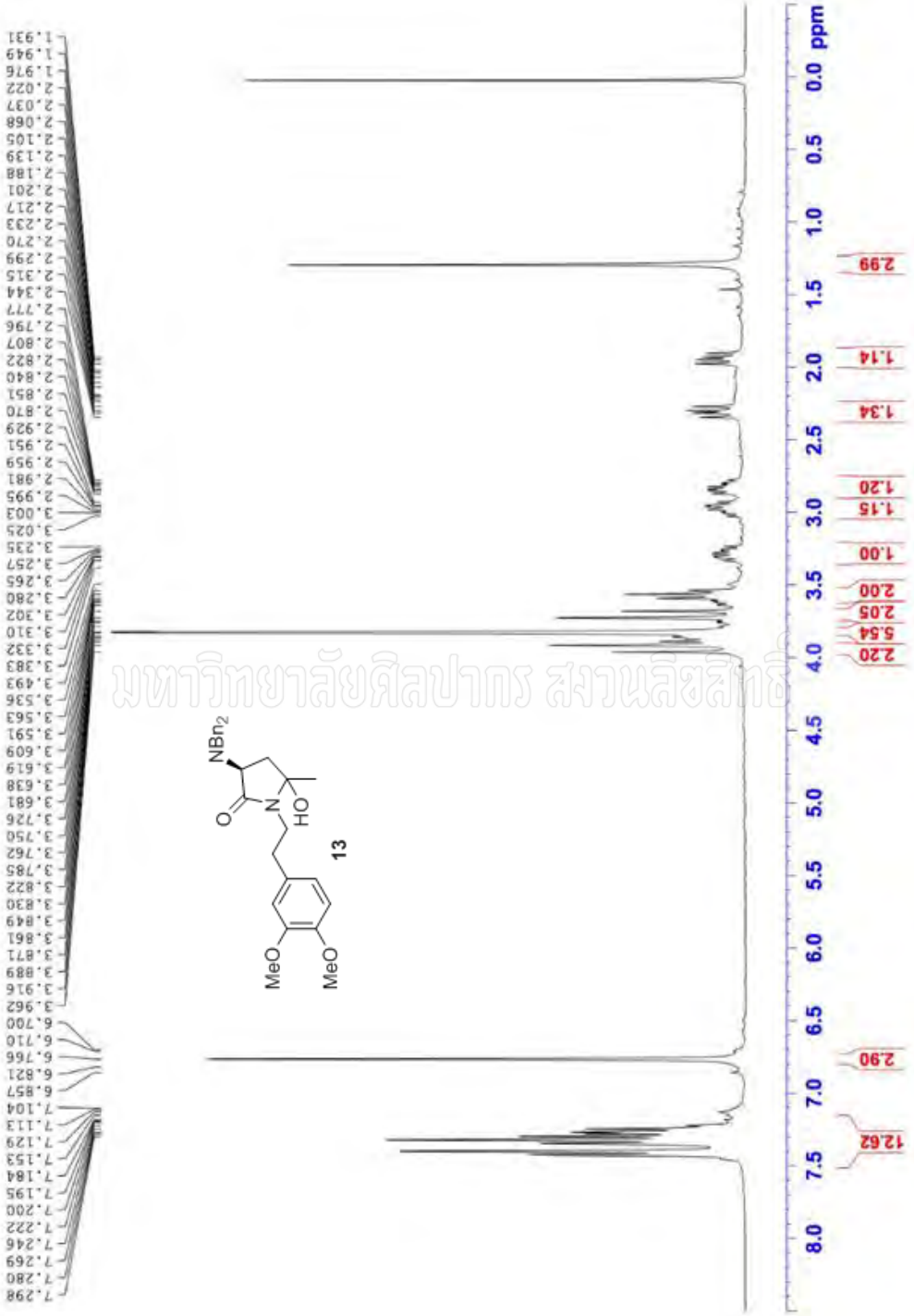
^{1}H NMR spectrum of Compound 4



^{1}H NMR spectrum of Compound 5

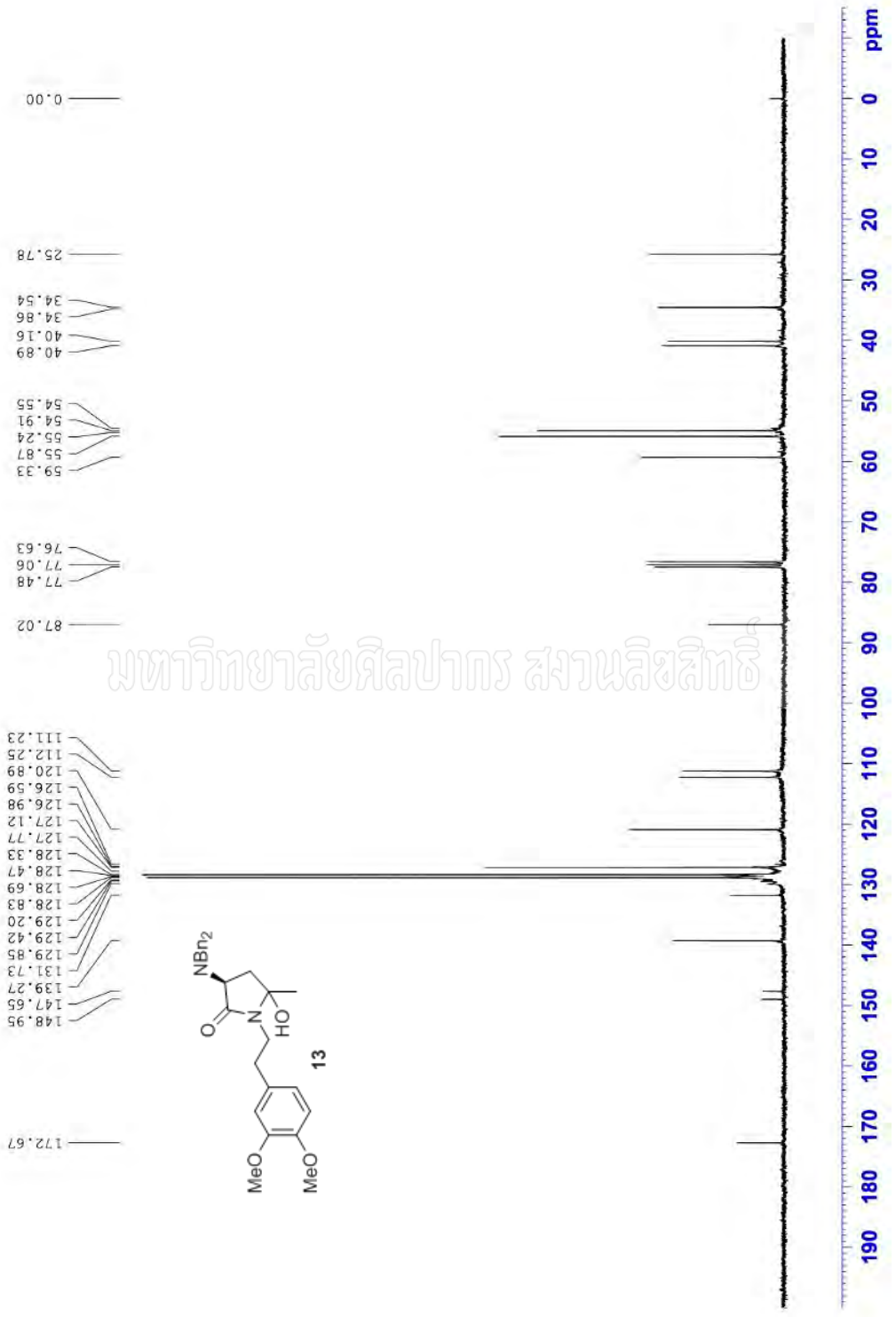


[1]H NMR spectrum of Compound 8



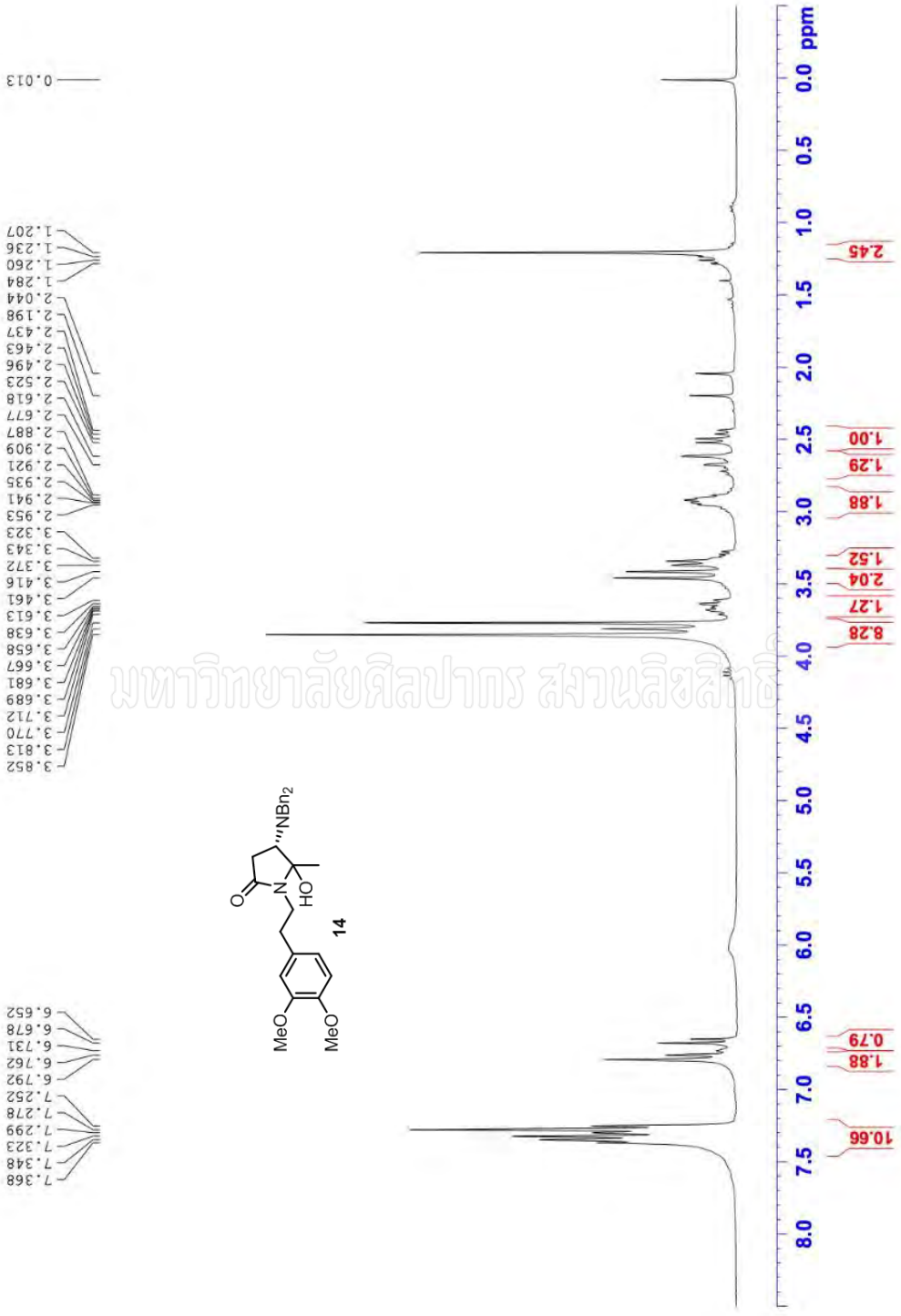
^{1}H NMR spectrum of Compound 13

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



^{13}C NMR spectrum of Compound 13

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



^{1}H NMR spectrum of Compound 14

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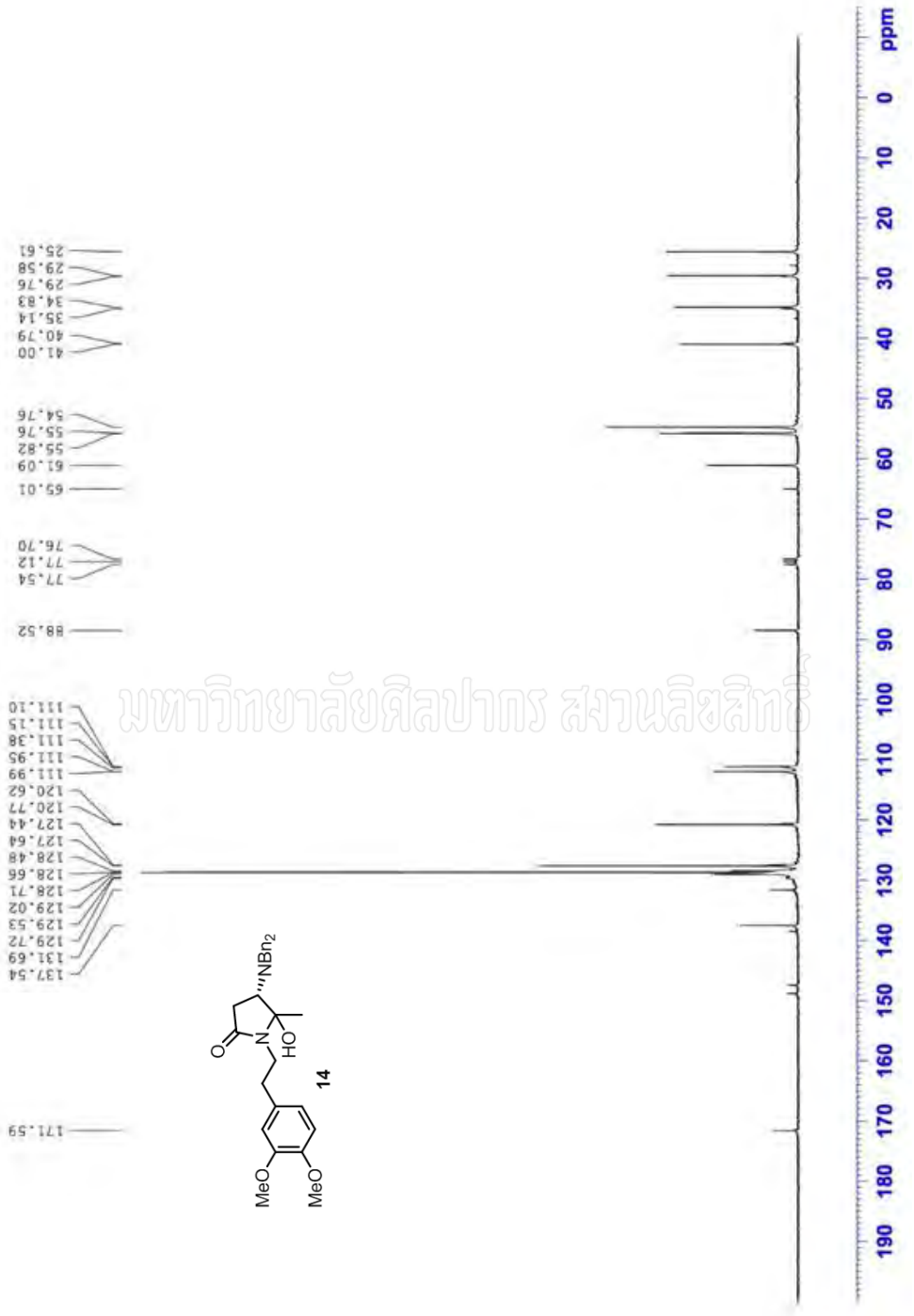

^{13}C NMR spectrum of Compound 14

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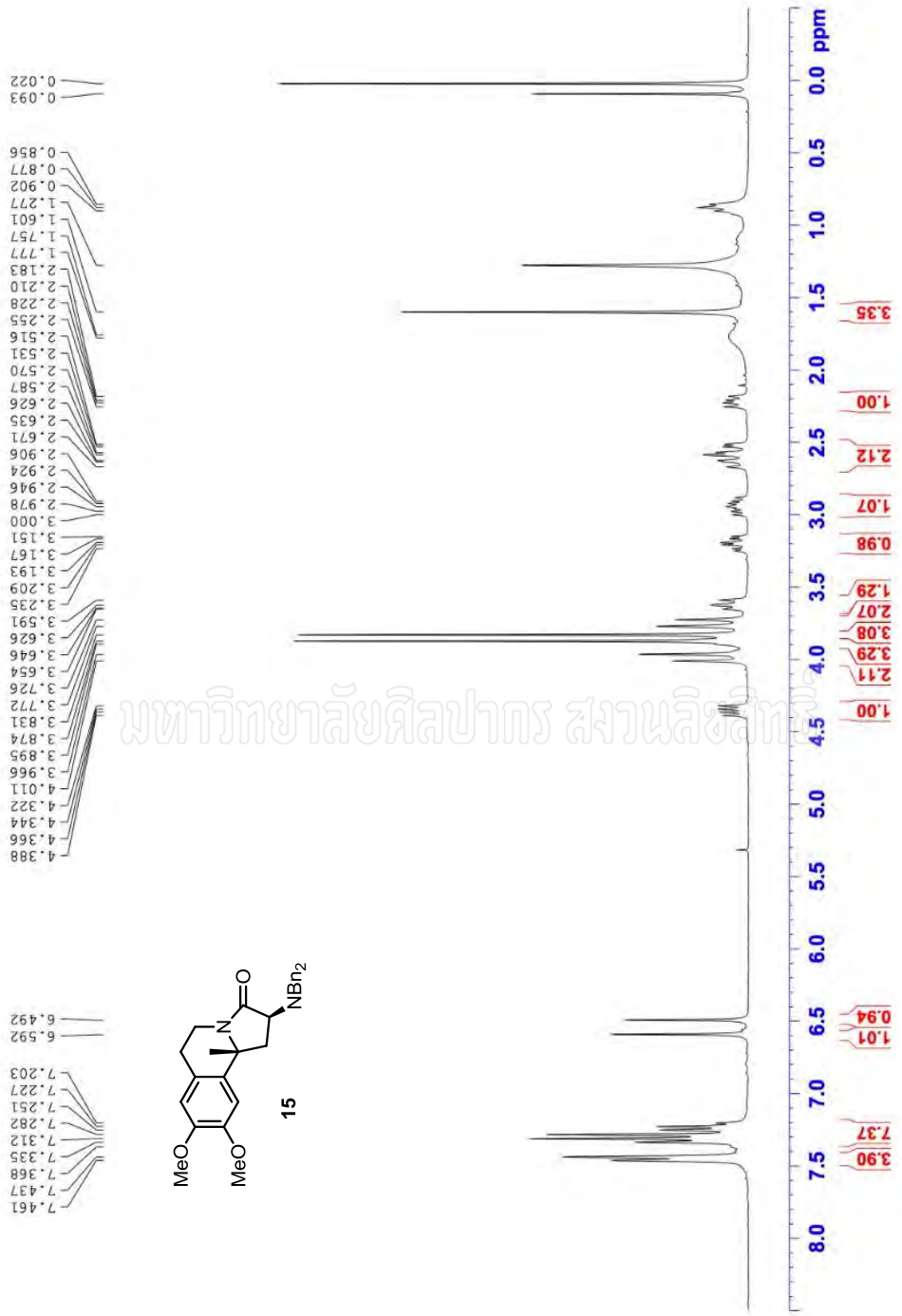
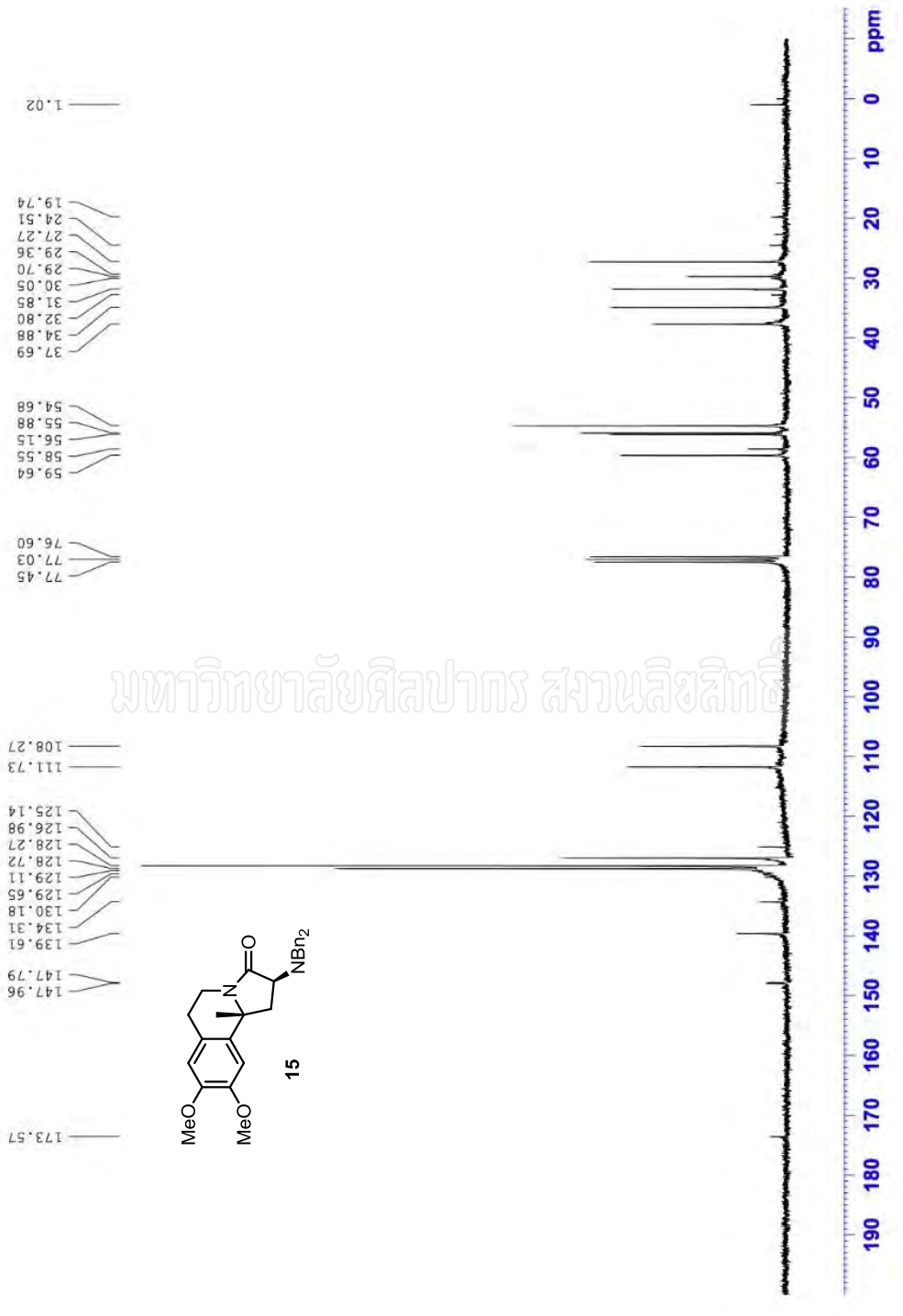


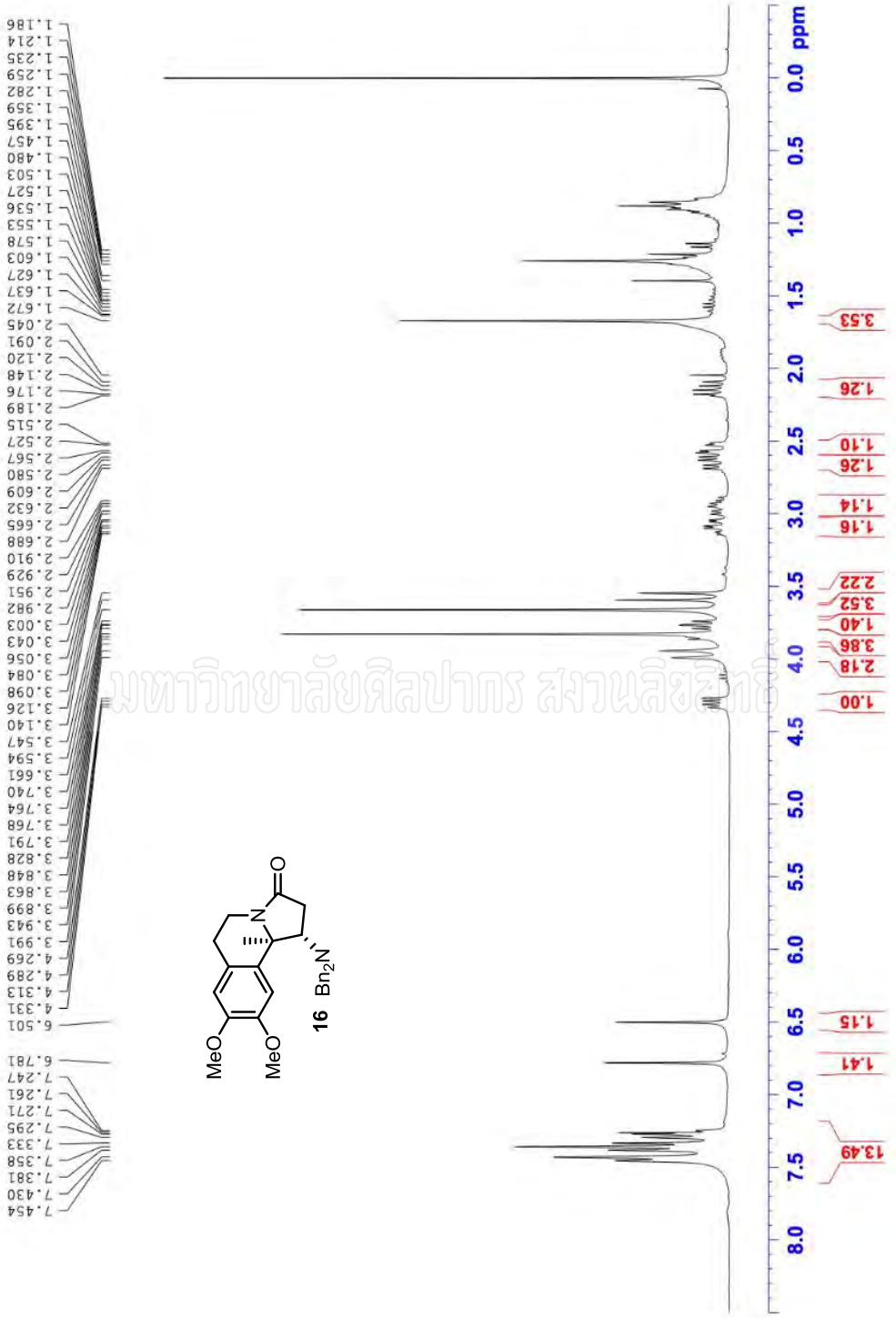
^{1}H NMR spectrum of Compound 15

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



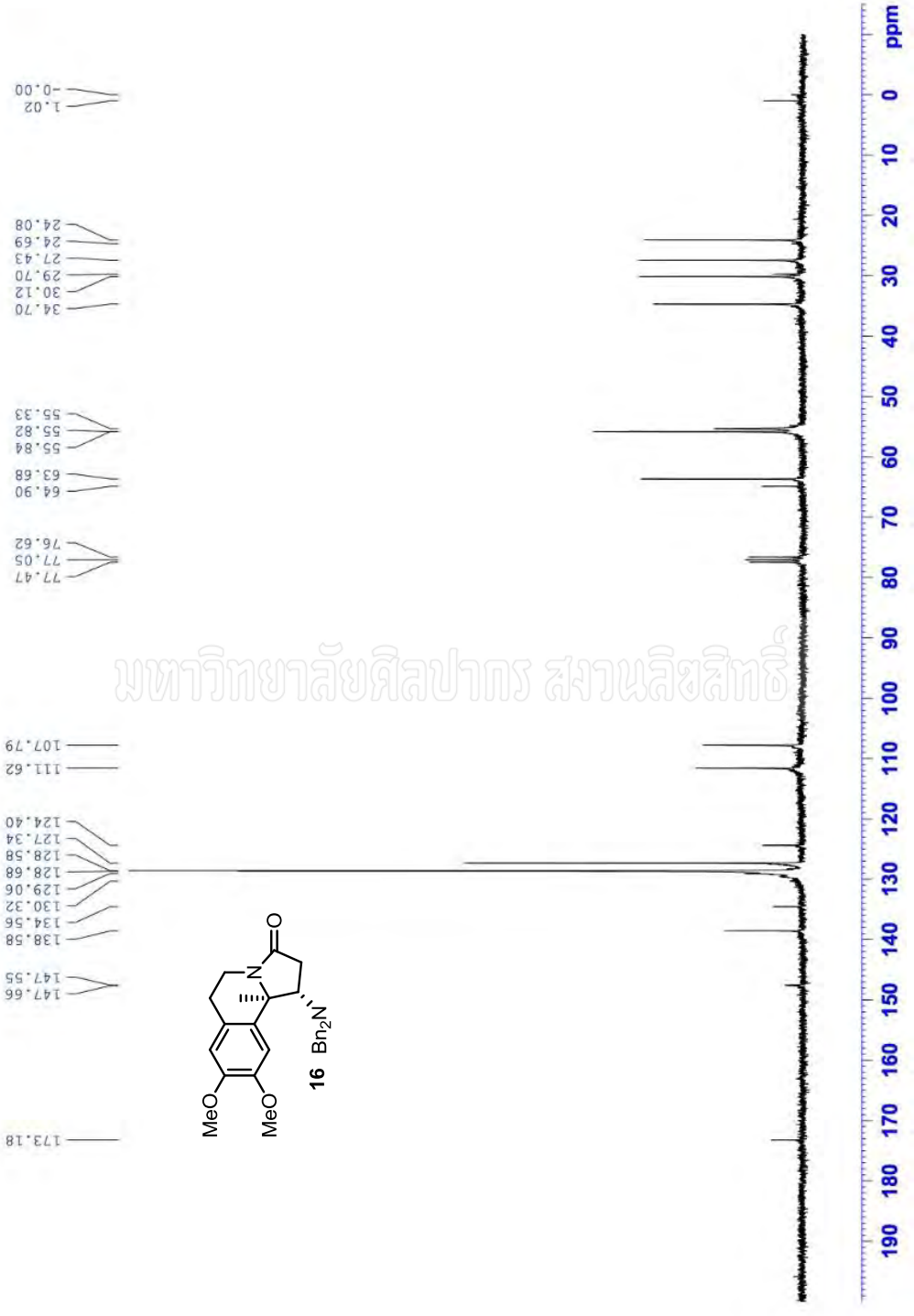
^{13}C NMR spectrum of Compound 15

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



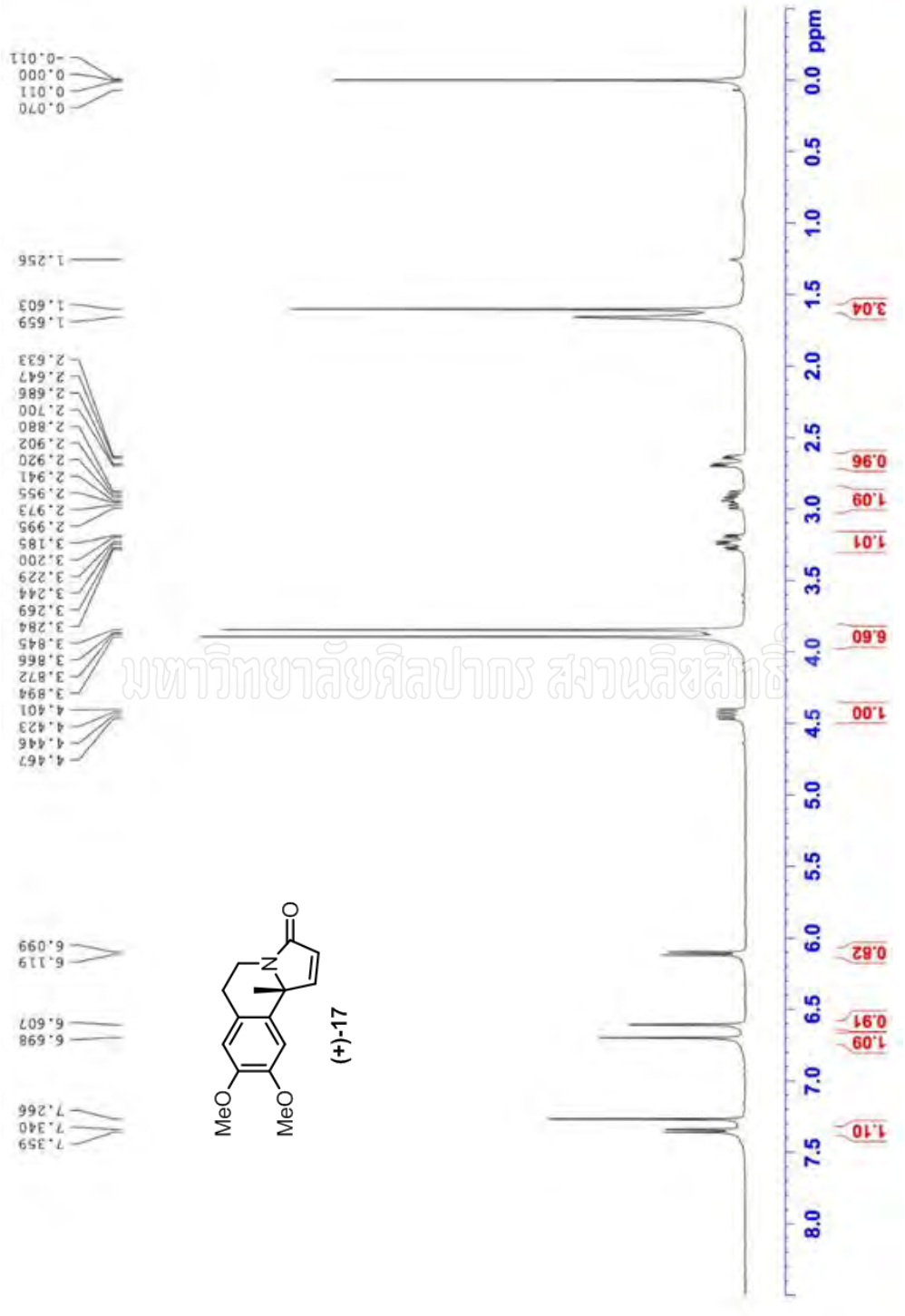
^{1}H NMR spectrum of Compound 16

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



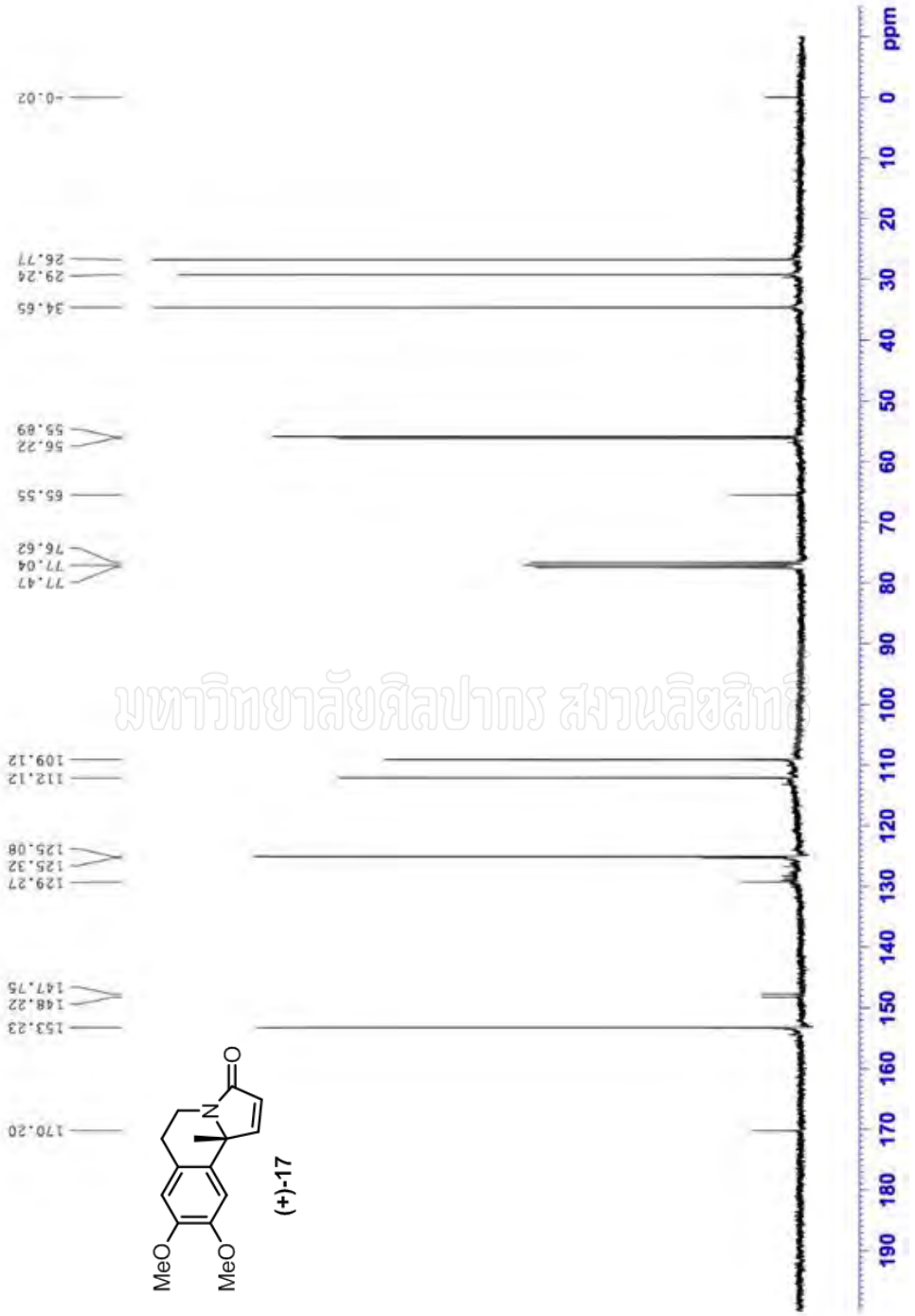
มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

^{13}C NMR spectrum of Compound 16



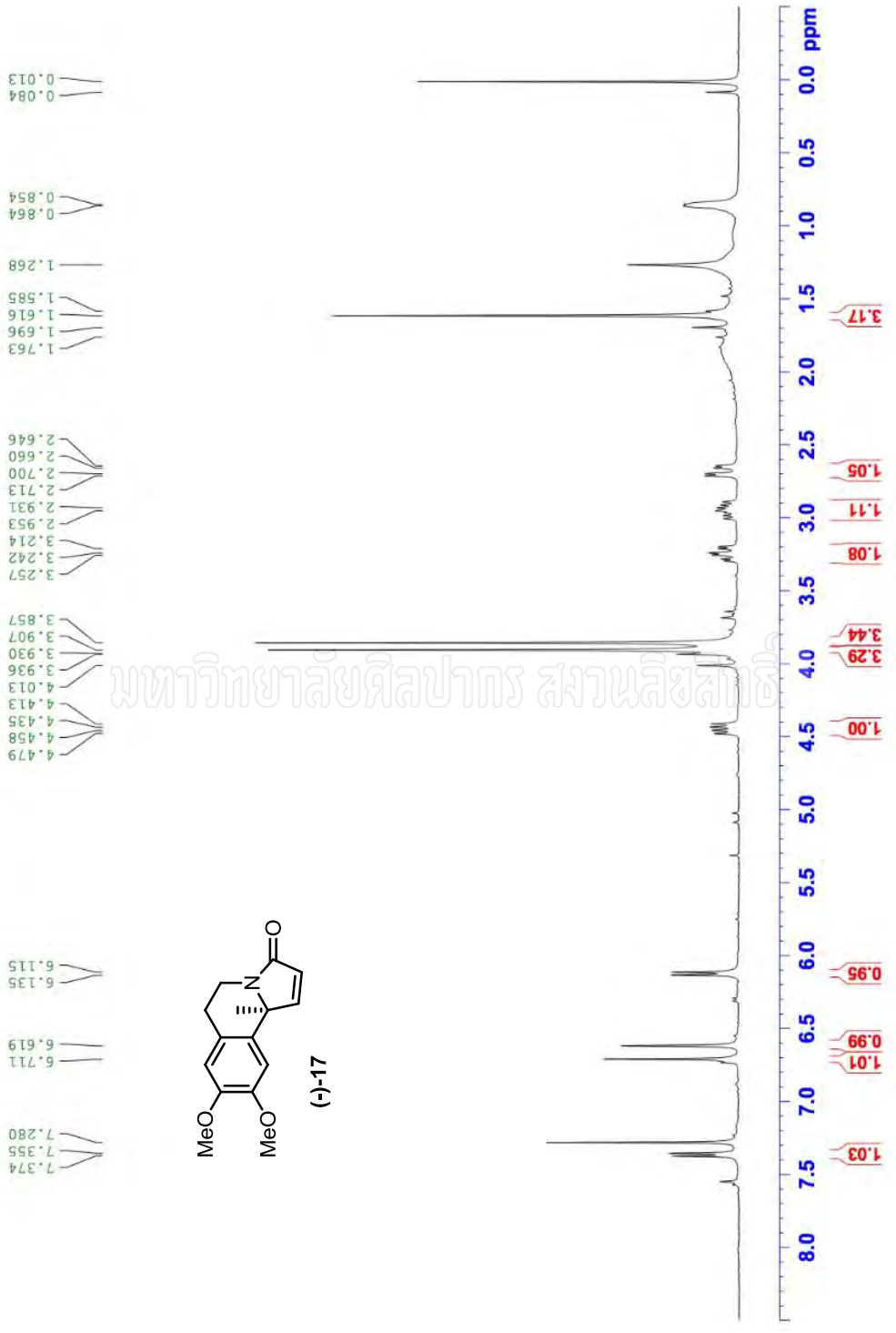
^{1}H NMR spectrum of Compound (+)-17

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



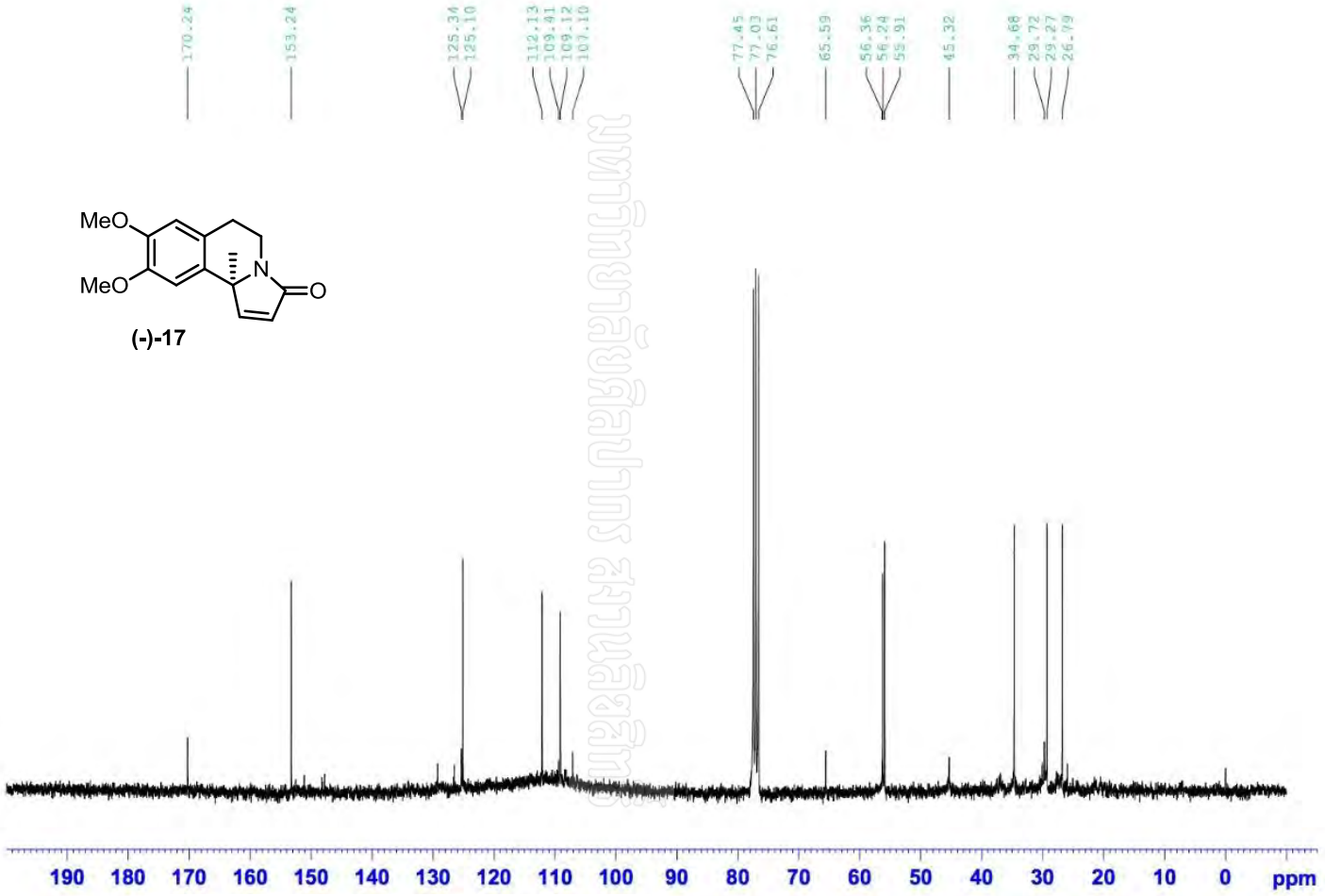
^{13}C NMR spectrum of Compound (+)-17

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

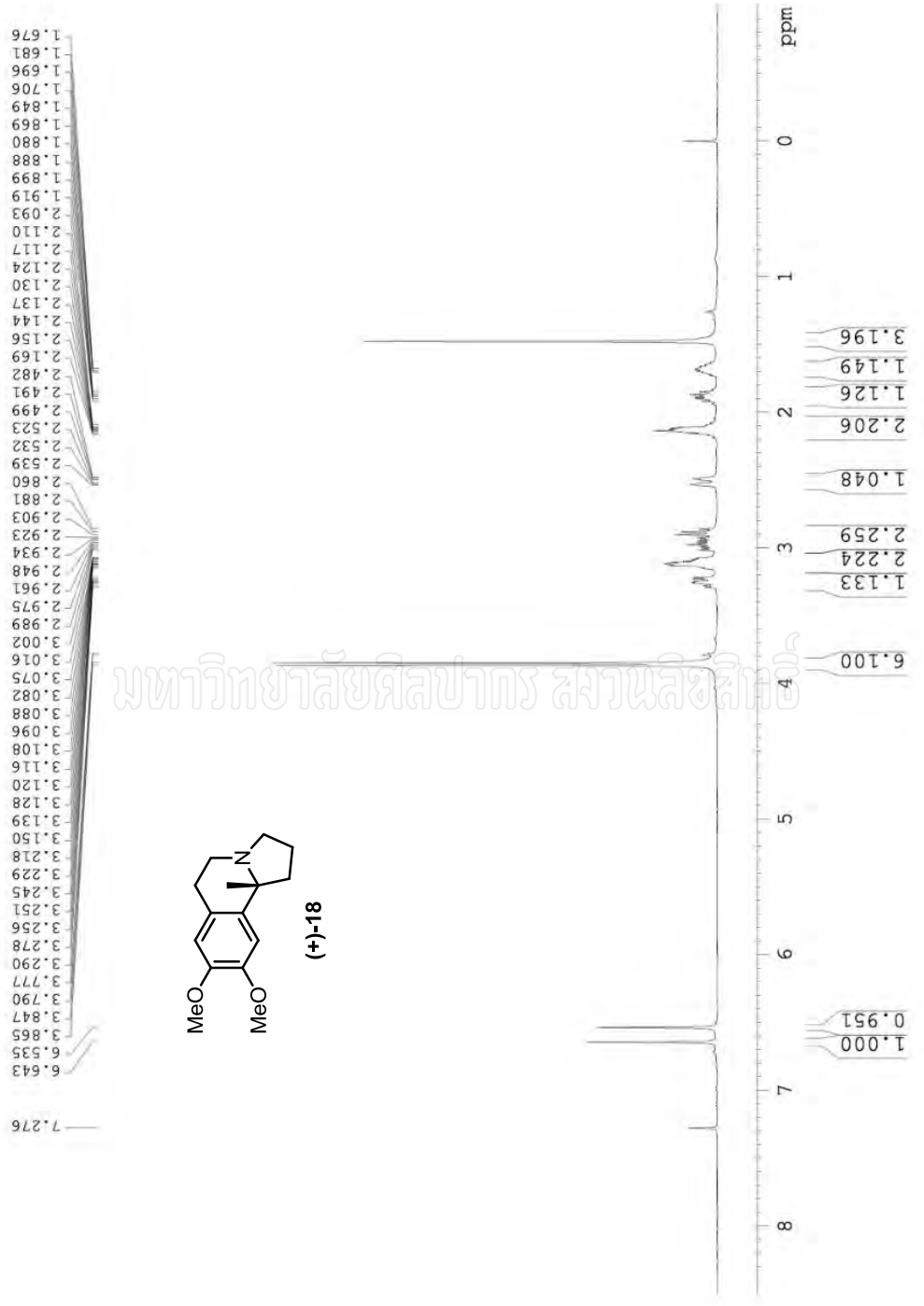


^{1}H NMR spectrum of Compound (-)-17

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

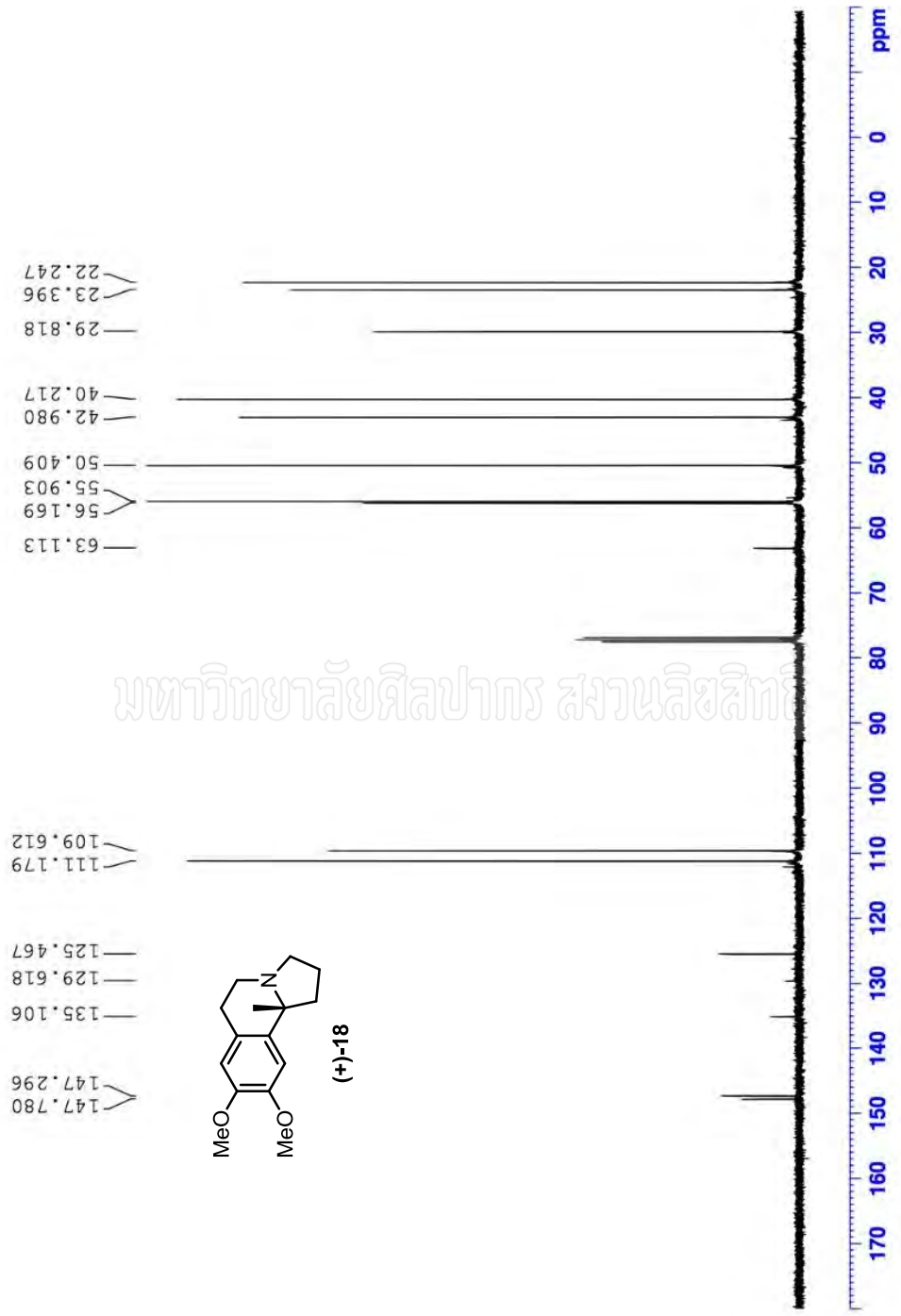


^{13}C NMR spectrum of Compound (-)-17



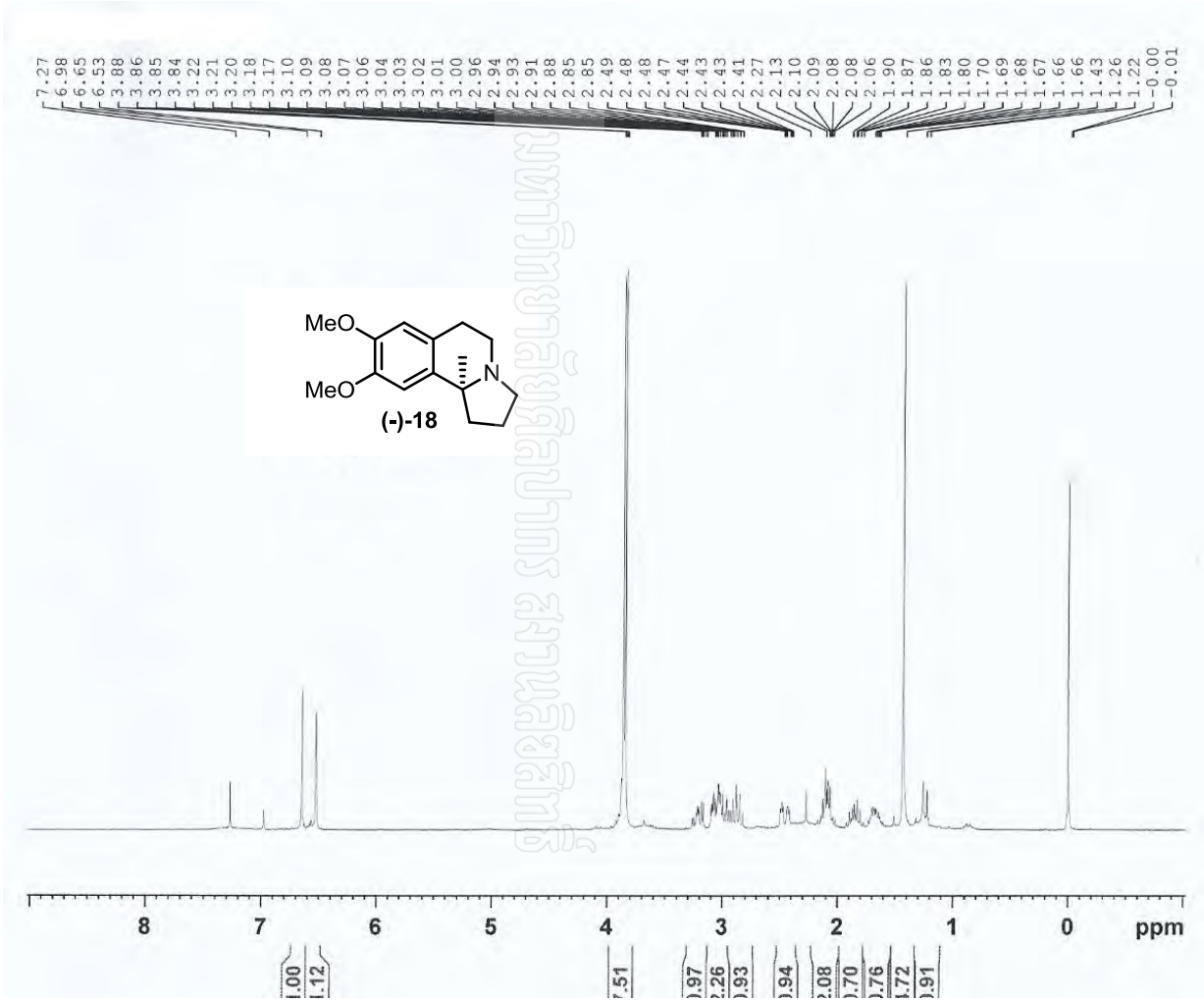
^{1}H NMR spectrum of Compound (+)-18

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

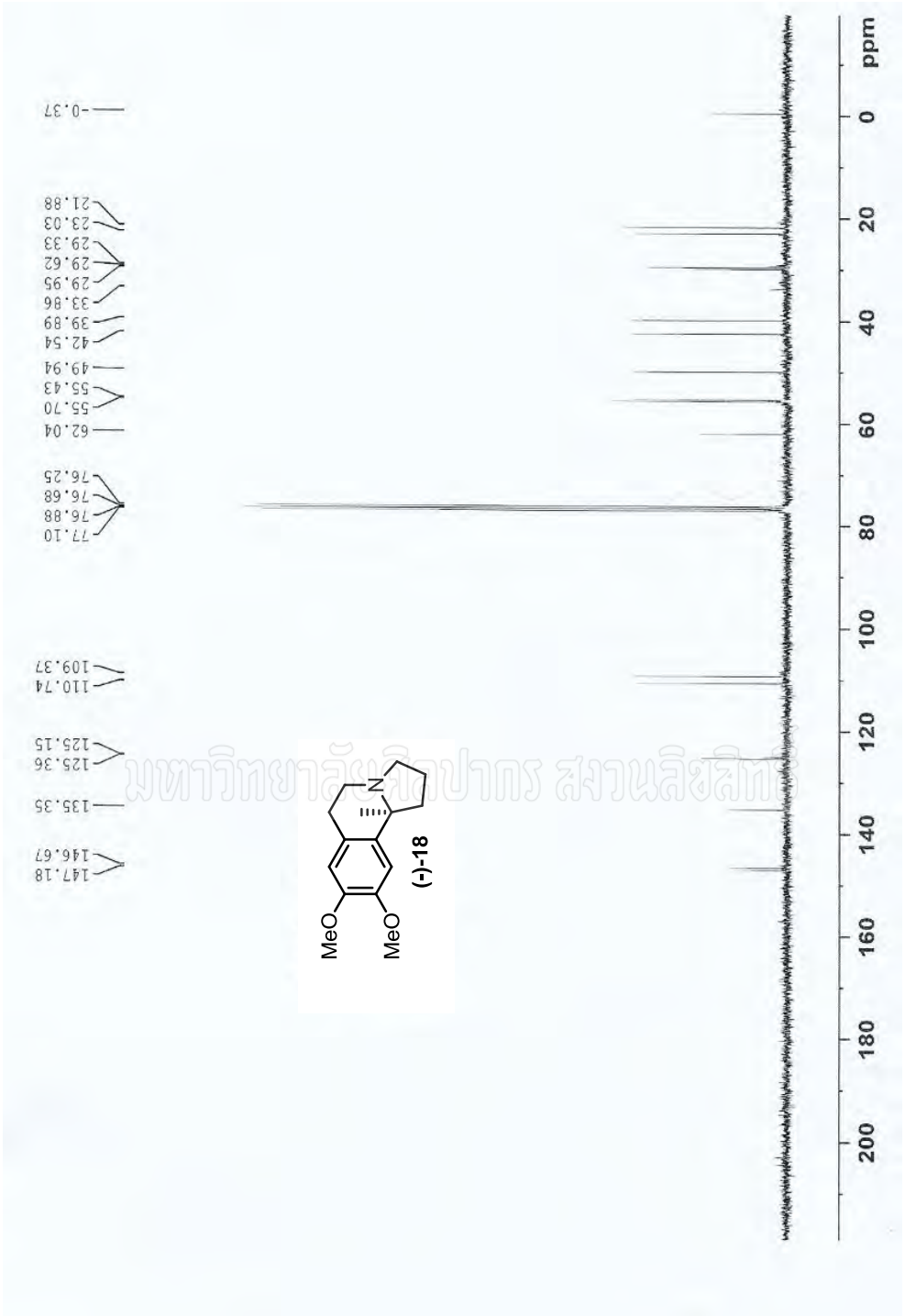


^{13}C NMR spectrum of Compound (+)-18

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

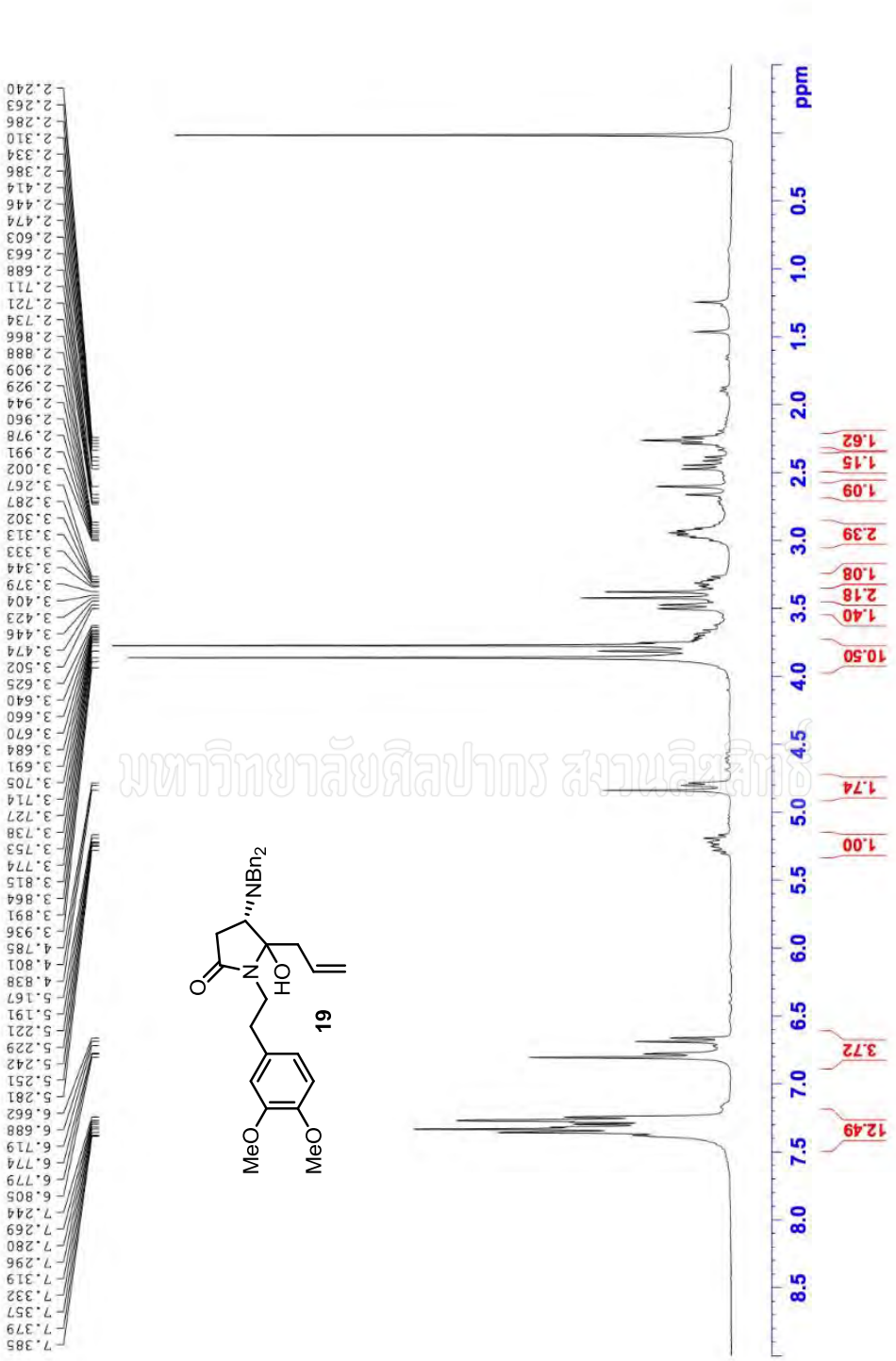


^{1}H NMR spectrum of Compound (-)-18



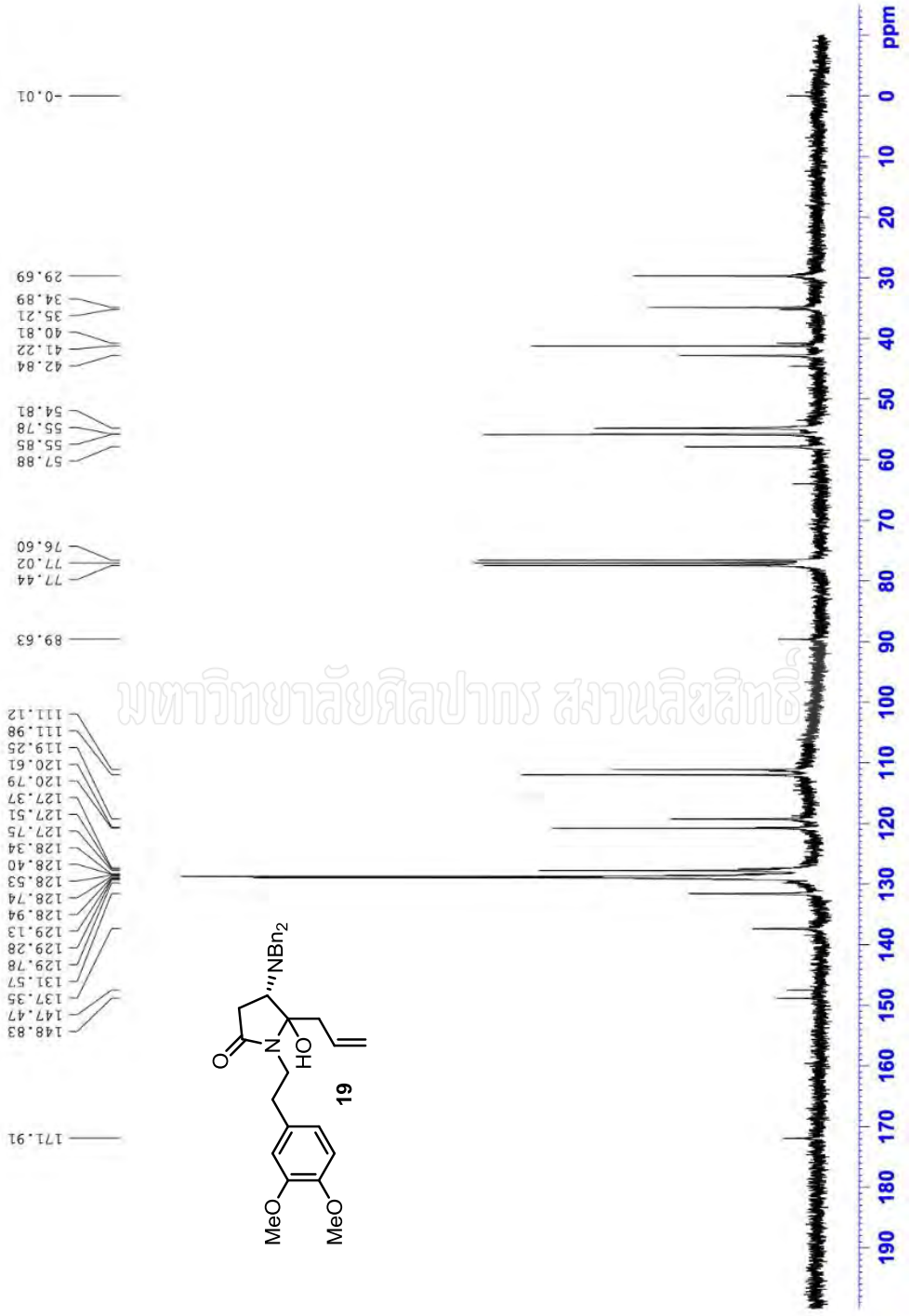
^{13}C NMR spectrum of Compound (-)-18

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



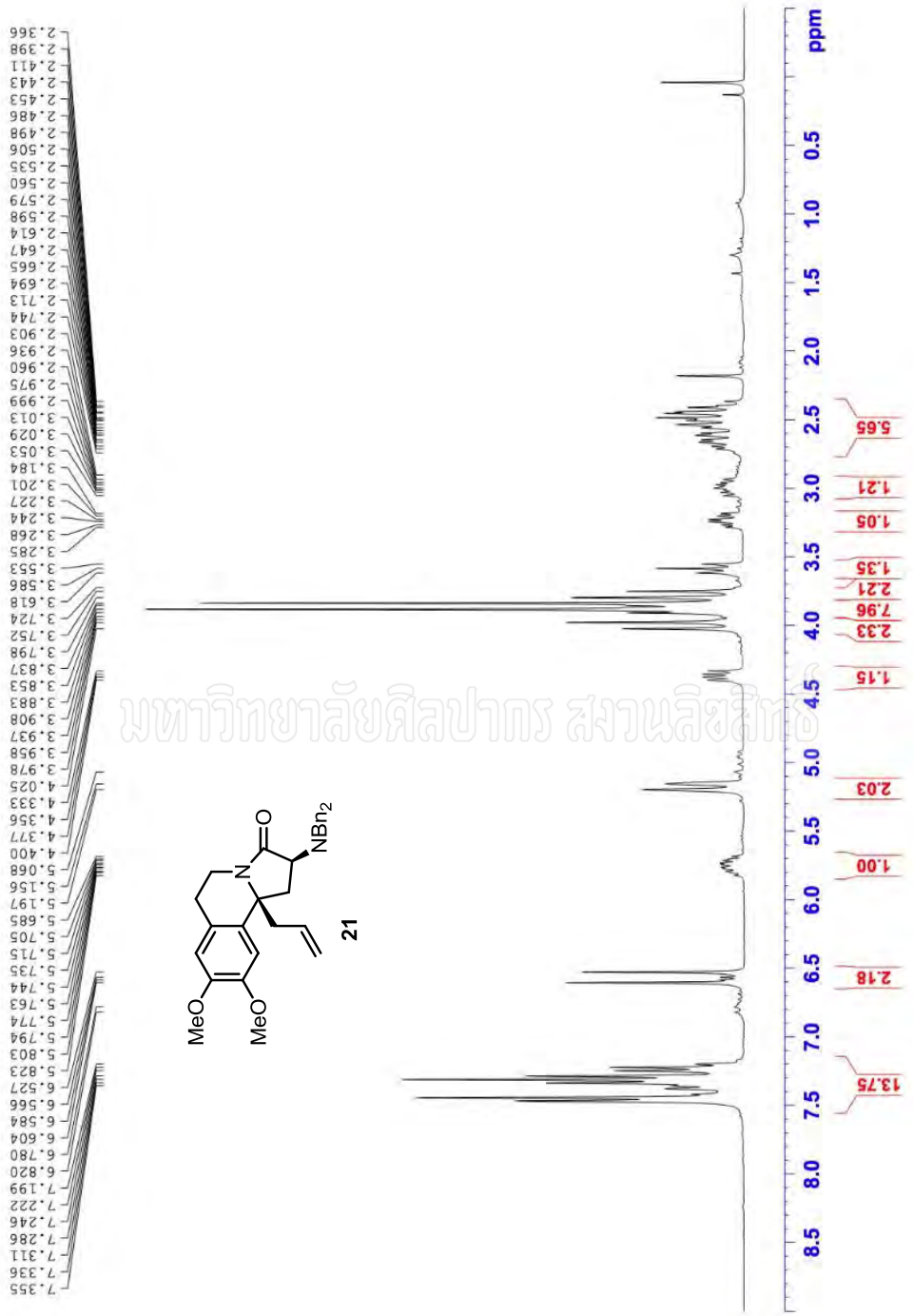
^{1}H NMR spectrum of Compound 19

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



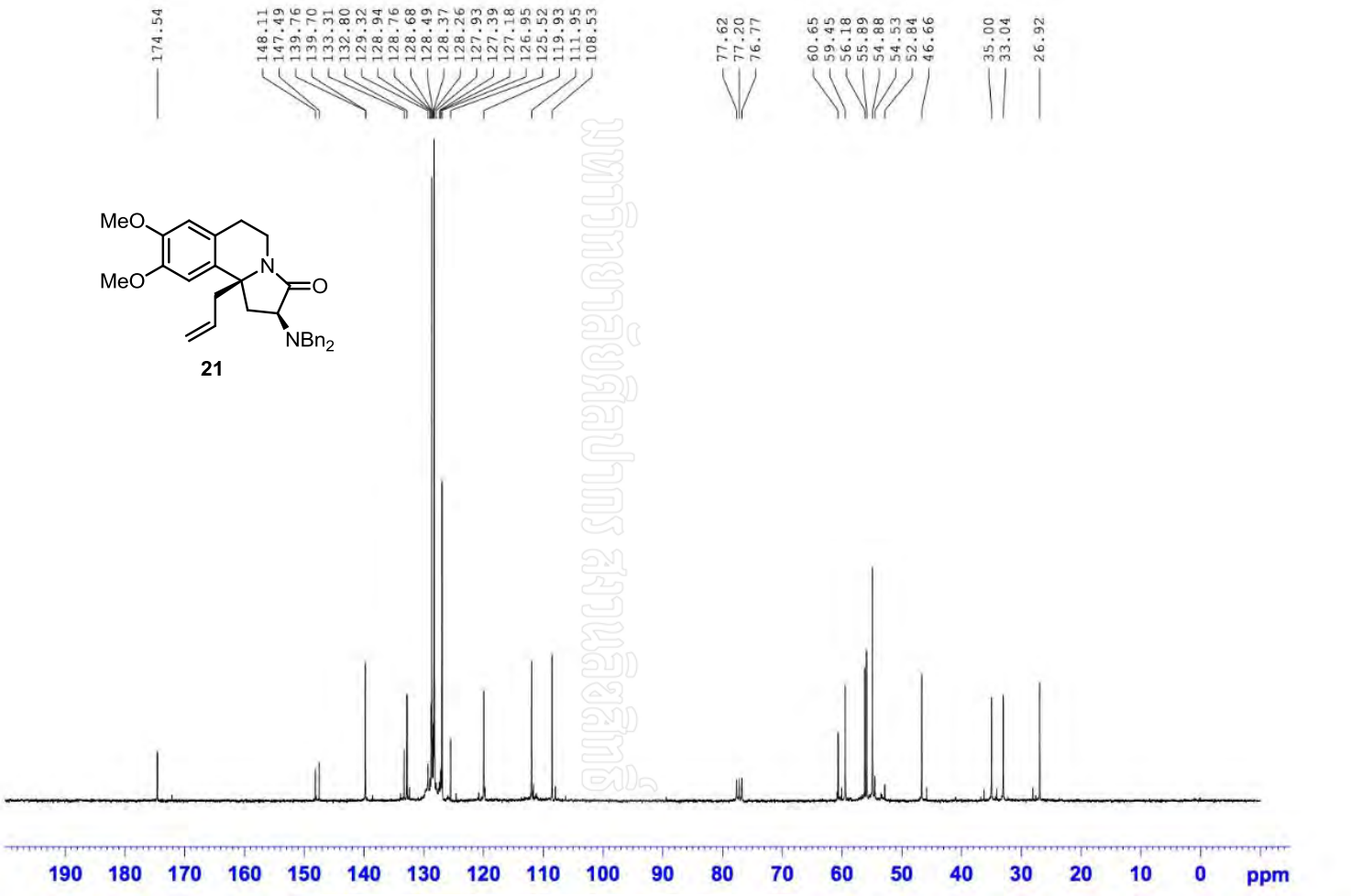
^{13}C NMR spectrum of Compound 19

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

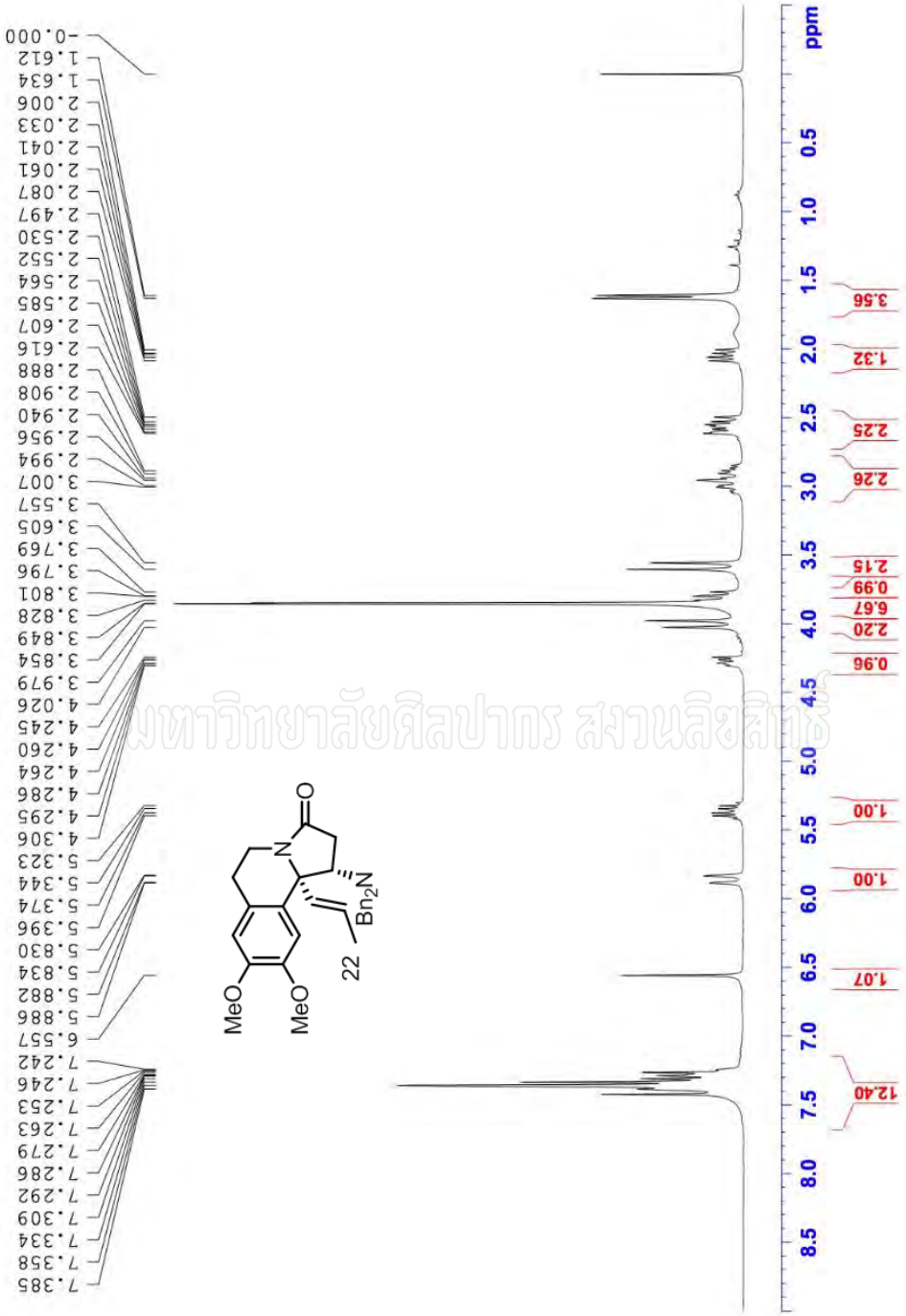


^{1}H NMR spectrum of Compound 21

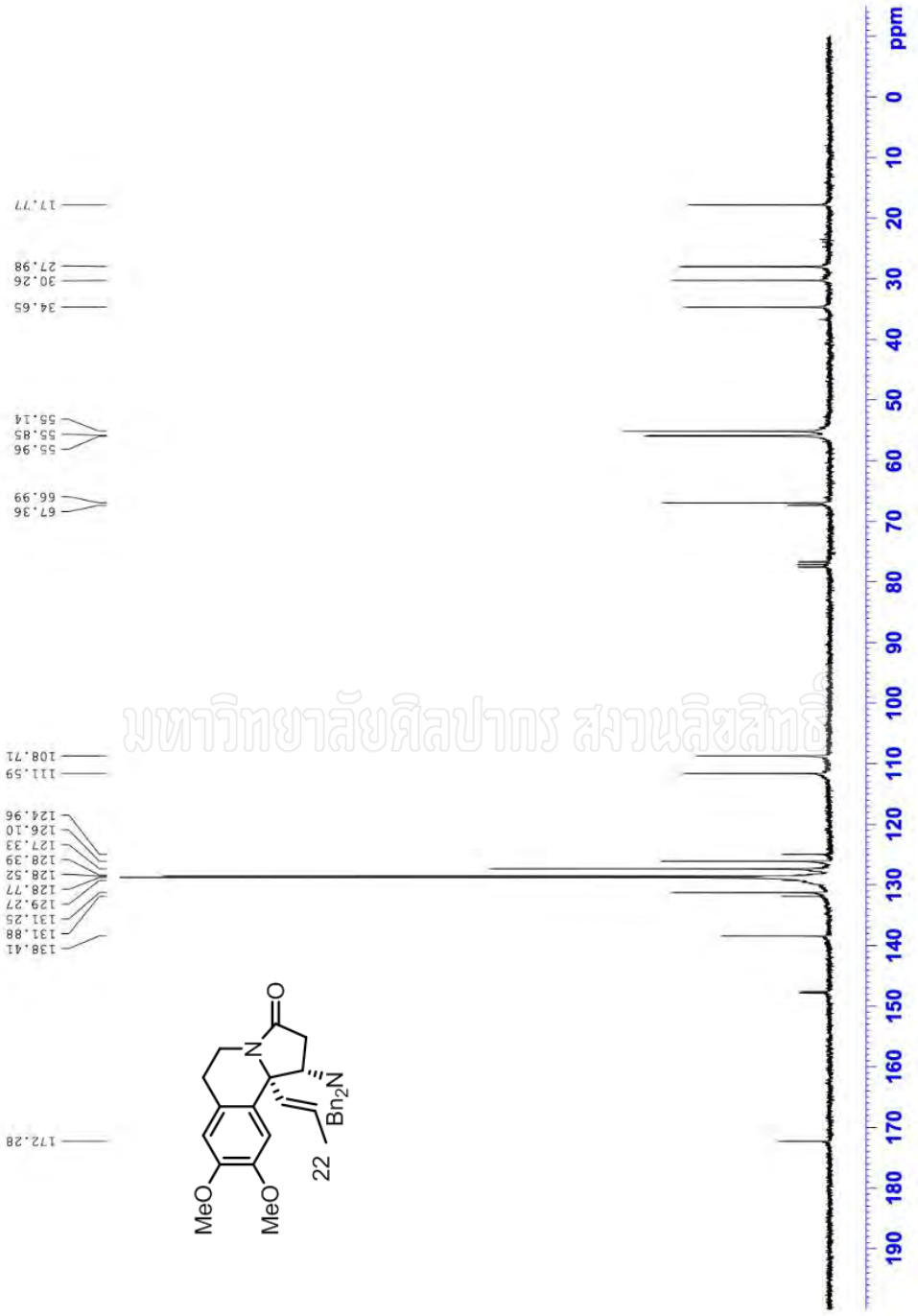
มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



^{13}C NMR spectrum of Compound 21

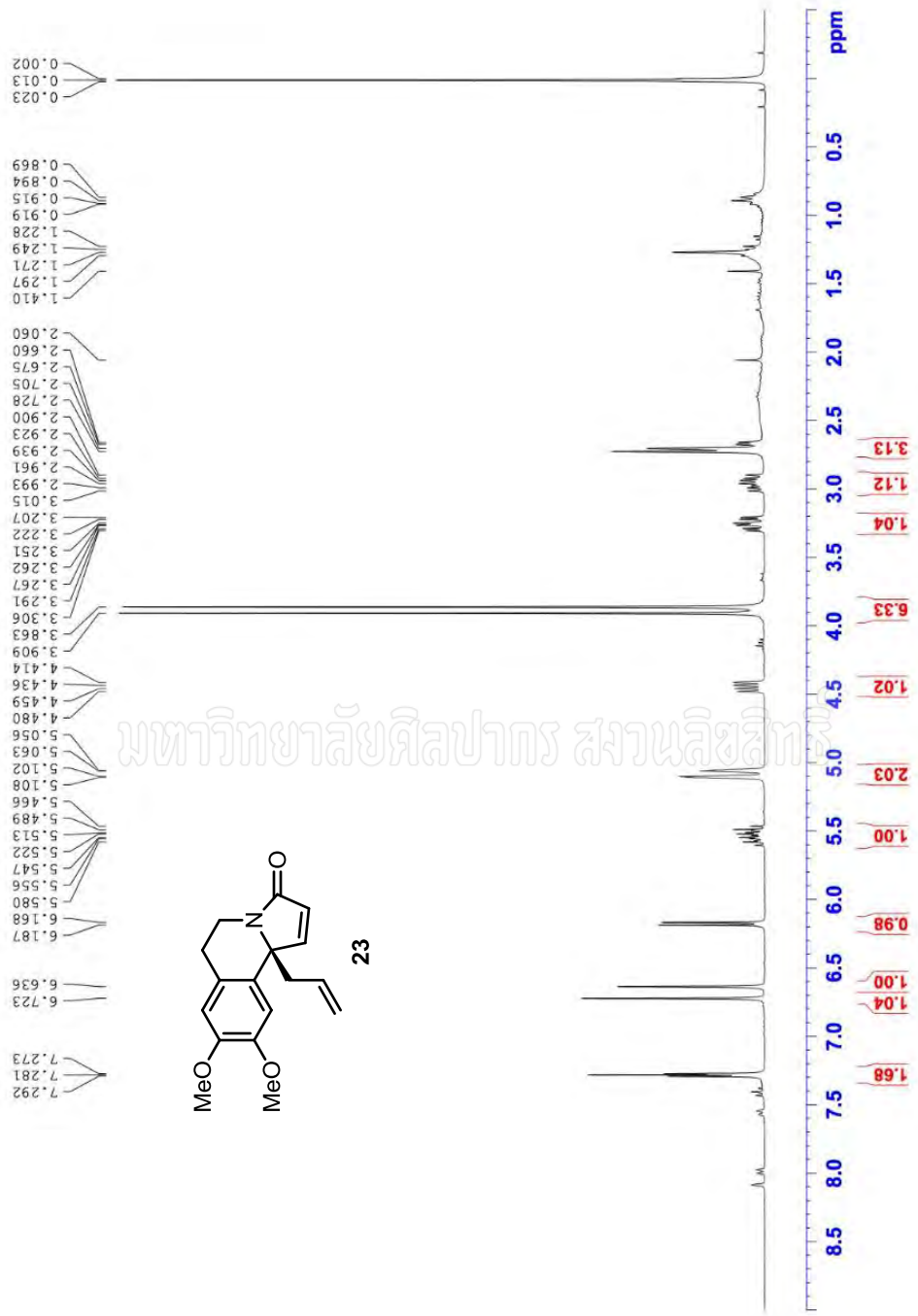


^{1}H NMR spectrum of Compound 22



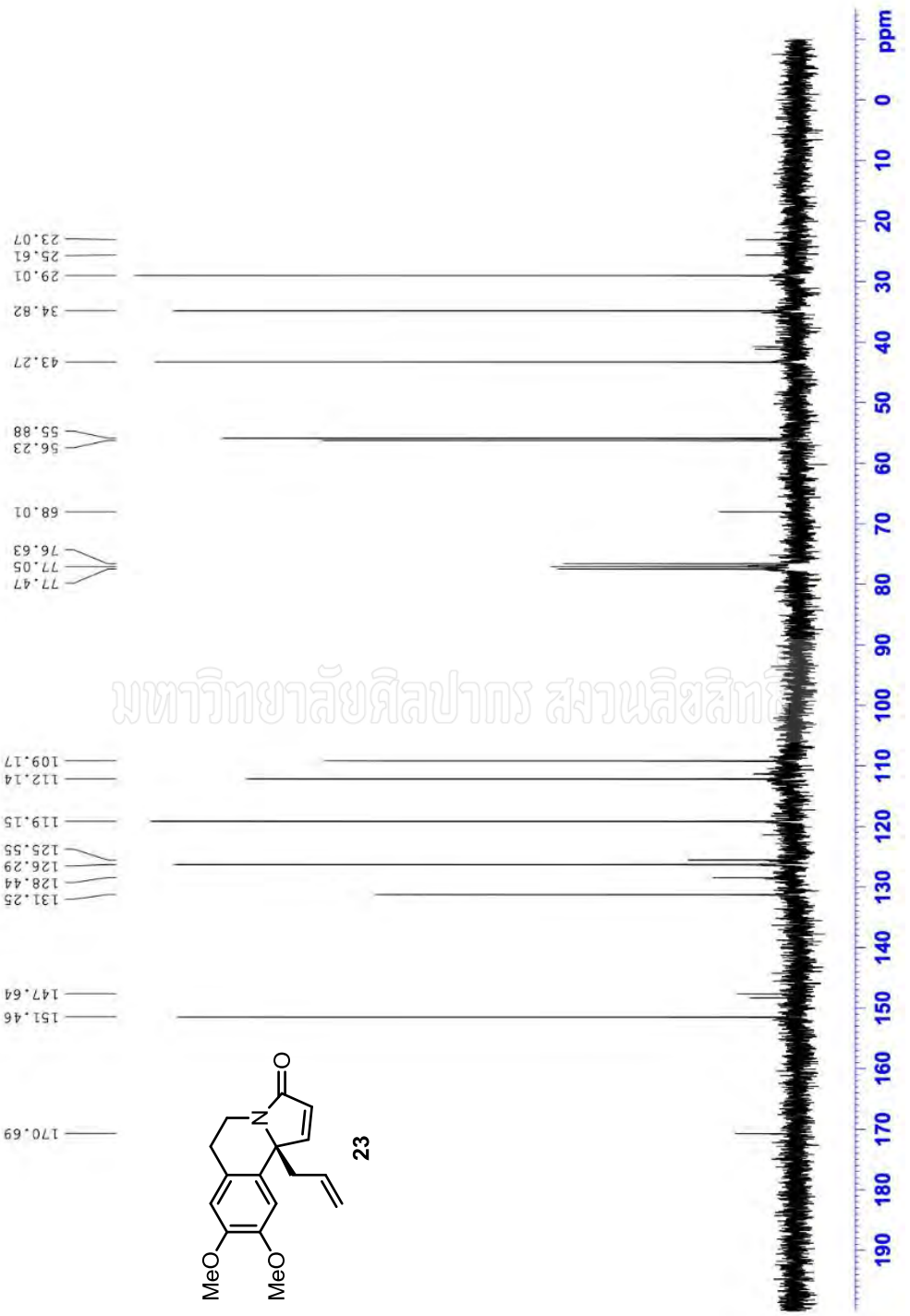
^{13}C NMR spectrum of Compound 22

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



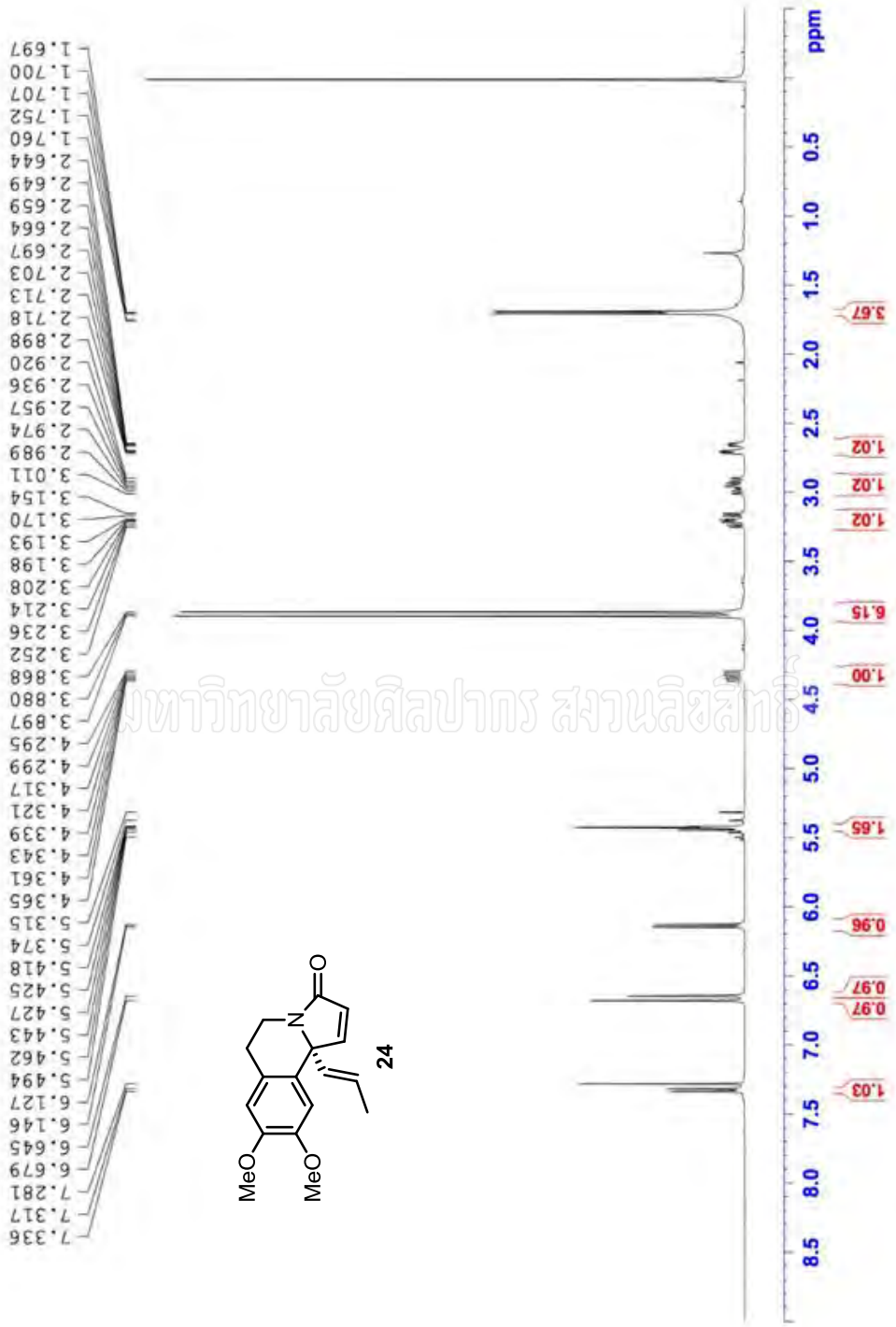
^{1}H NMR spectrum of Compound 23

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



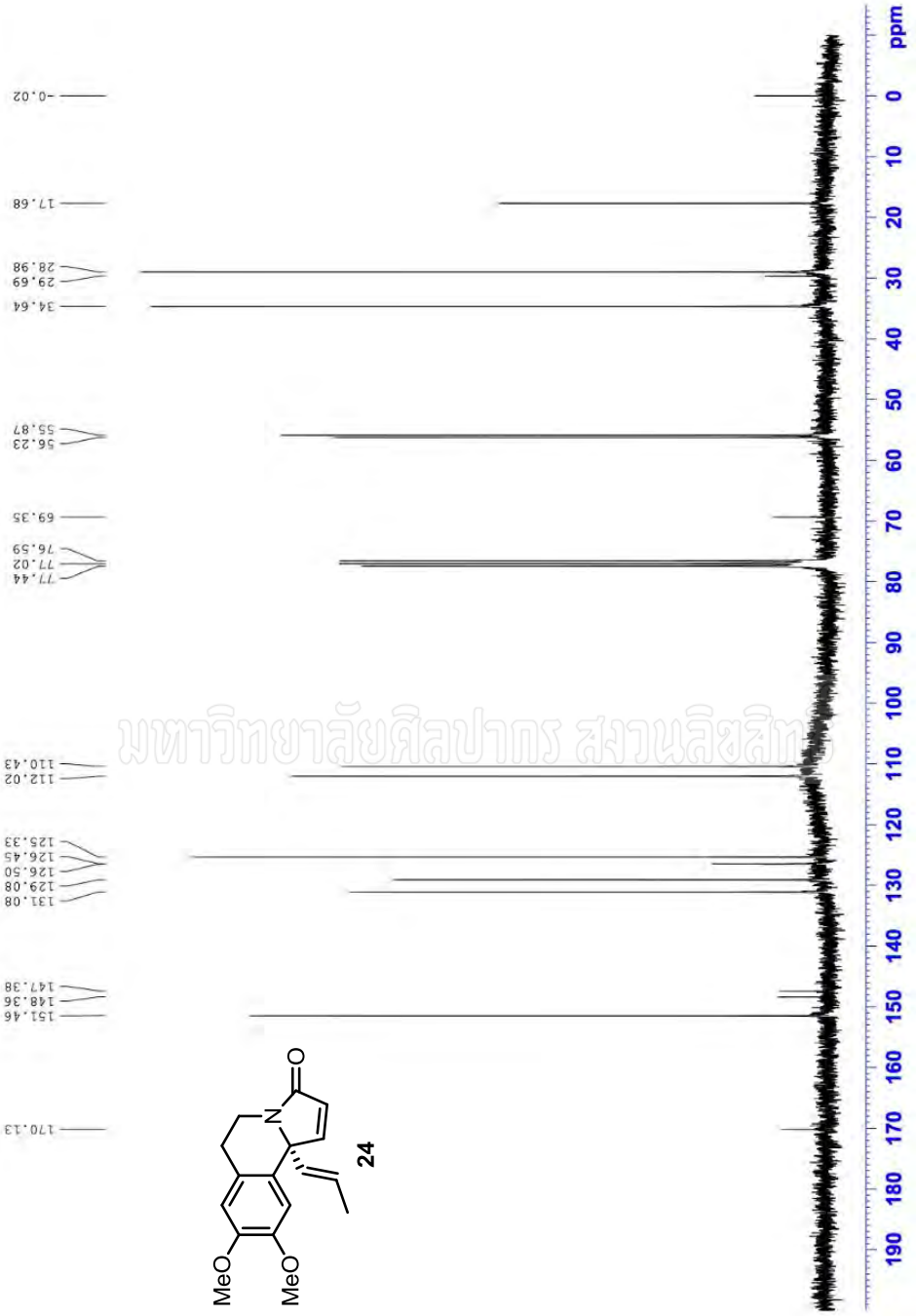
^{13}C NMR spectrum of Compound 23

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



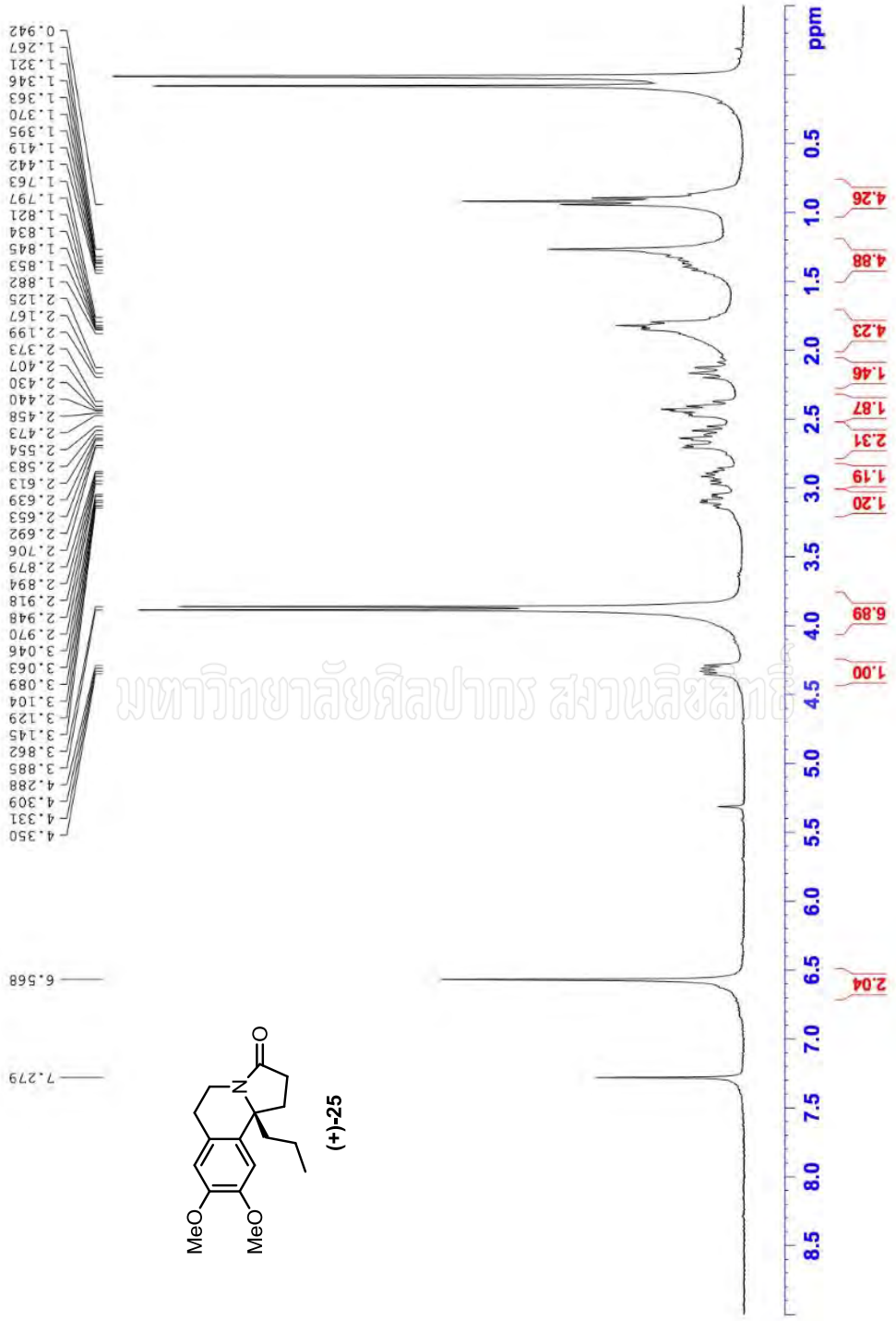
^{1}H NMR spectrum of Compound 24

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



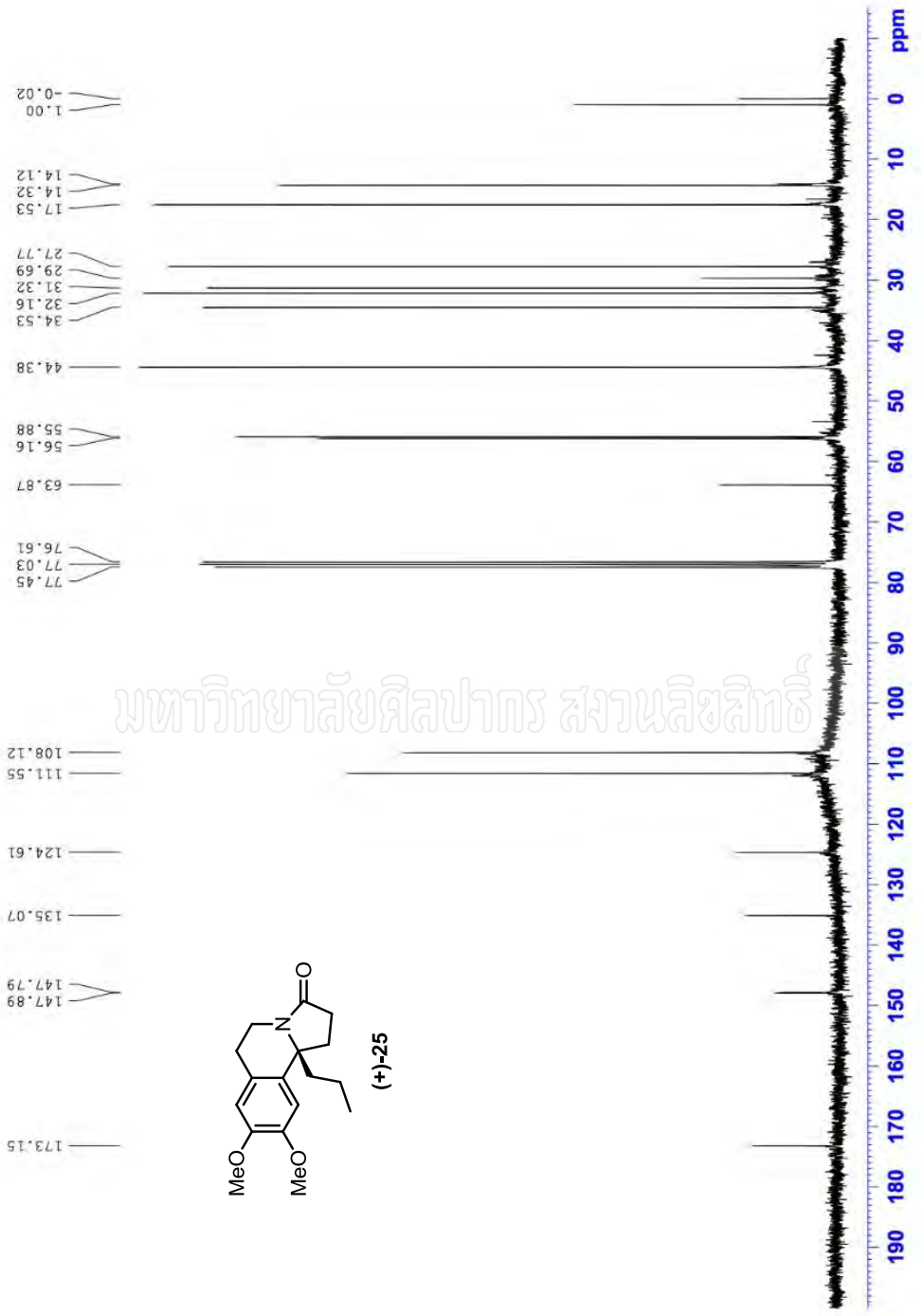
^{13}C NMR spectrum of Compound 24

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



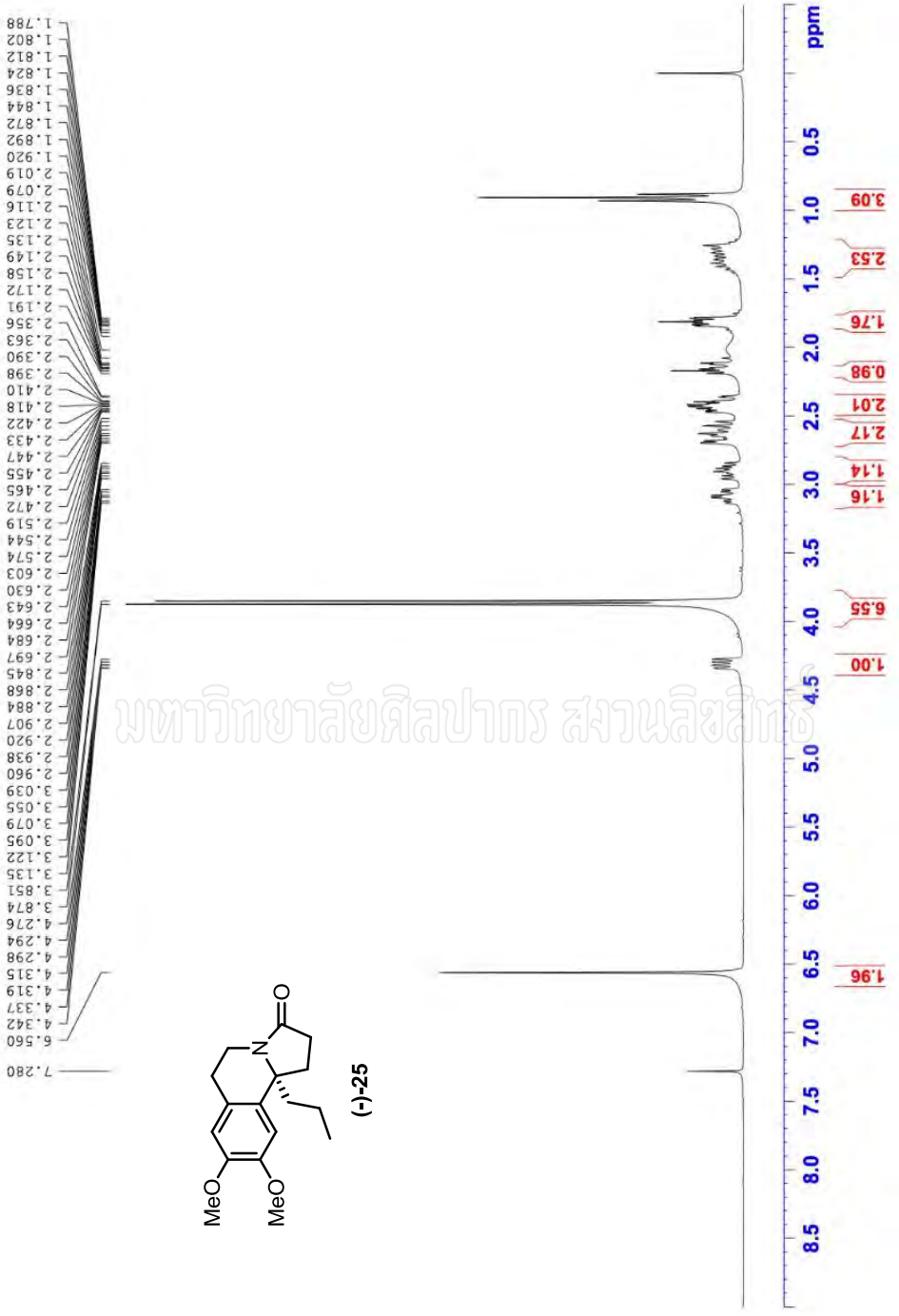
^{1}H NMR spectrum of Compound (+)-25

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



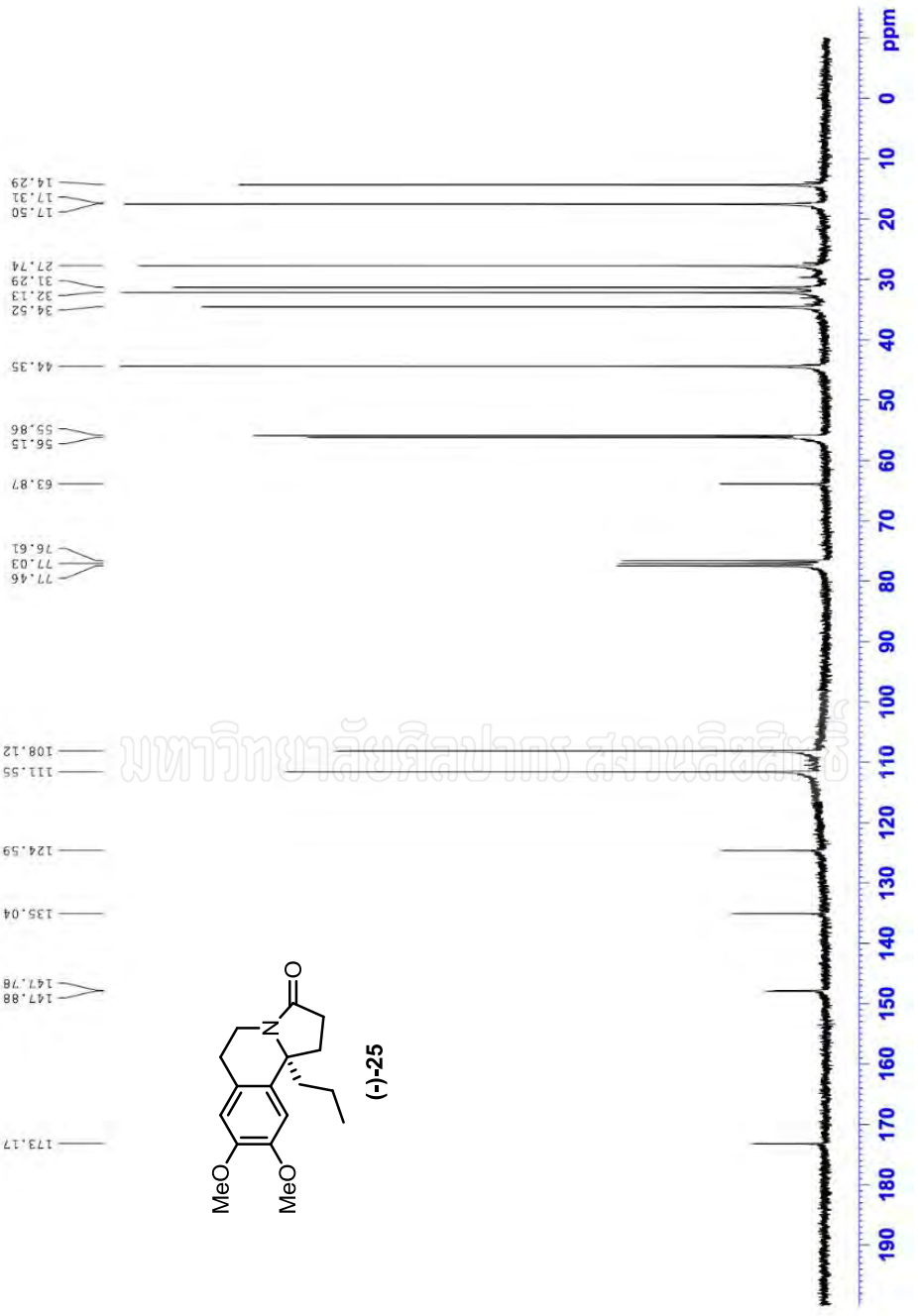
^{13}C NMR spectrum of Compound (+)-25

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



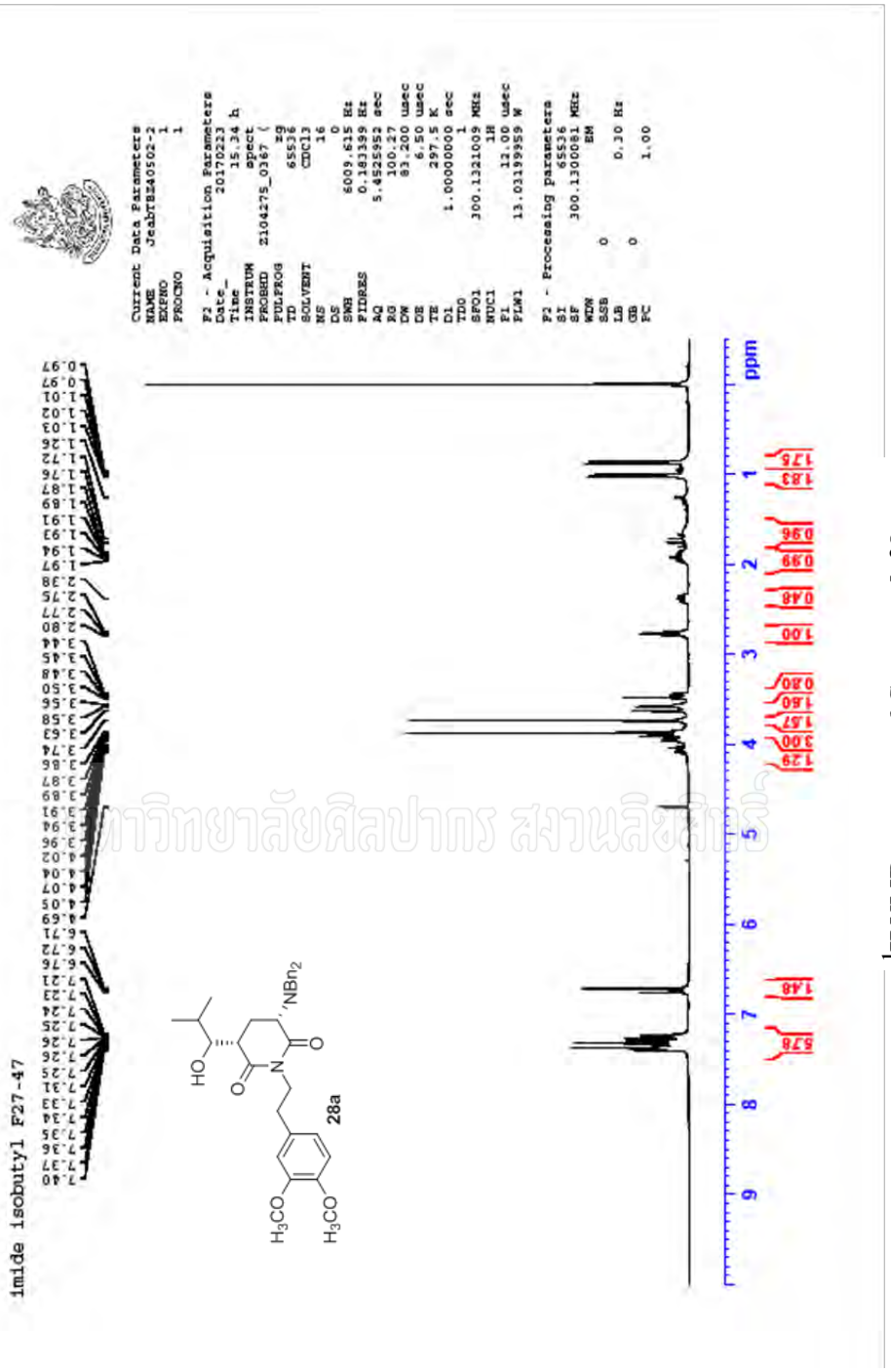
^{1}H NMR spectrum of Compound (-)-25

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



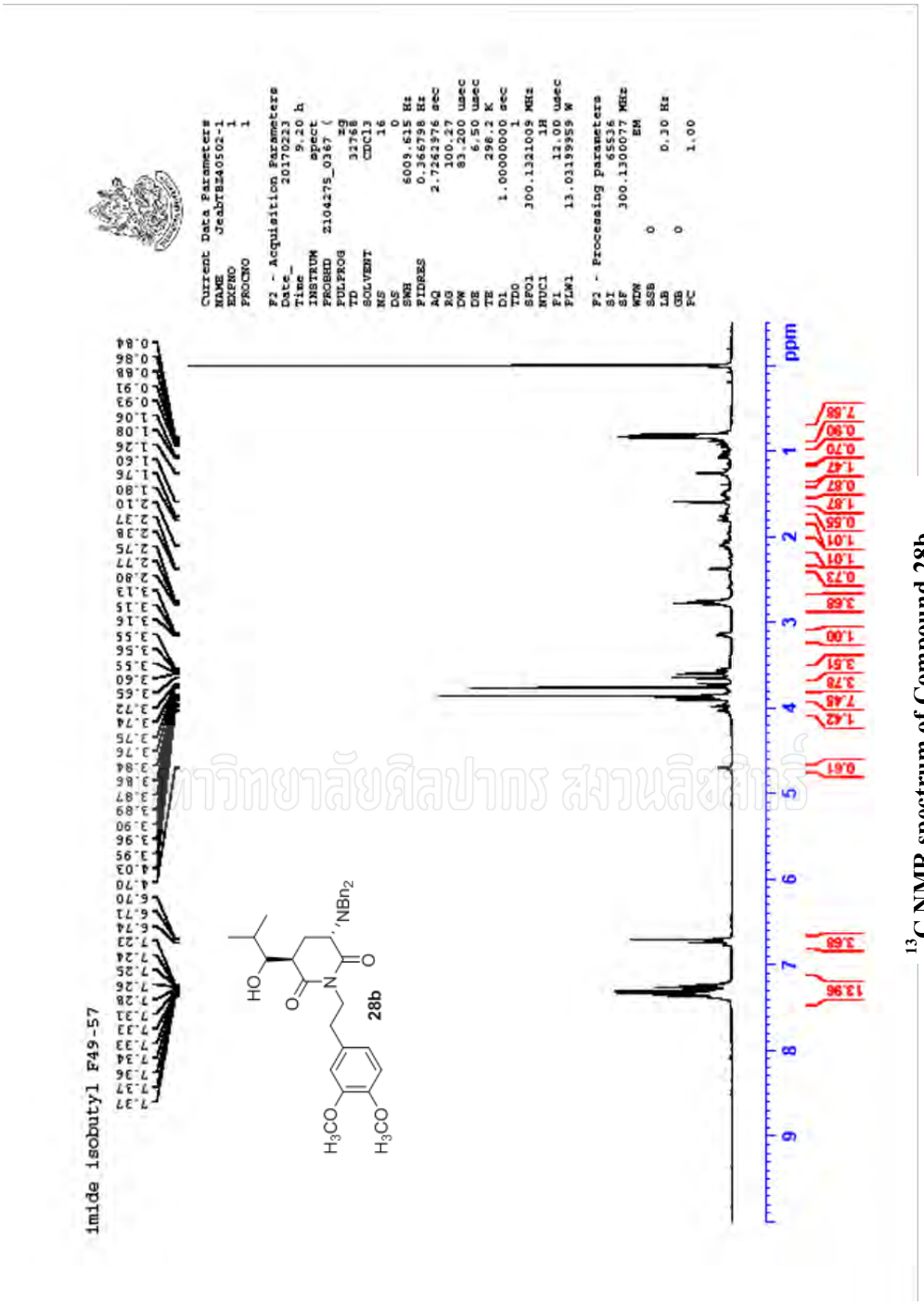
^{13}C NMR spectrum of Compound (-)-25

มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์

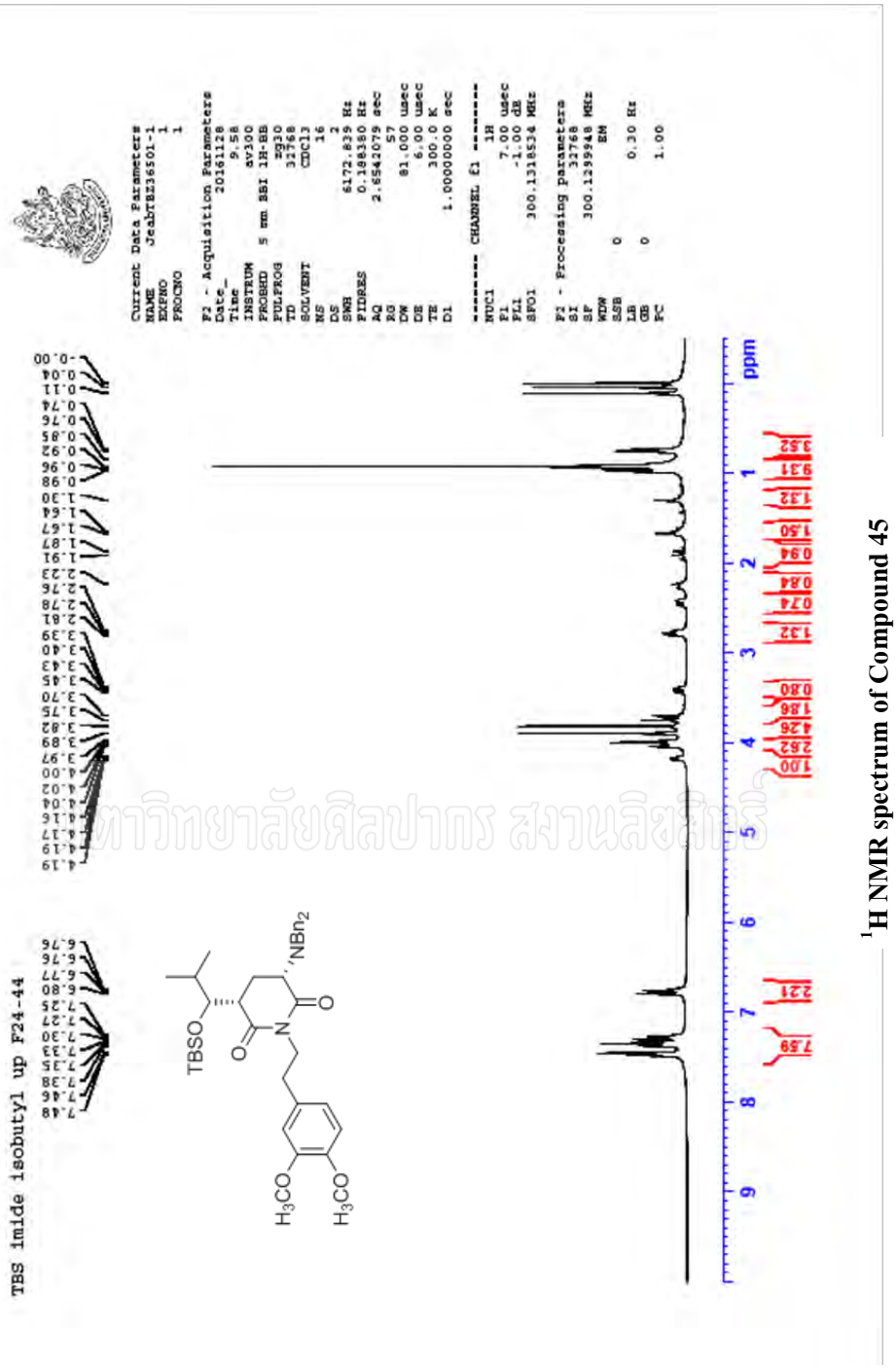


^{1}H NMR spectrum of Compound 28a

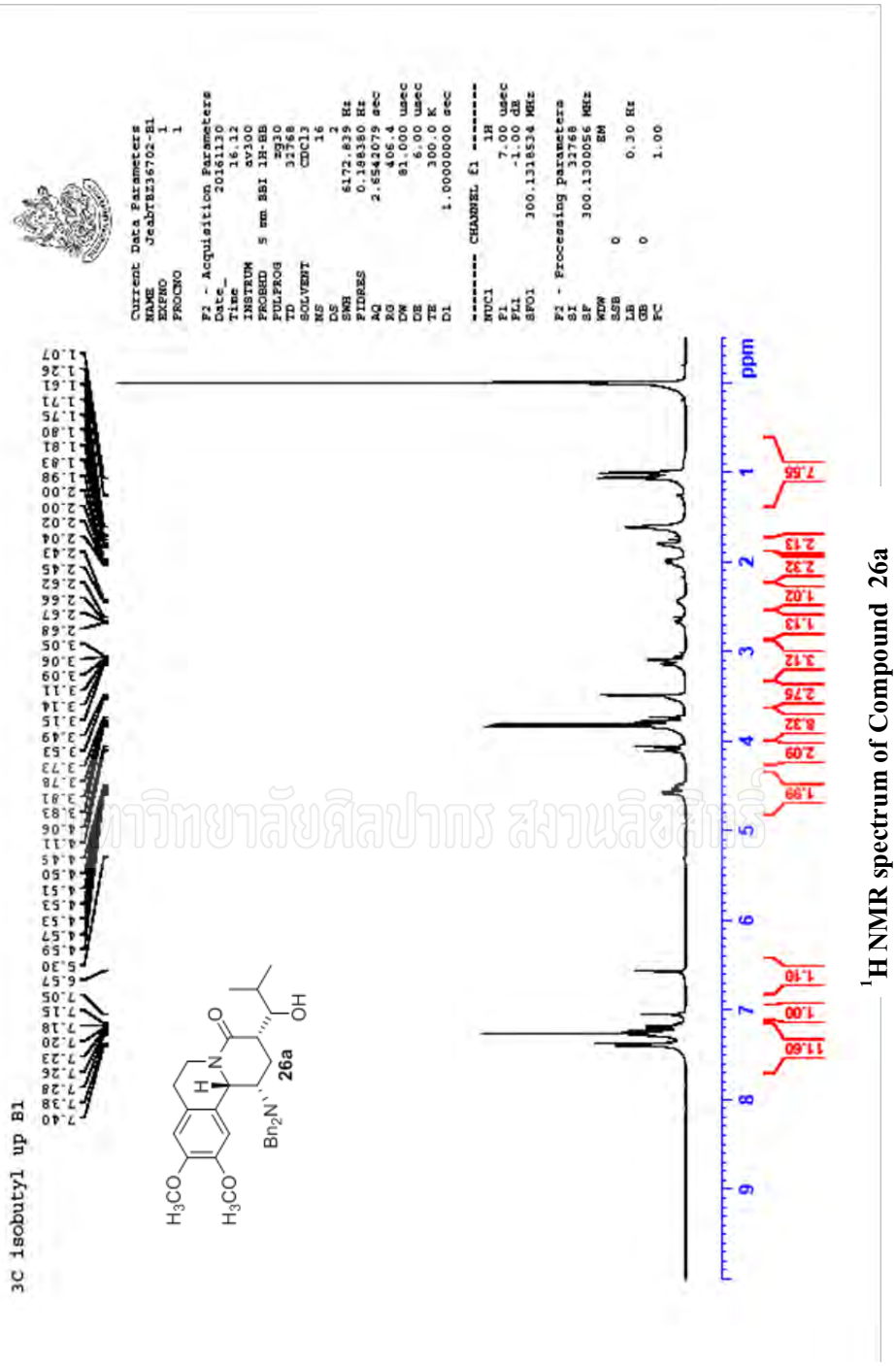
มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



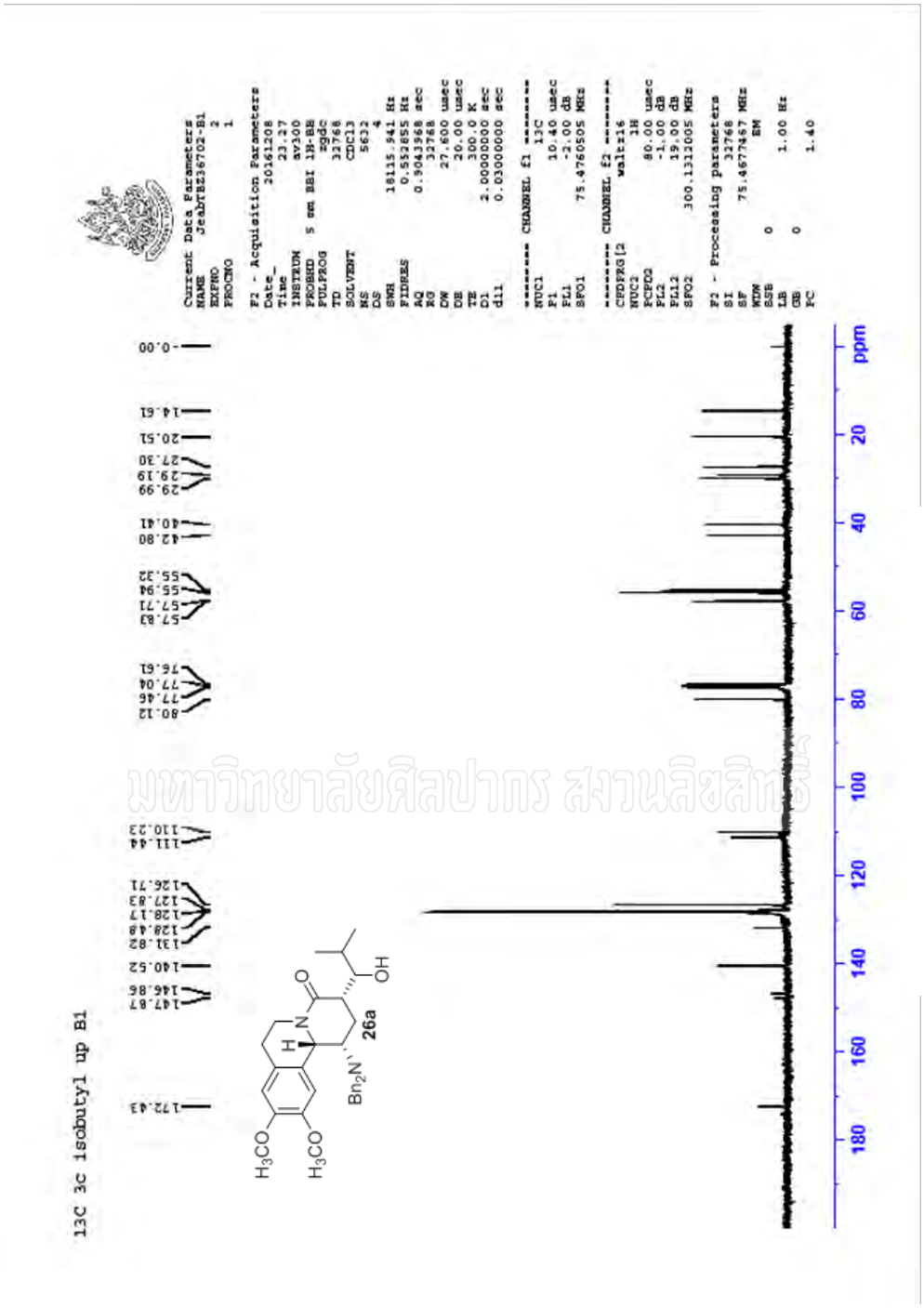
^{13}C NMR spectrum of Compound 28b



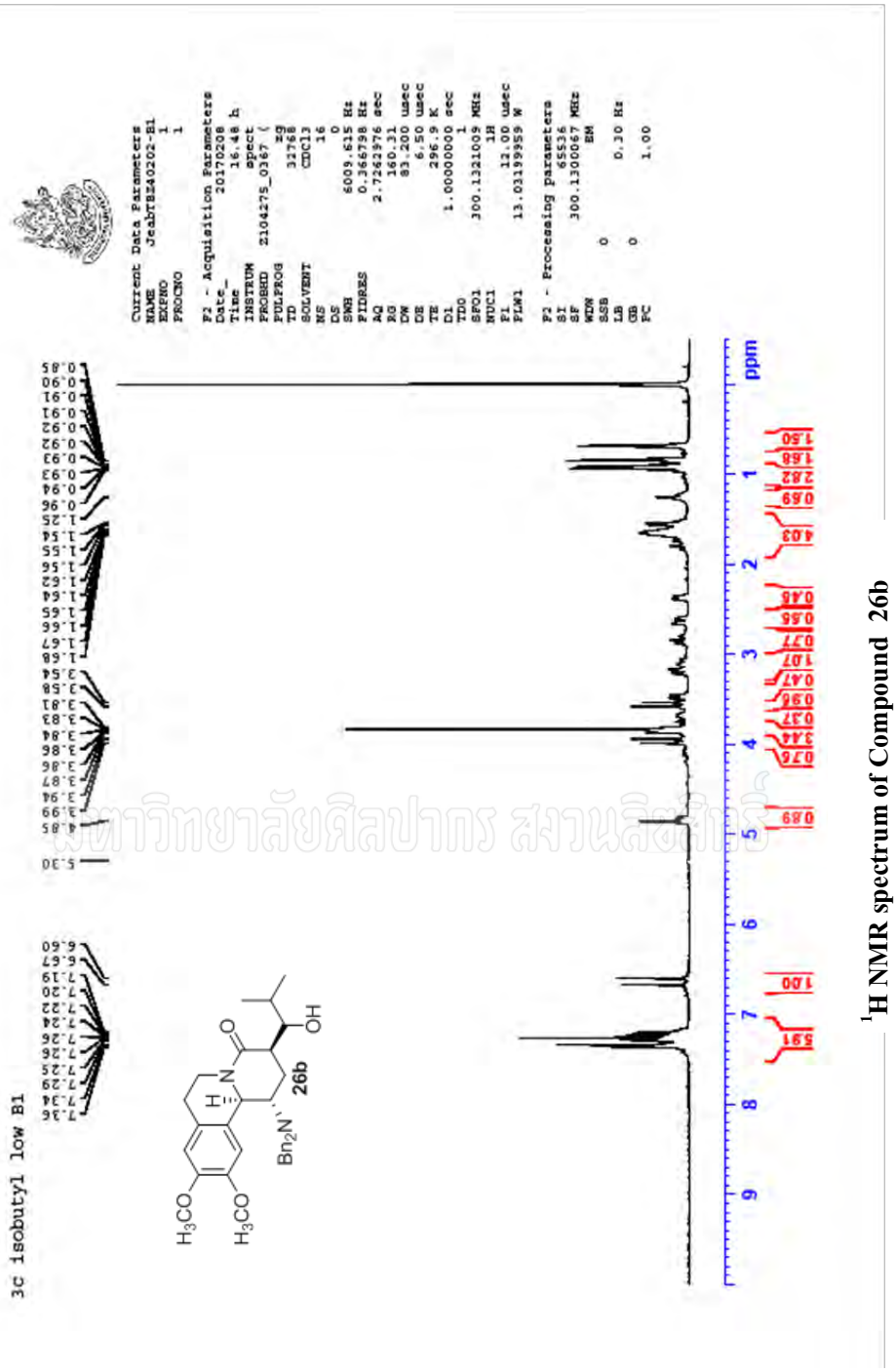
^{1}H NMR spectrum of Compound 45



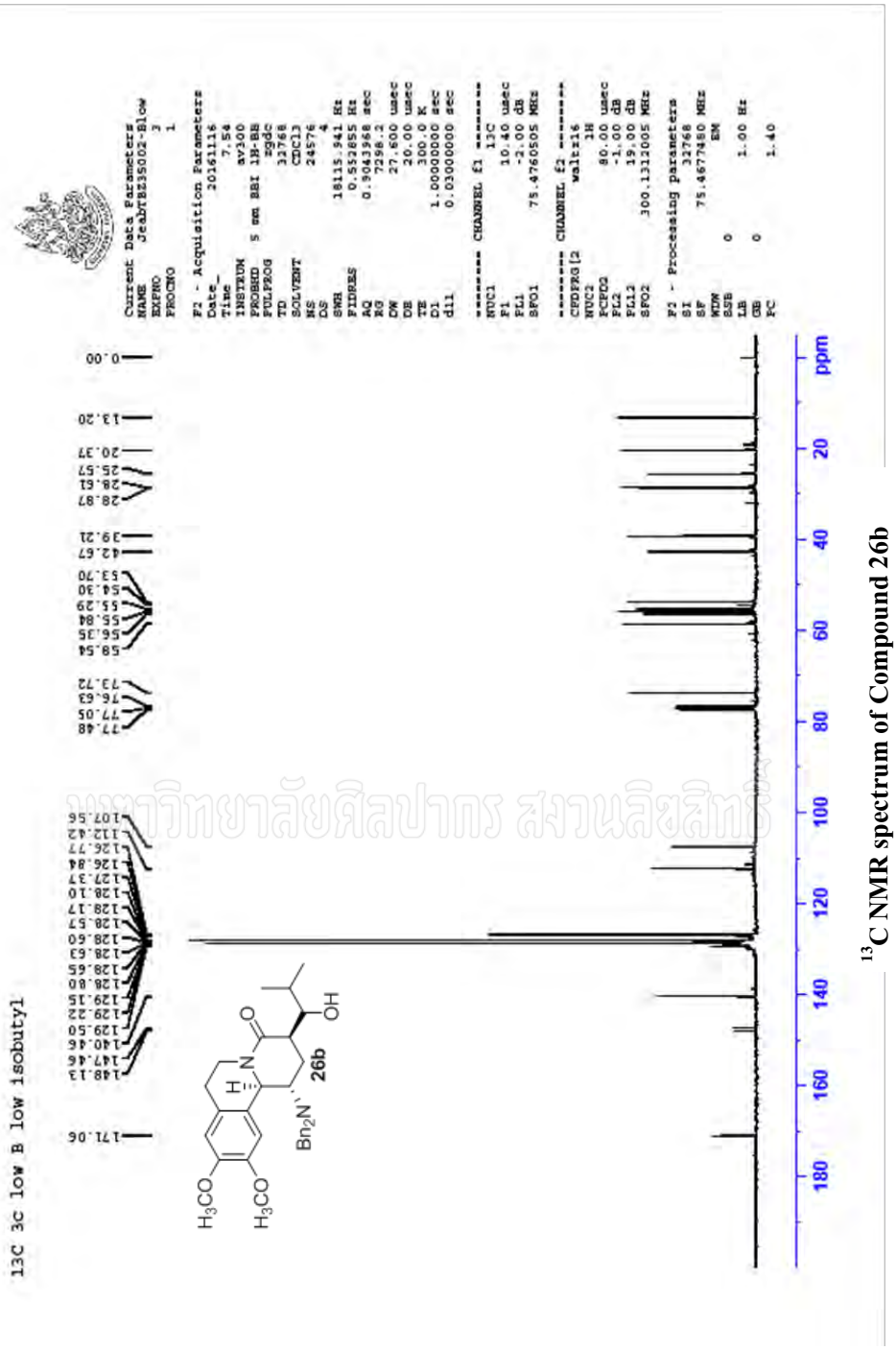
^{1}H NMR spectrum of Compound 26a



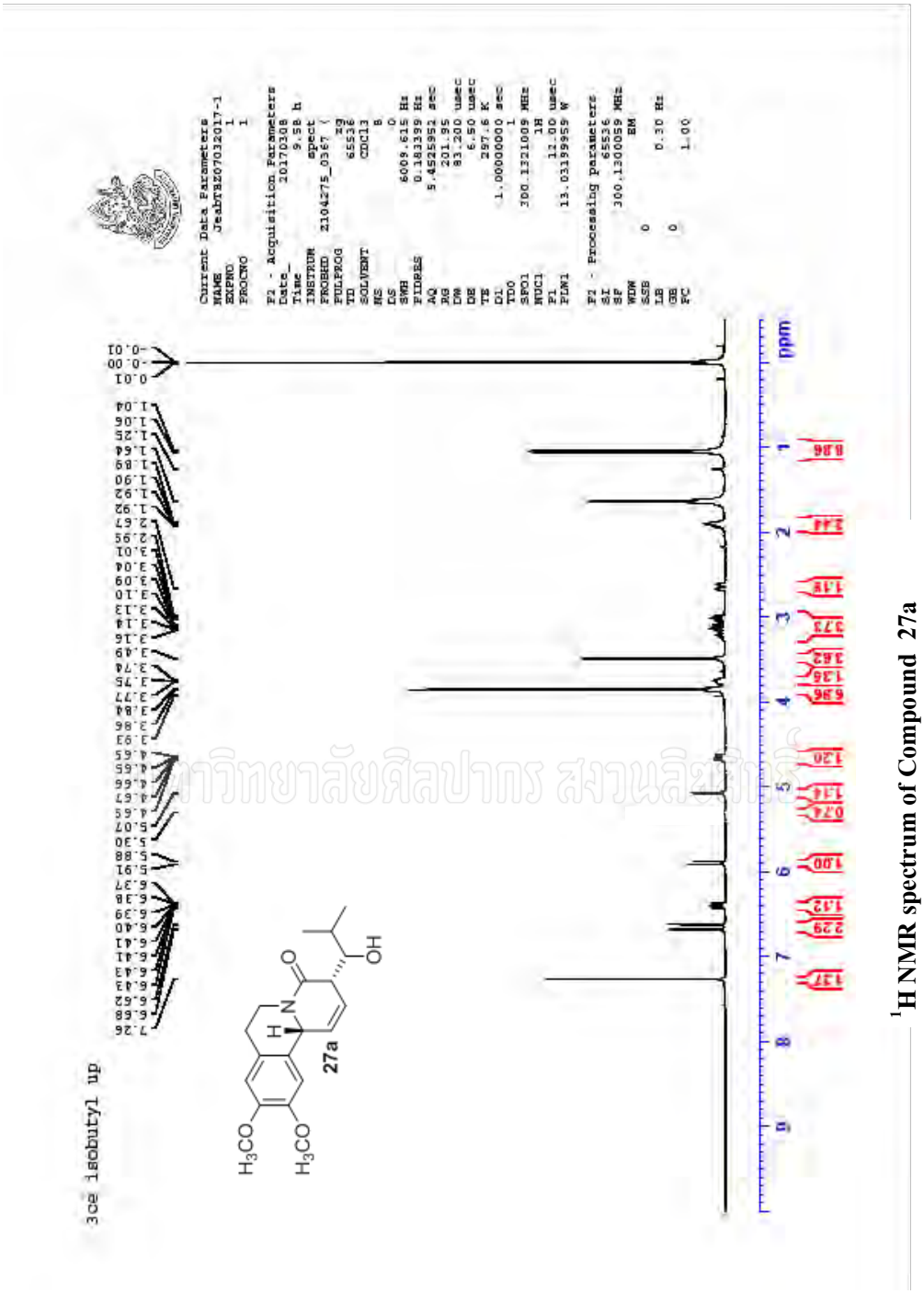
^{13}C NMR spectrum of Compound 26a



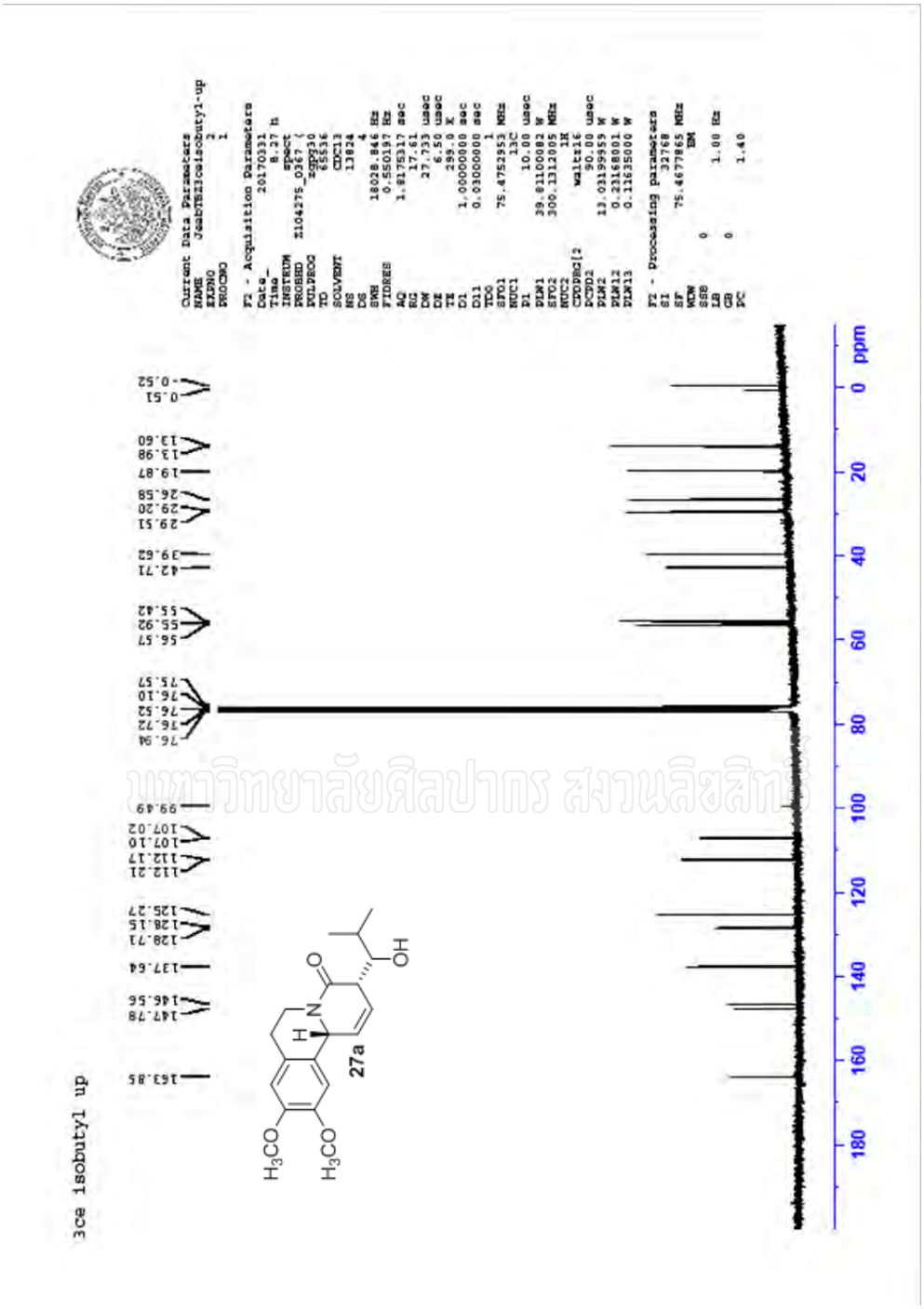
^{1}H NMR spectrum of Compound 26b



^{13}C NMR spectrum of Compound 26b



^{1}H NMR spectrum of Compound 27a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27a
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H3CO
OH
O
N
H
Current Data Parameters
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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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Time 8.27 h
INSTRUM spect
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TD 65536
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FIDRES 0.550197 Hz
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DW 27.733 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
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P1 10.00 usec
PLW1 39.81100082 W
SFO2 300.1312005 MHz
NUC2 1H
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PCPD2 90.00 usec
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PLW12 0.23168001 W
PLW13 0.11635000 W
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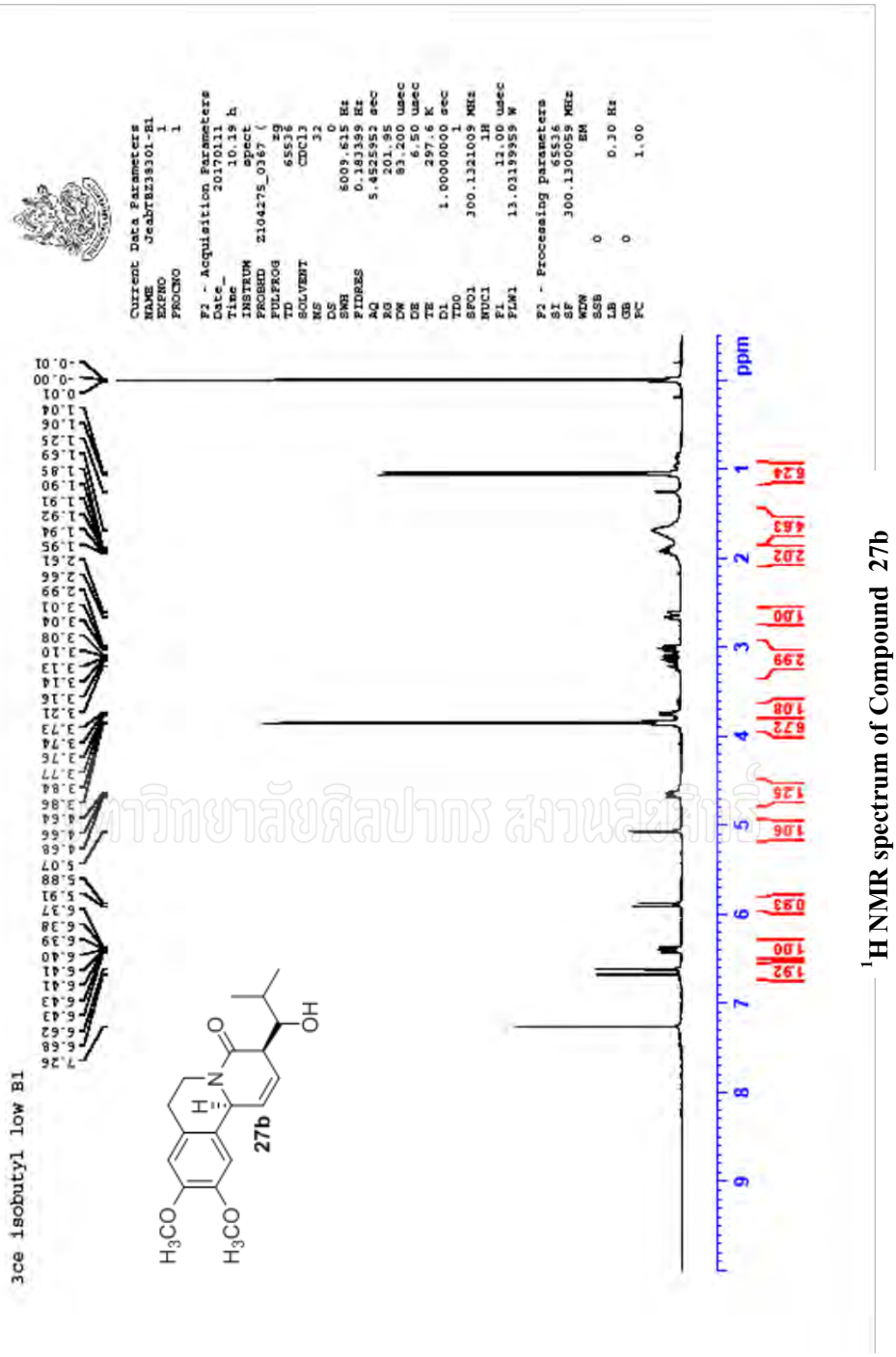
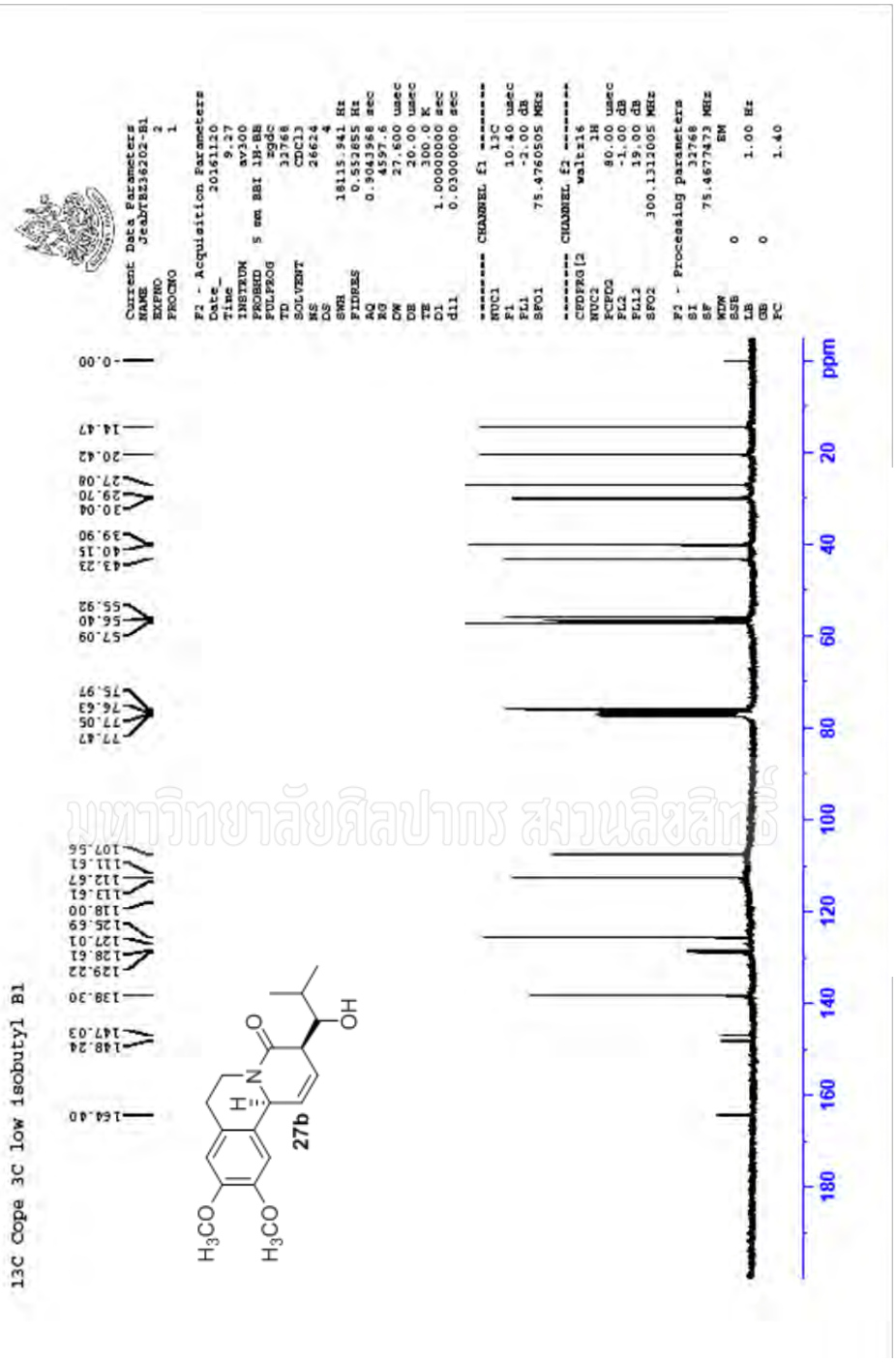
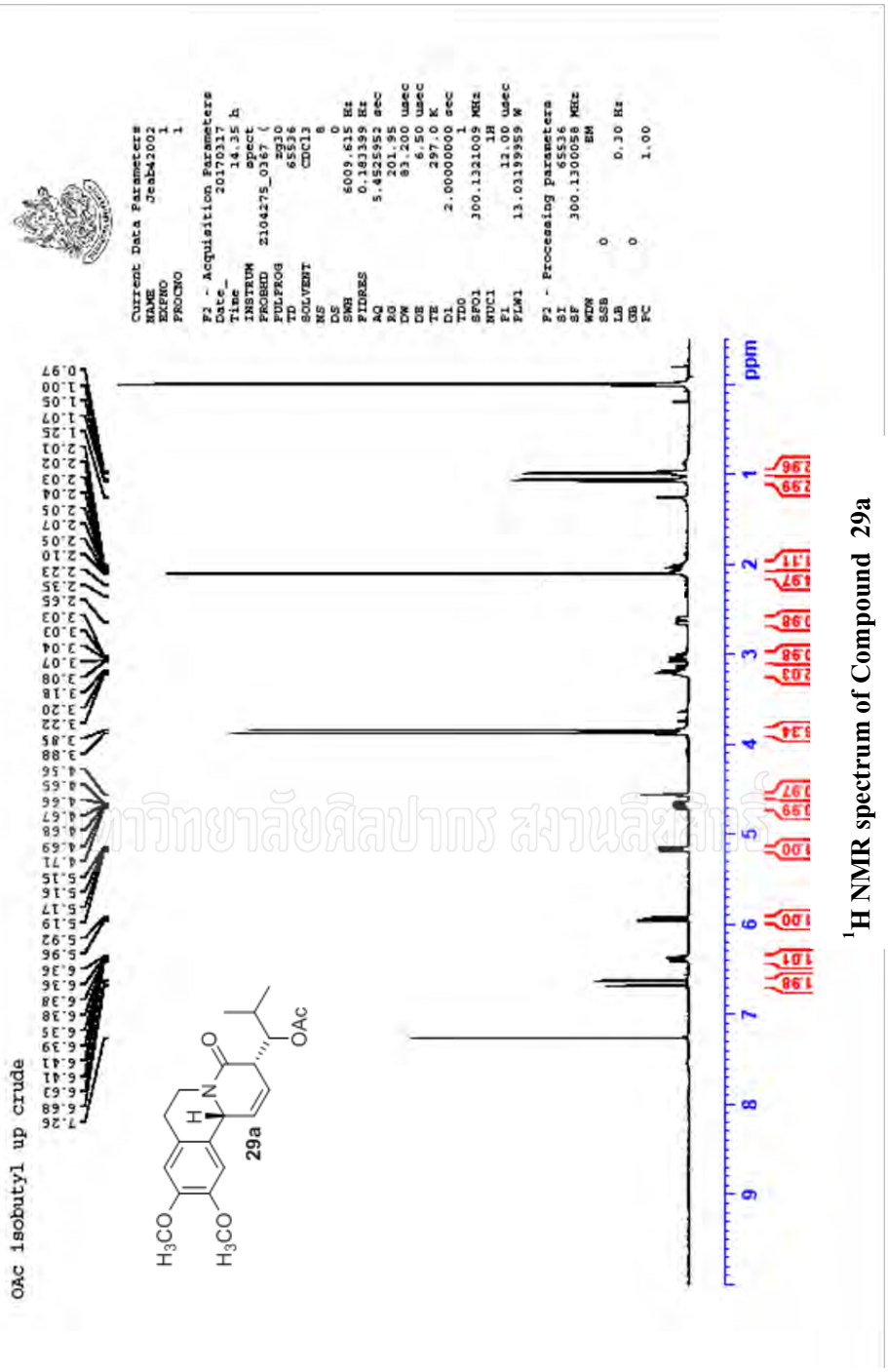


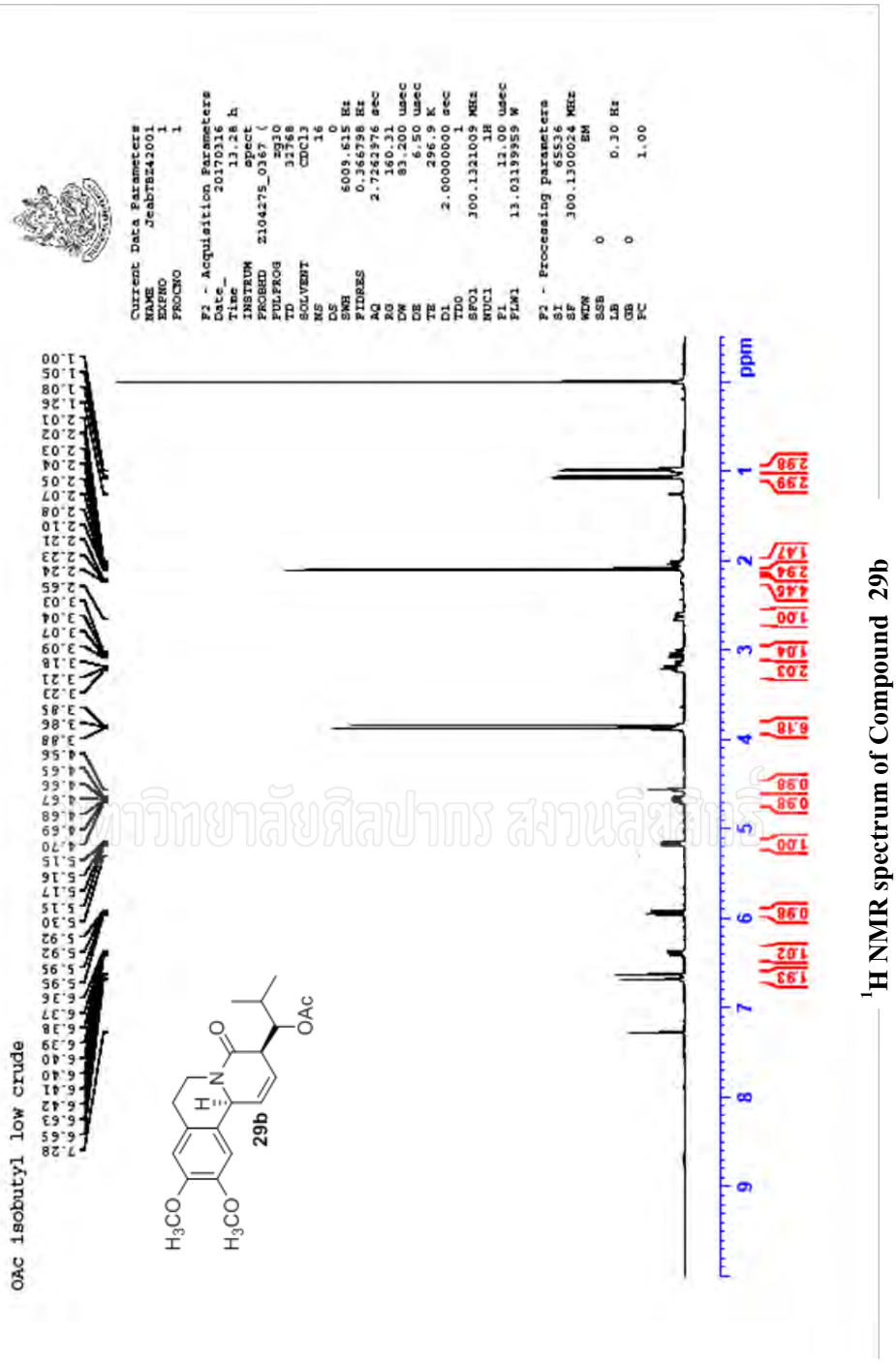
^{1}H NMR spectrum of Compound 27b



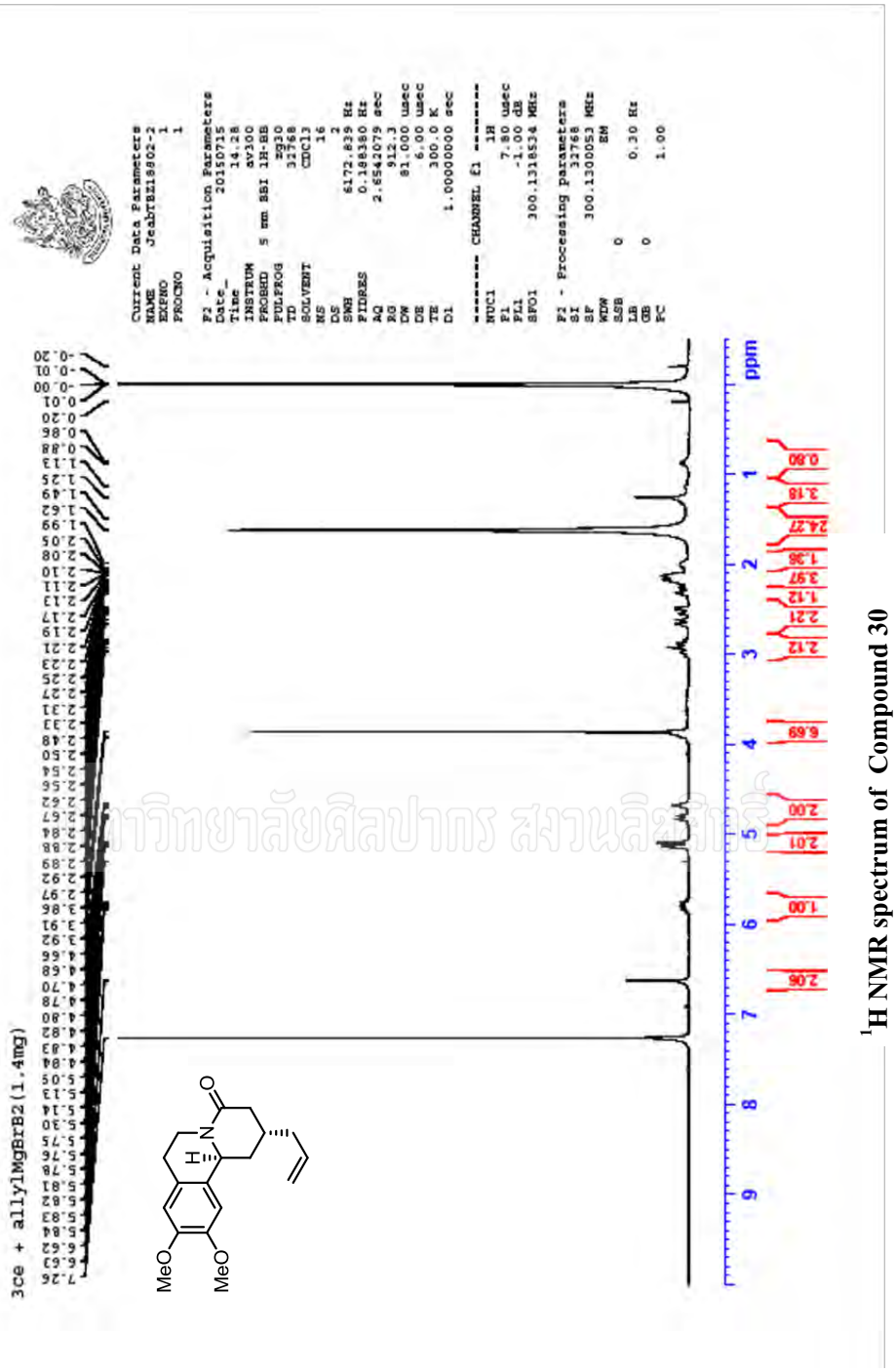
^{13}C NMR spectrum of Compound 27b



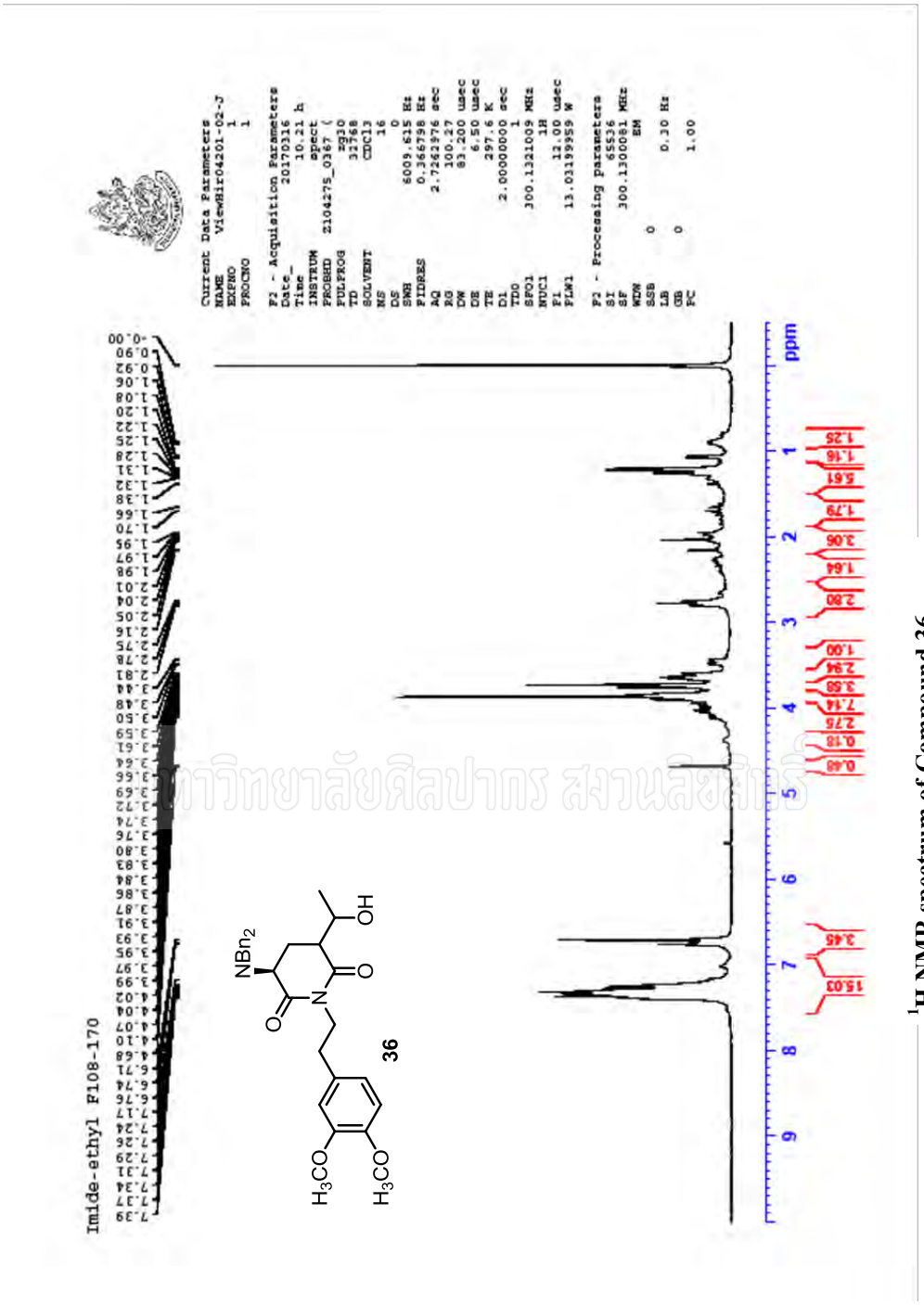
^{1}H NMR spectrum of Compound 29a



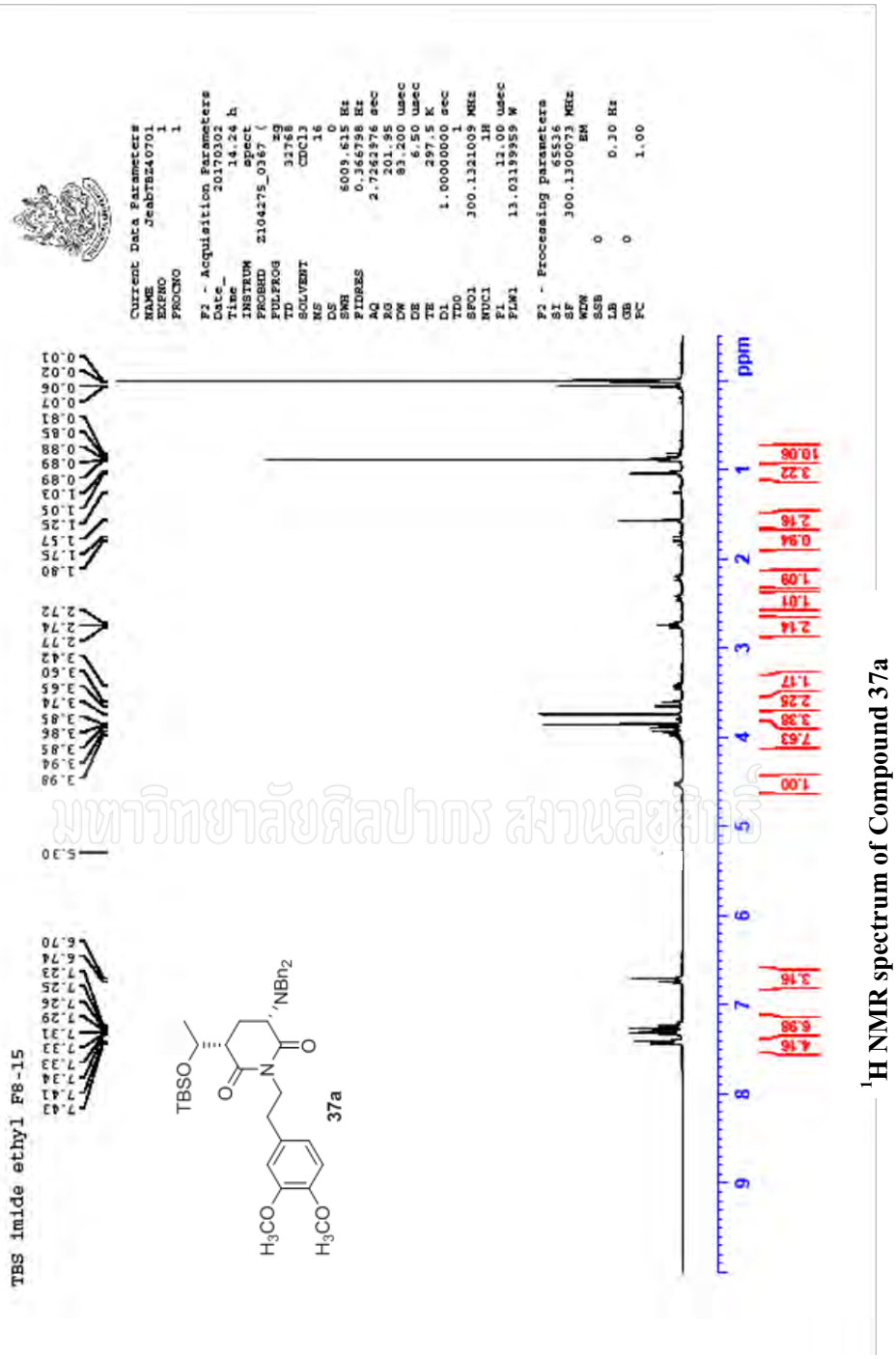
^{1}H NMR spectrum of Compound 29b



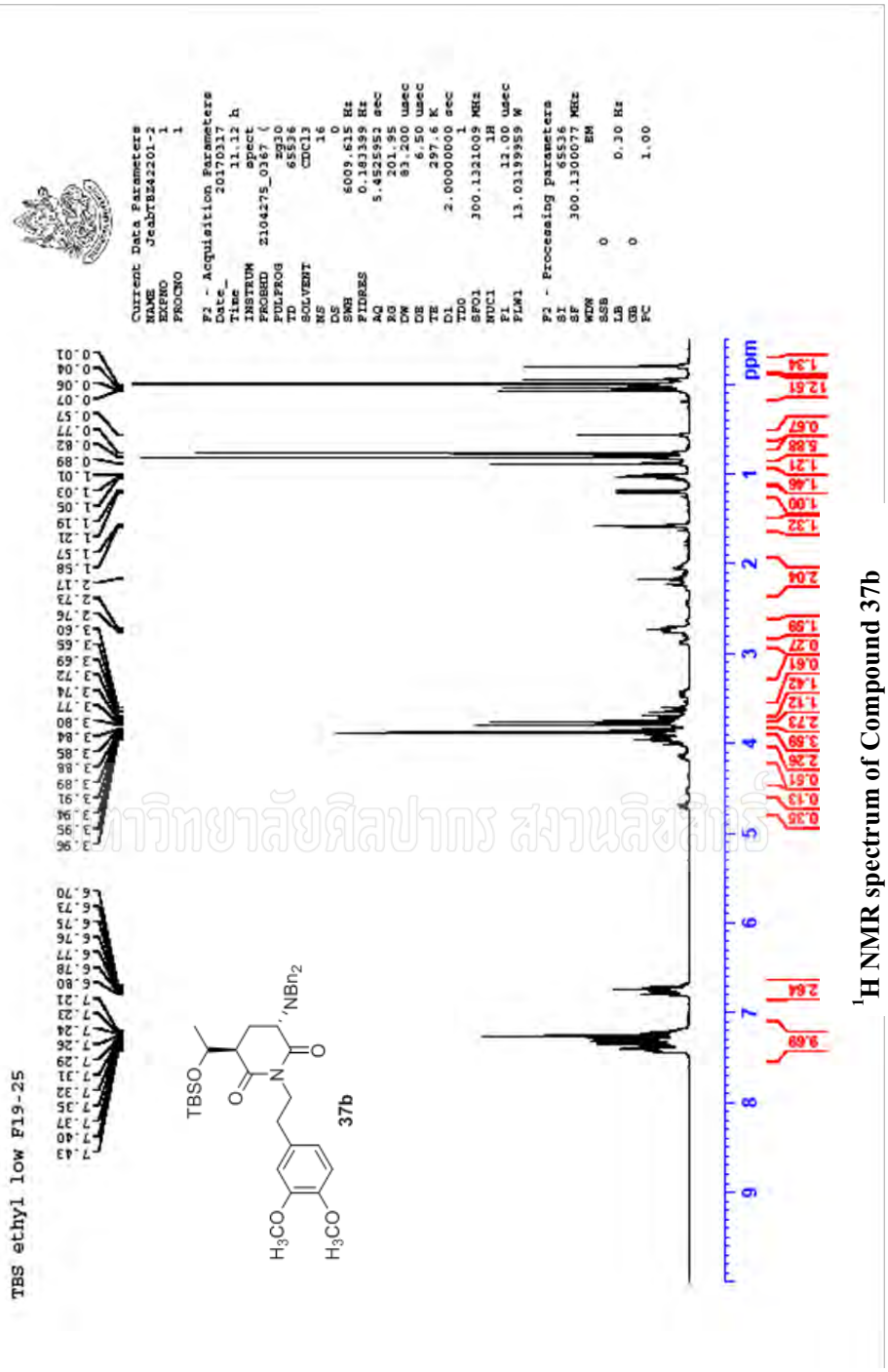
^{1}H NMR spectrum of Compound 30



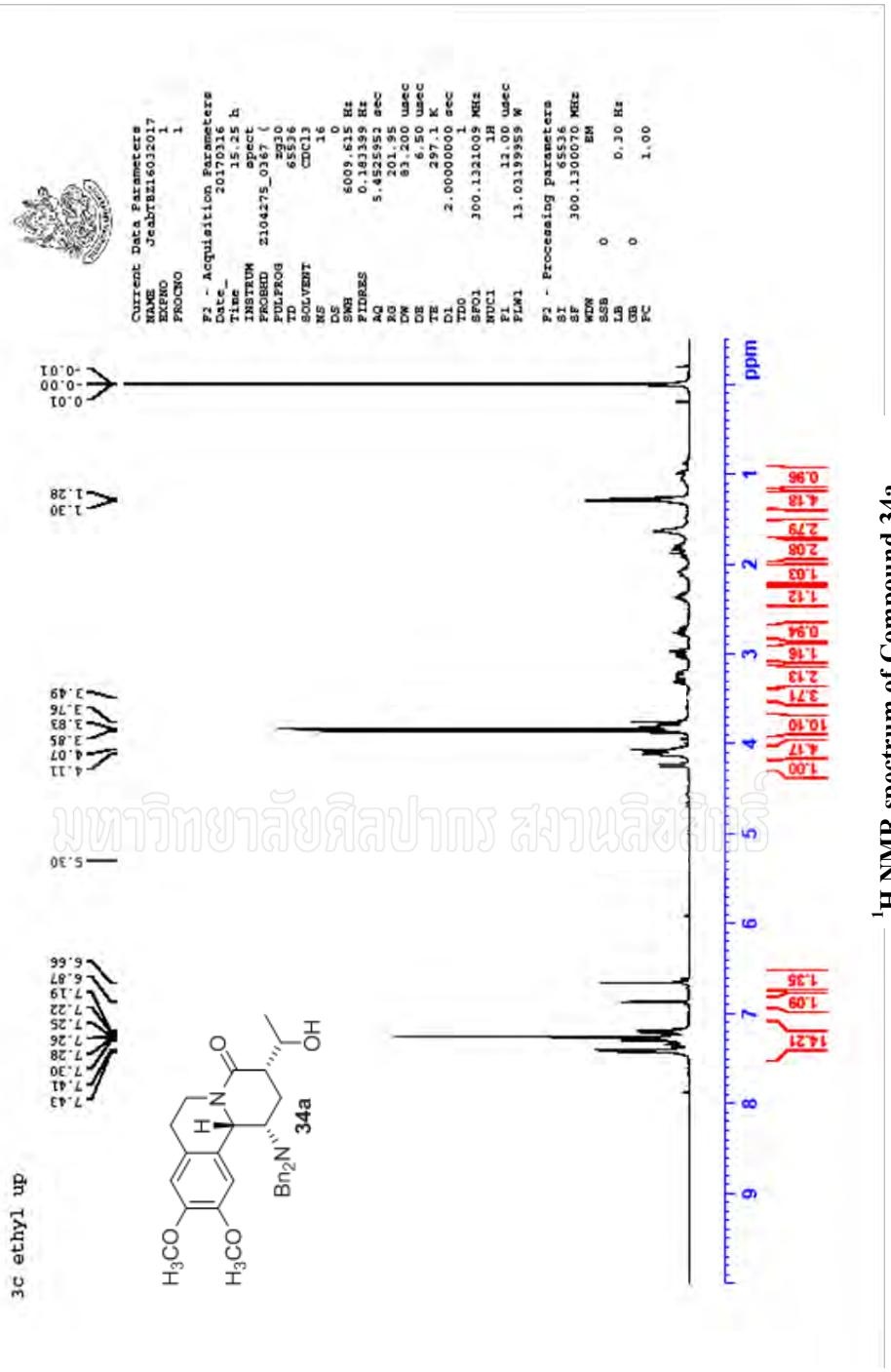
^{1}H NMR spectrum of Compound 36



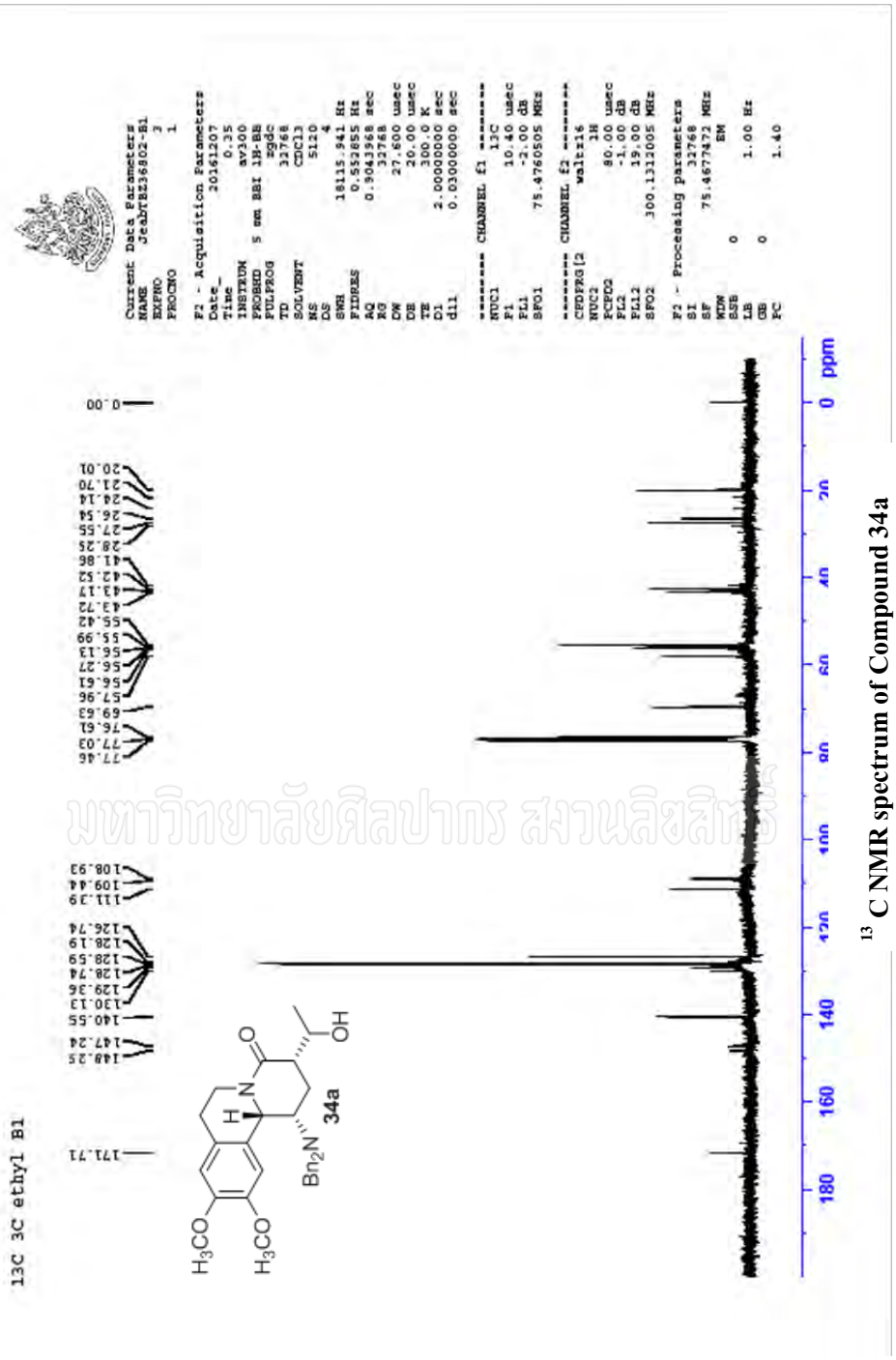
^{1}H NMR spectrum of Compound 37a



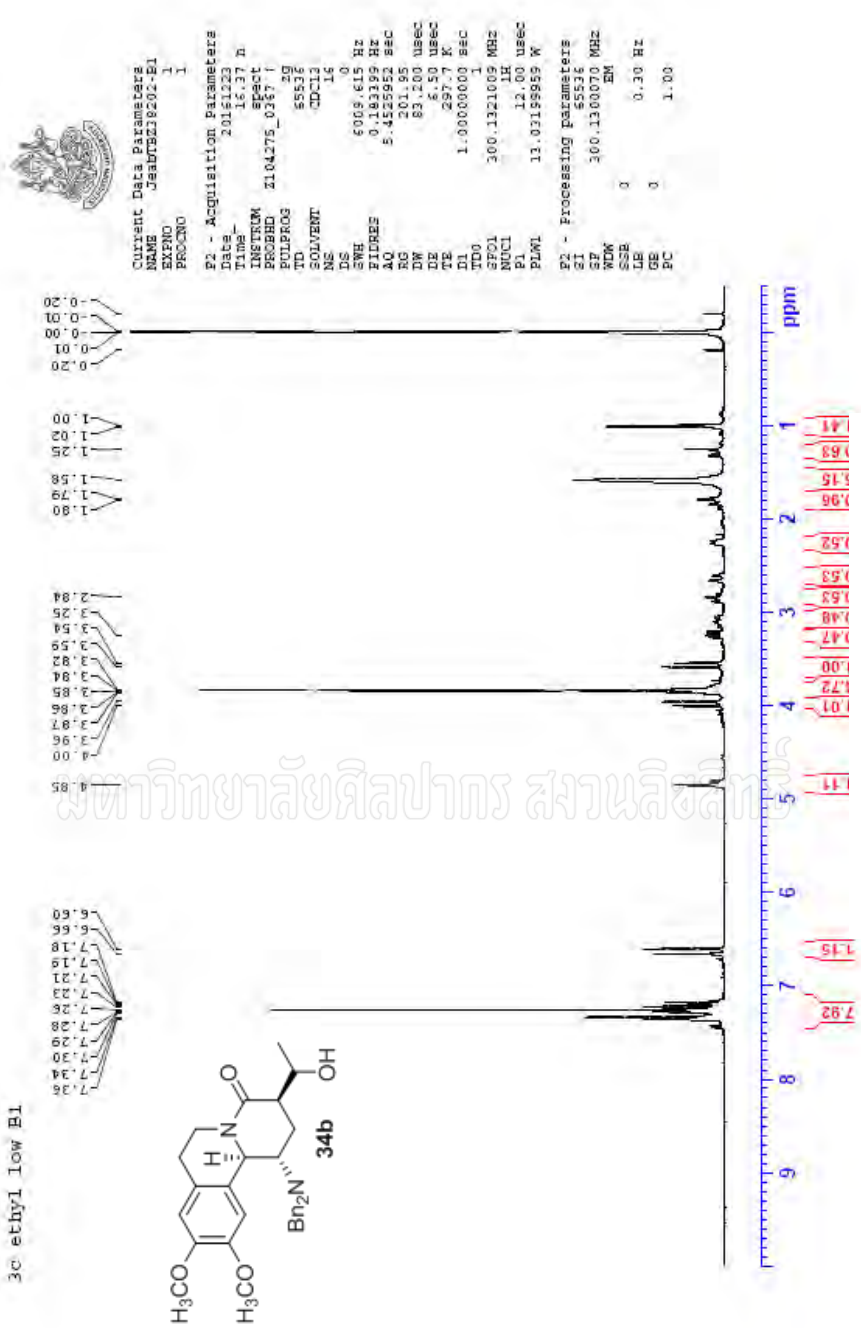
^{1}H NMR spectrum of Compound 37b



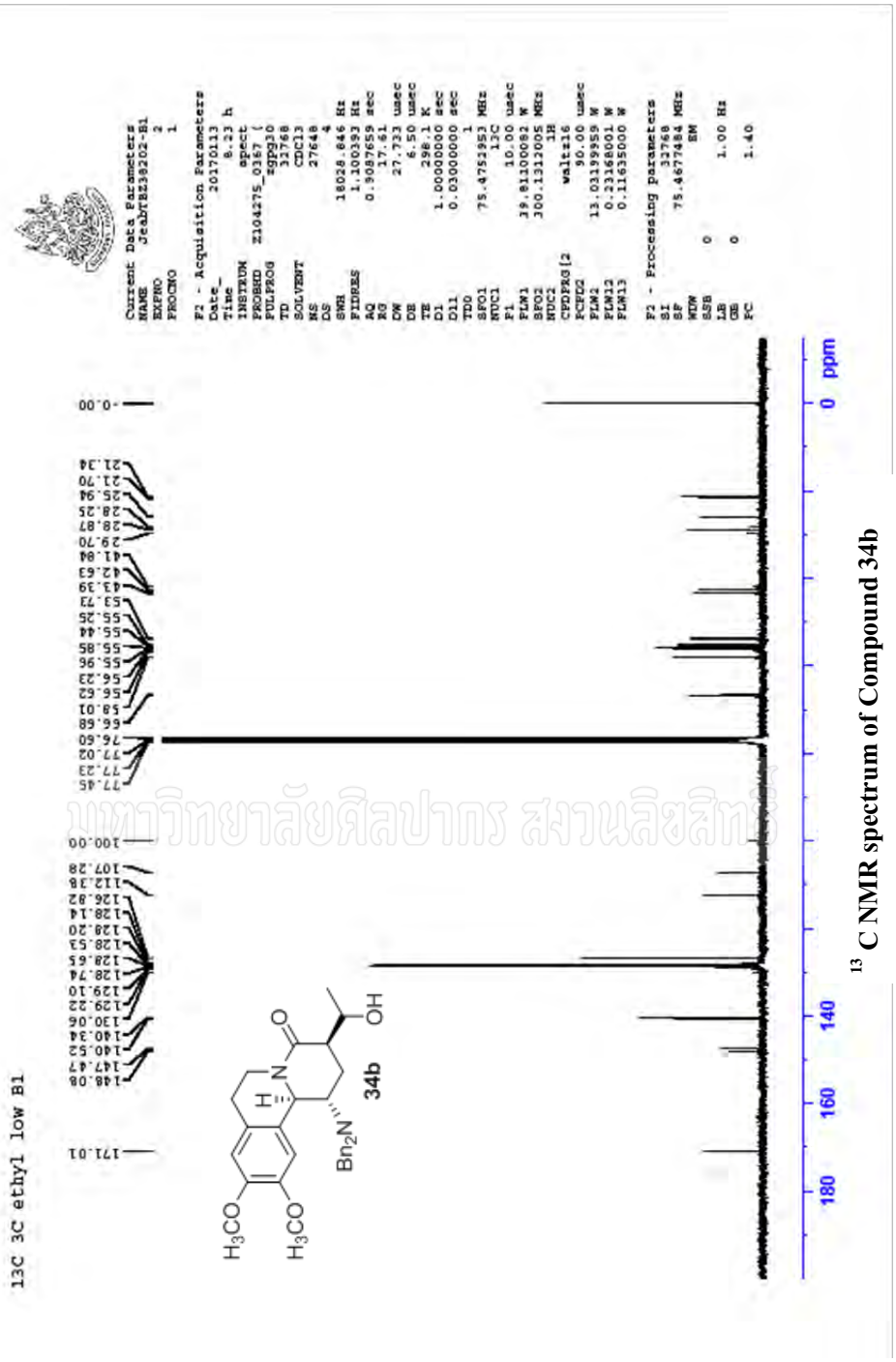
^{1}H NMR spectrum of Compound 34a



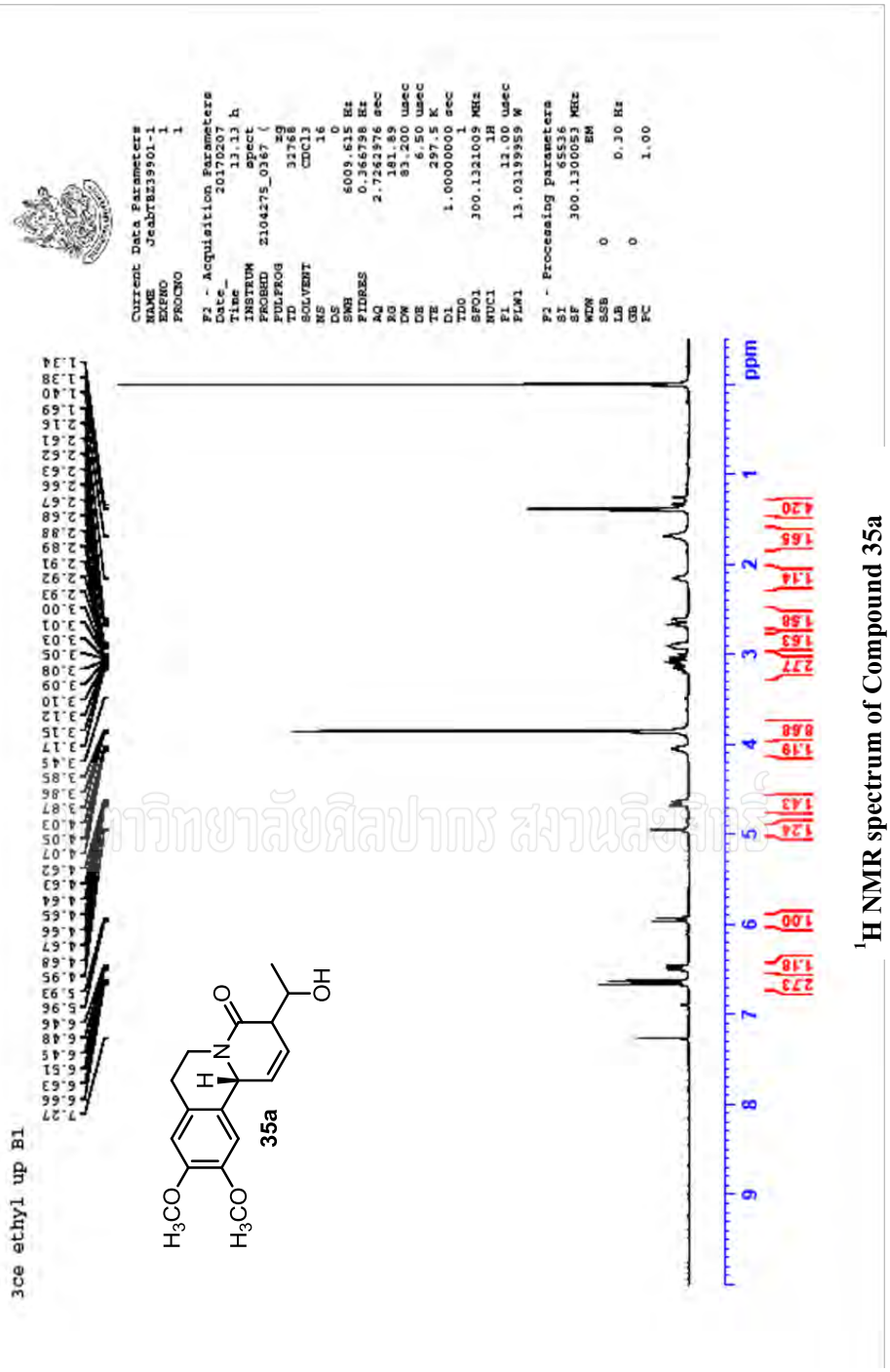
^{13}C NMR spectrum of Compound 34a



^{1}H NMR spectrum of Compound 34b

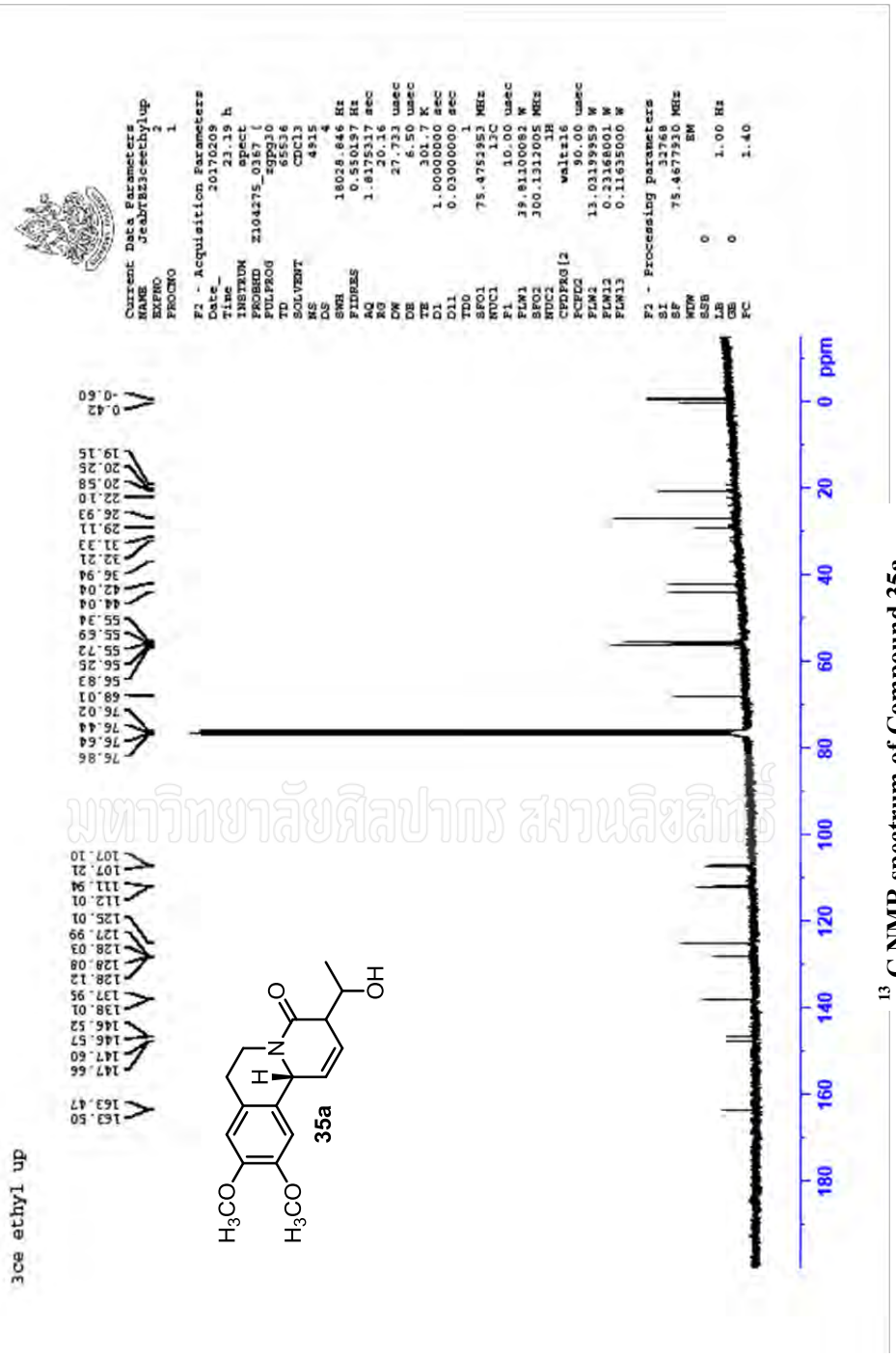


^{13}C NMR spectrum of Compound 34b

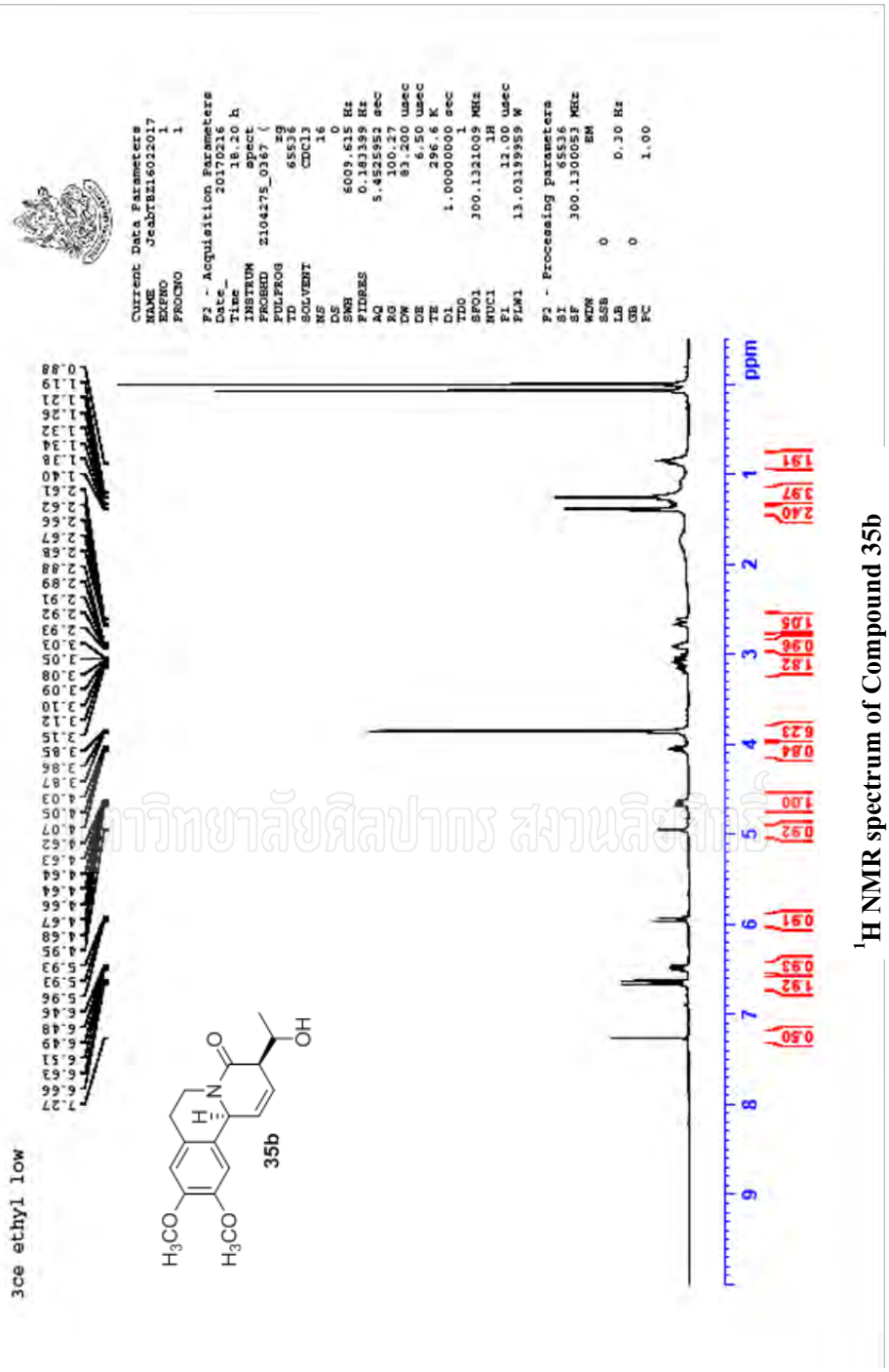


^{1}H NMR spectrum of Compound 35a

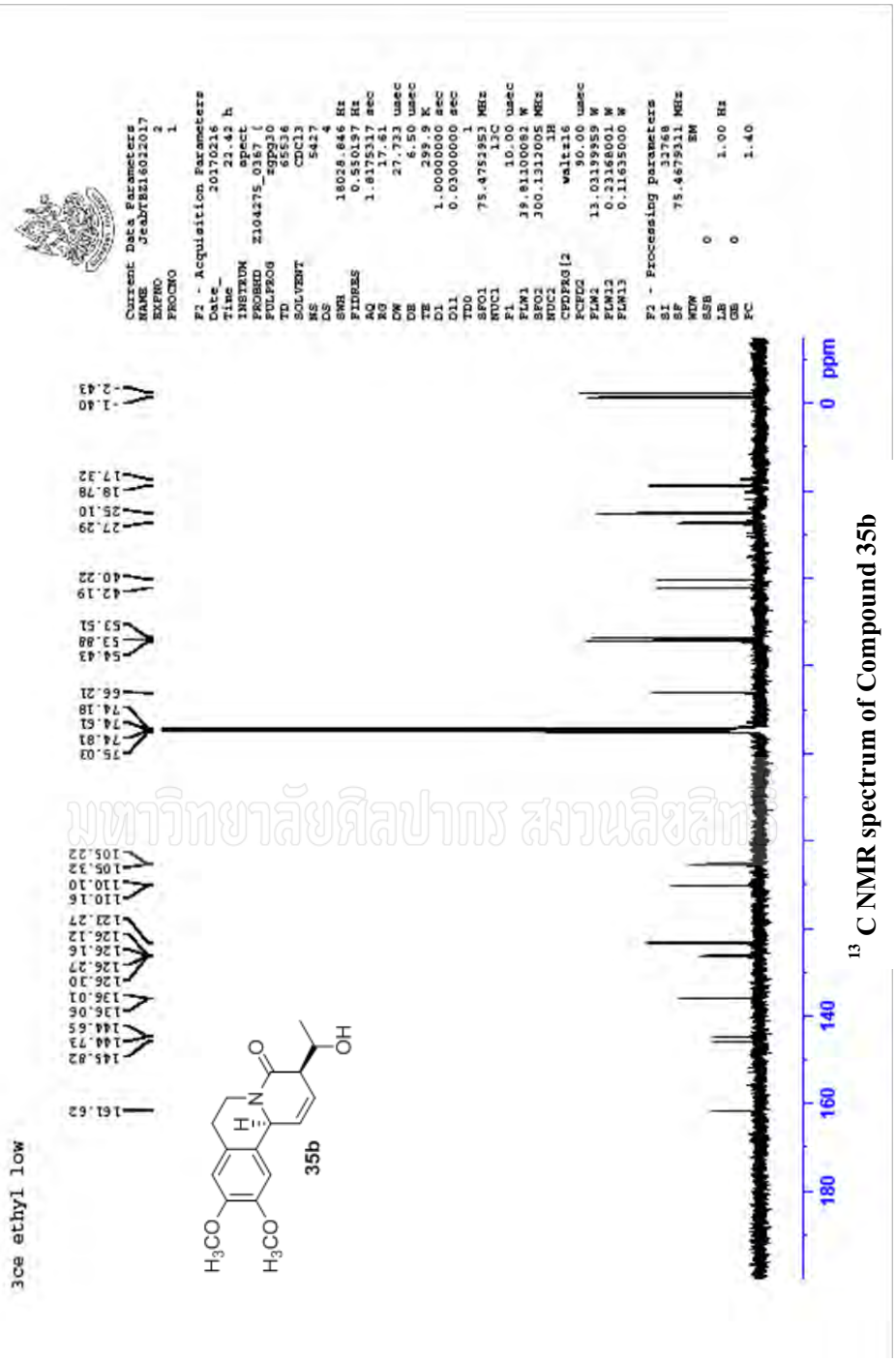
ศูนย์วิทยทรัพยากร จุฬาลงกรณ์มหาวิทยาลัย



^{13} C NMR spectrum of Compound 35a

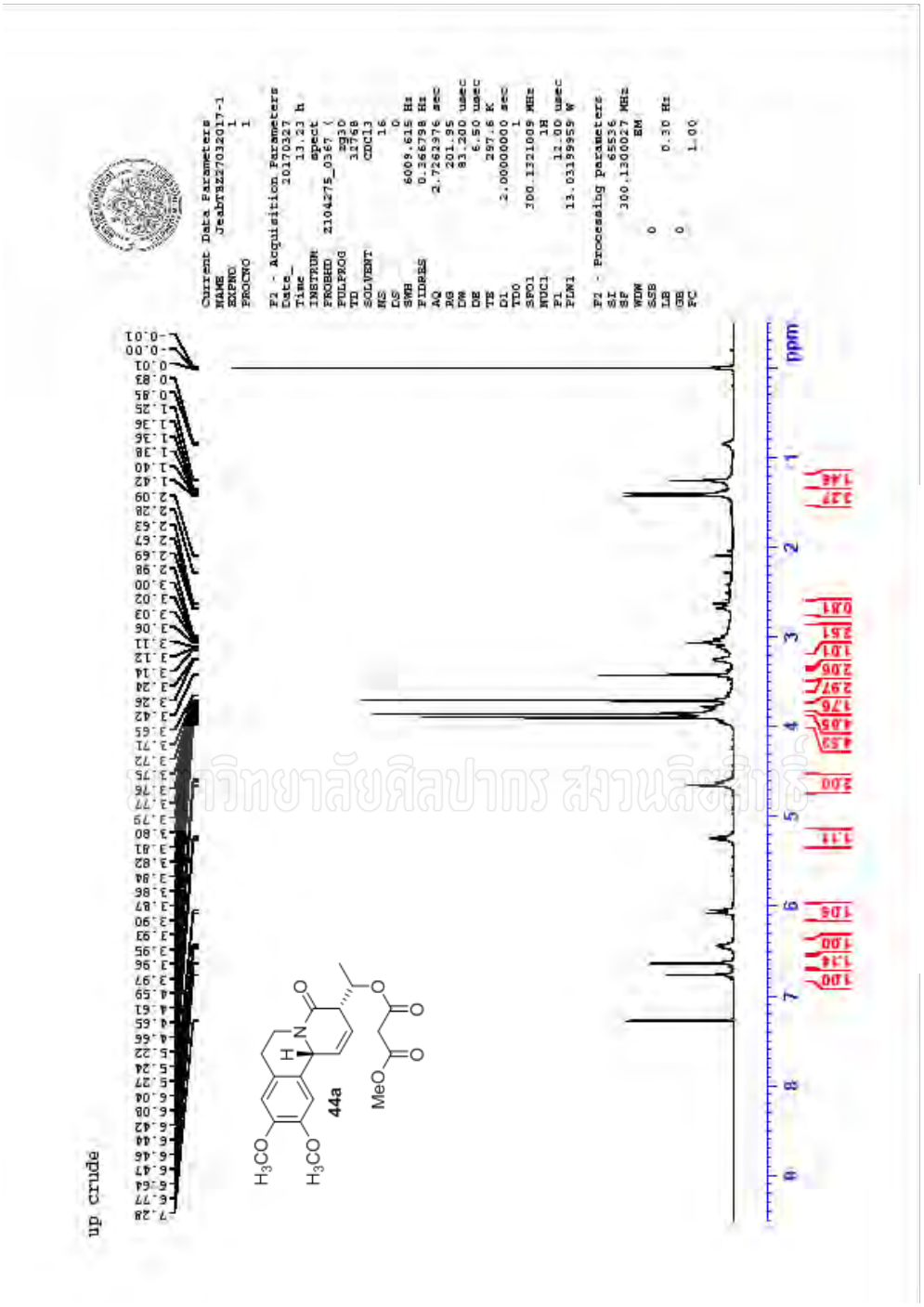


^{1}H NMR spectrum of Compound 35b

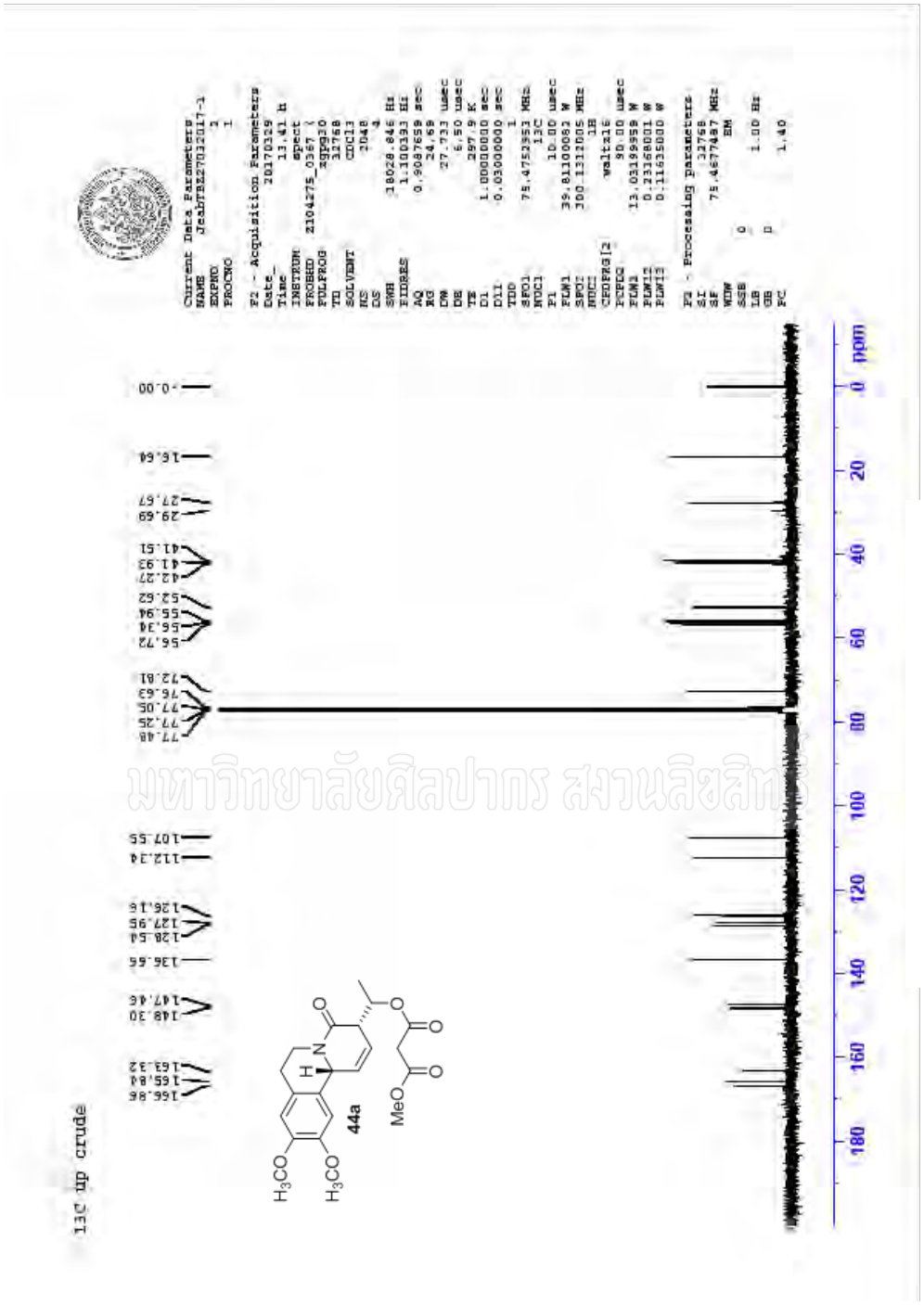


^{13}C NMR spectrum of Compound 35b

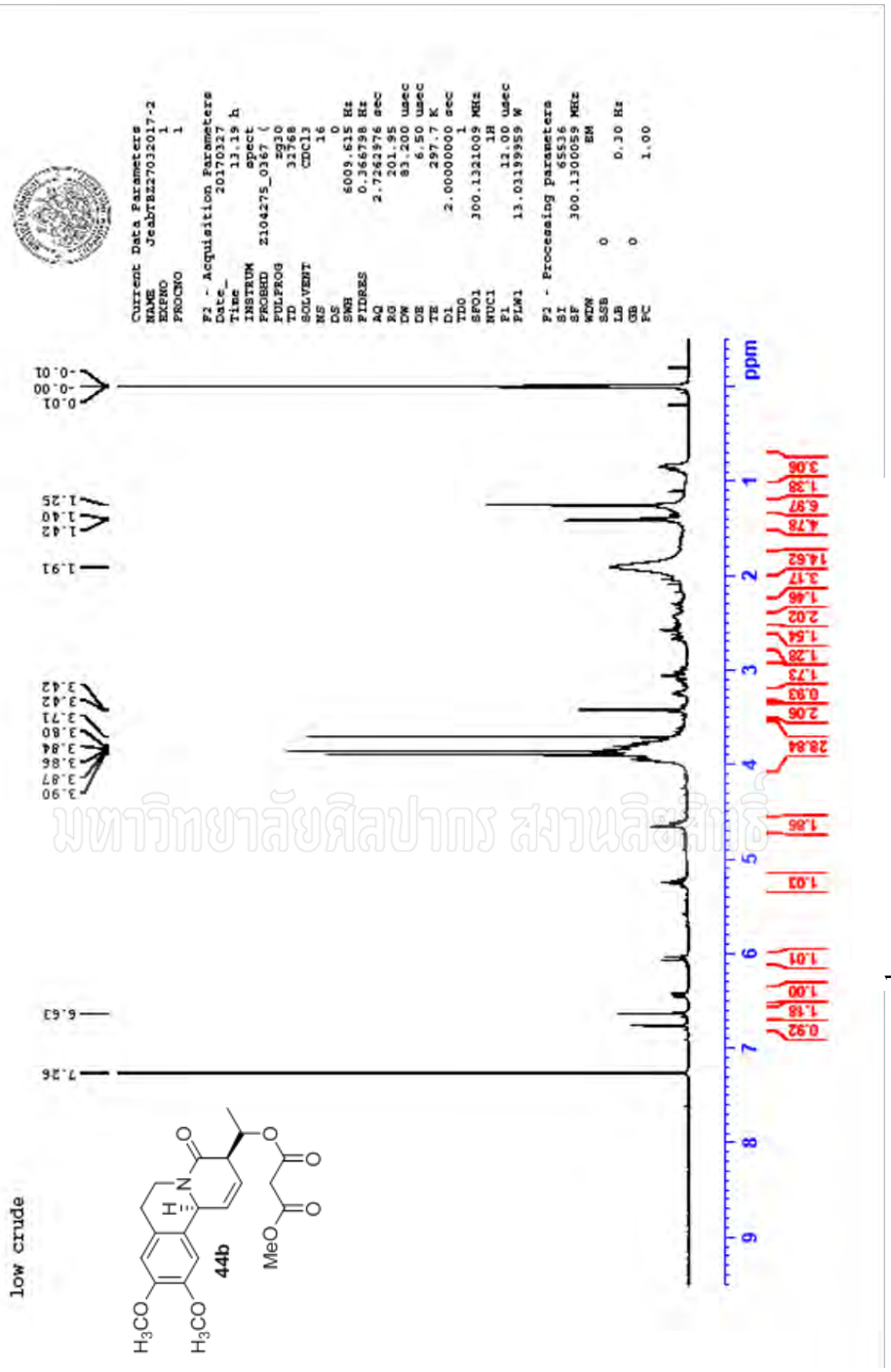
มหาวิทยาลัยศิลปากร สงวนลิขสิทธิ์



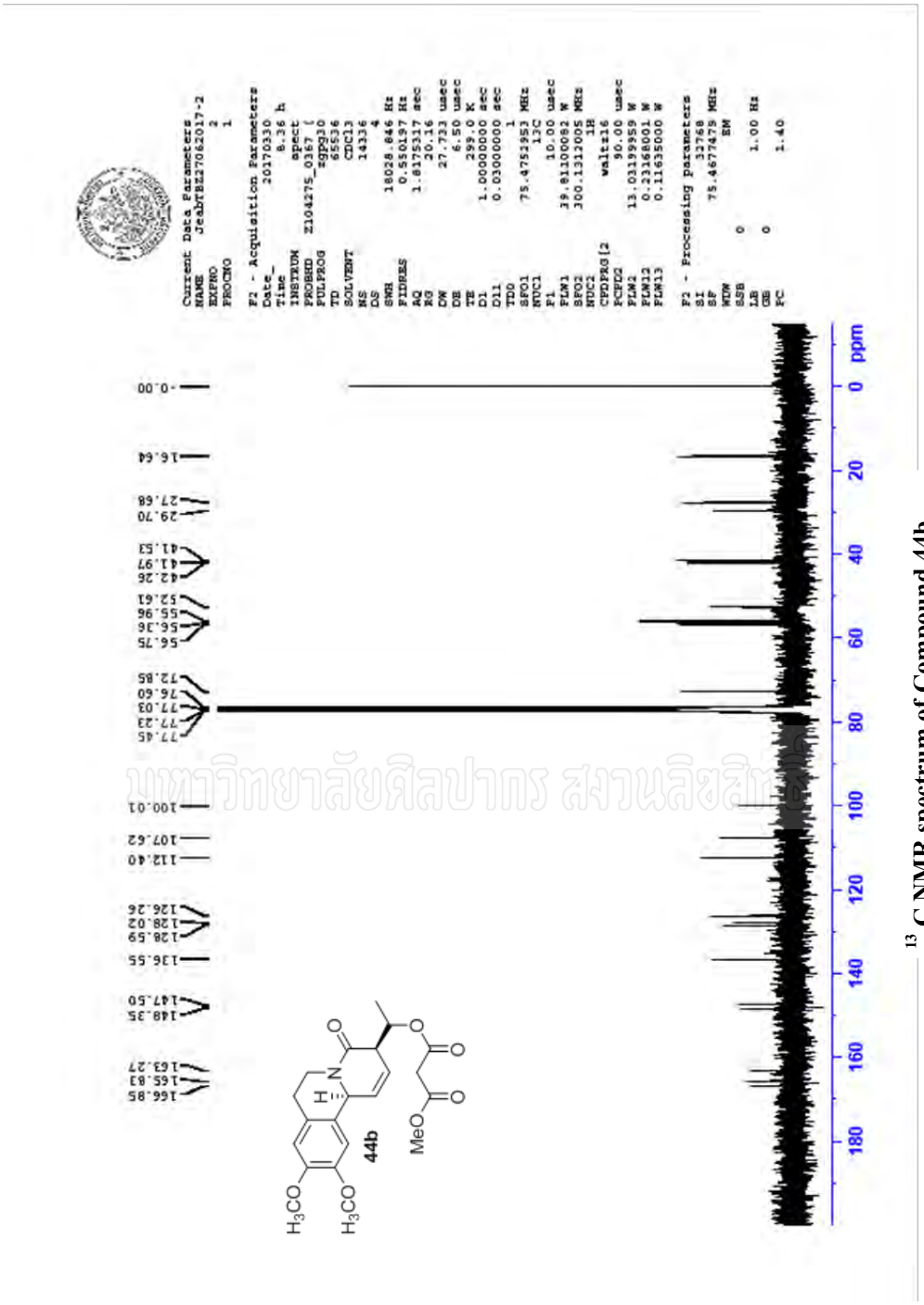
^{1}H NMR spectrum of Compound 44a



^{13}C NMR spectrum of Compound 44a



^{1}H NMR spectrum of Compound 44b



^{13}C NMR spectrum of Compound 44b

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