การสังเคราะห์อนุพันธ์ของ 3-เมทิล-1,2,3,4-เททระไฮโดรไอโซควิโนลีน

นางสาวเพลินทิพย์ ภูทองกิ่ง

SYNTHESIS OF 3-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES

Miss Pleonthip Puthongking

Thesis Title	SYNTHESIS OF 3-METHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINE DERIVATIVES
By	Miss Pleonthip Puthongking
Field of Study	Pharmaceutical Chemistry
Thesis Advisor	Assistant Professor Chamnan Patarapanich, Ph.D.
Thesis Co-advisor	Associate Professor Sunibhond Pummangura, Ph.D.

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…………………………………….Dean of Faculty of Pharmaceutical Sciences

(Associate Professor Boonyong Tantisira, Ph.D.)

THESIS COMMITTEE

………………………………..Chairman

(Assistant Professor Mitr Pathipvanich, Ph.D.)

………………………………..Thesis Advisor

(Assistant Professor Chamnan Patarapanich, Ph.D.)

………………………………..Thesis Co-advisor

(Associate Professor Sunibhond Pummangura, Ph.D.)

………………………………...Member

(Mr. Khanit Suwanborirux, Ph.D.)

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      การวิจัยครั้งนี้เป็นการศึกษาและพัฒนาวิธีการสังเคราะห์ 3-เมทิล-1,2,3,4-เททระไฮโดรไอ
โซควิโนลีน และ อนุพันธ์ โดยใช้แอนซีสโตรเทคโทลีนเป็นสารแม่แบบ ซึ่งกระบวนการสังเคราะห์
เริ่มจากปฏิกิริยาคอนเดนเซชั่น ระหว่าง 3,5-ไดเมทท๊อกซี่เบนซาวดีไฮ และ ไนโตรอีเทน ได้สาร
กลุ่มไนโตรสไตลีนเป็นผลิตภัณฑ์ โดยผลิตภัณฑ์ดังกล่าวถูกนำมาทำปฏิกิริยารีดักชั่น และตาม
ด้วย ปฏิกิริยาการเกิดซิพเบส ได้เป็นเอน-เบนซิลฟีนิลเอททิลเอมีน ซึ่งใช้เป็นสารเริ่มต้นสำหรับการ
ศึกษาการปิดวงแหวนผ่านสารตัวกลางที่เป็น เอน,โอ-อะซีทาว ในการศึกษาครั้งนี้ได้ทำการปิดวง
แหวนด้วย พาราฟอร์มาลดีไฮ และ บิวทิลไกลอ๊อกซาเลต   ได้ผลิตภัณฑ์ เป็นสารกลุ่ม 1,2,3,4-
เททระไฮโอรไอโซควิโนลีน หลังจากนั้นได้ทำการเปลี่ยนหมู่แทนที่ที่ตำแหน่ง 1 และ 2 เพื่อให้ได้เป็น
อนุพันธ์ต่างๆ โดยสารที่สามารถสังเคราะห์ได้ในครั้งนี้สามารถพิสูจน์เอกลักษณ์ด้วยเทคนิคทาง
สเปคโตรสโคปี

ภาควิชา	เภสัชเคมี	ลายมือชื่อนิสิต...
สาขาวิชา	เภสัชเคมี	ลายมือชื่ออาจารย์ที่ปรึกษา...
ปีการศึกษา	2544	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม...

Using the structure of ancistrotectorine as the lead molecule, a design and
synthetic strategy for the preparation of 3-methyl-1,2,3,4-tetrahydro-isoquinoline and
derivatives have been studied.   The condensation of 3,5-dimethoxy benzaldehyde with
nitroethane afforded the nitrostyrene, which was subsequently reduced to obtain the
amine and follow by schiff base formation which was reduced to afford the *N*-benzyl
phenylethylamine.   The *N*-benzyl phenylethylamine was treated with paraformaldehyde
or butyl glyoxalate, via the *N,O*-acetal intermediate and was further intramolecular
cyclized with acidic catalysis to afford the 1,2,3,4-tetrahydroisoquinolines.   Compounds
with variations of the substituents on positions 1 and 2 of the tetrahydroisoquinoline were
also prepared.   The structures of the compounds synthesized were determined by the
spectroscopic techniques.

Department   Pharmaceutical chemistry   Student's signature…………………

Field of study   Pharmaceutical chemistry   Advisor's signature………………...

Academic year   2001   Co-advisor's signature……………..

ACKNOWLEDGEMENT

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LIST OF ABBREVIATIONS

%	percent
ν	stretching vibration (for IR spectra)
ν_{as}	asymmetrical stretching (for IR spectra)
ν_{s}	symmetrical stretching (for IR spectra)
μl	micro litter
^{o}C	degree celsius
^{13}C-NMR	carbon-13-nuclear magnetic resonance
cm^{-1}	reciprocal centimeter (for IR spectra)
d	doublet (for NMR spectra)
dd	doublet of doublet (for NMR spectra)
^{1}H-NMR	proton nuclear magnetic resonance
h	hour
Hz	hertz
IR	infrared spectrometry
J	coupling constant (for NMR spectra)
m	multiplet (for NMR spectra)
M^{+}	molecular ion
mg	milligram
MHz	megahertz
min	minute
ml	milliliter
mmol	millimole
m.p.	melting point
m/z	mass per charge ratio
Pd/C	palladium on activated charcoal
PNMT	phenyl ethanolamine *N*-methyltransferase
ppm	part(s) per million
rt	room temperature
s	singlet (for NMR spectra)

t	triplet (for NMR spectra)
THIQ	tetrahydroisoquinoline

CHAPTER I

INTRODUCTION

Ancistrotectorine is one of the naphthylisoquinoline alkaloids that was found in the leaves of the Thai medicinal plant; *Ancistrocladus tectorius* (Lour) Merr. This plant is known in Thai as " Khon-maa-daeng ". Its leaves have been used in a folk medicine in Thailand for the treatment of edema and dermatitis (Na Songkla, 1982). In Burma and Malaysia, its roots have been used for the treatment of malaria and dysentery diseases (Burkill, 1935, vol.1). In 1985, Ruangrungsi and co-workers isolated ancistrotectorine, the 7-3′ - naphthylisoquinoline linkage from the leaves of "Khon-maa-daeng" (Ruangrungsi *et al*, 1985), while the first 7-3′ -naphthylisoquinoline linkage is ancistrocladidine from *Ancistrocladus beyneanus* Wall (Govindachari, 1973).

ancistrotectorine   ancistrocladidine
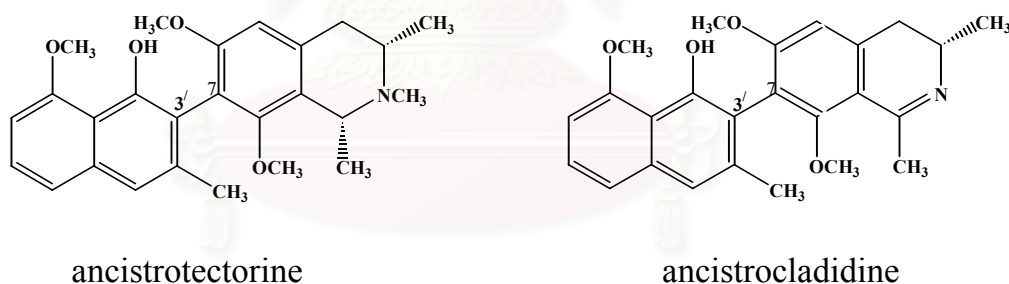
The pharmacological activity of ancistrotectorine has been studied. Ancistrotectorine exhibits antispasmodic activity on the intestinal contraction induced by acetylcholine, histamine, serotonin, barium chloride, and potassium chloride, and also inhibits the contraction induced by oxytocin, serotonin in the uterus of rat and guinea-pig ileum (Pasupat, 1985). This compound also exhibits similar action on the smooth muscle of blood vessel and aorta (Phusiraphan, 1987), which are induced by potassium chloride, calcium chloride, norepinephrine, serotonin, and histamine. It was suggested that

ancistrotectorine might have direct effect on the smooth muscle and caused a non-specific relaxation. The effects of ancistrotectorine were also compared with those of atropine, verapamil, and papaverine, respectively.

atropine   verapamil
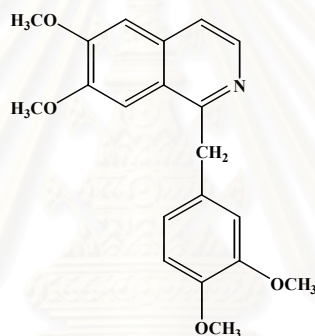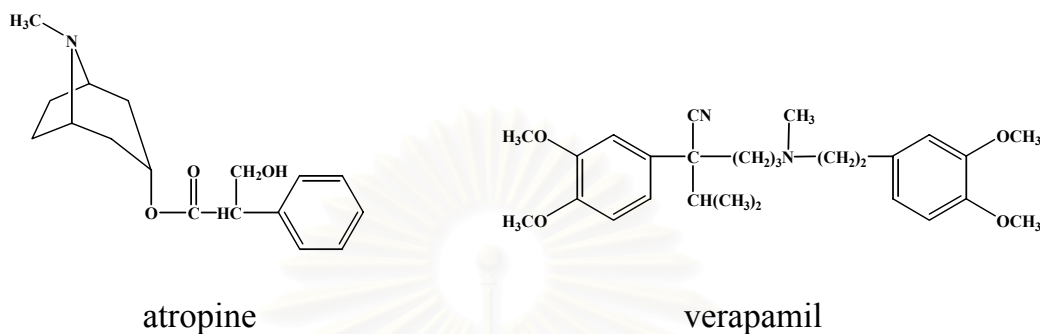
papaverine

The effect of ancistrotectorine was differ from that of atropine in blocking acetylcholine. Atropine is a competitive antagonist of acetylcholine at the muscarinic cholinergic receptors. In contrast, the antispasmodic activity of ancistrotectorine is similar to verapamil and papaverine (Boonprashai *et al*, 1990). Verapamil is the calcium antagonist with antiarrhythmic, antianginal, and antihypertensive properties. In addition, papaverine is a non-specific antagonist, which reduced the contraction of smooth muscle through various following mechanisms.

1) inhibition of receptor-operated calcium channel and voltage-dependent calcium channels.

2) inhibition of mitochrondrial respiration in the process of electron transport chain.

3) stimulation of the beta-adrenergic receptors at the smooth muscle membrane resulting in the inhibition of phosphodiesterase activity and hence increase in cyclic-adrenosine-$3'$, $5'$-monophosphate (cAMP) and calcium storage.

In addition, the β-phenylethylamine is an ideal pharmacophore of adrenergic drug (Delgado and Remeis, 1998) and also exhibits phenyl-ethanolamine N-methyltransferase (PNMT) inhibition. PNMT was referred to norepinephrine N-methyltransferase (NMT), and catalyzed the terminal step in the biosynthesis of epinephrine (E).

norepinephrine   epinephrine
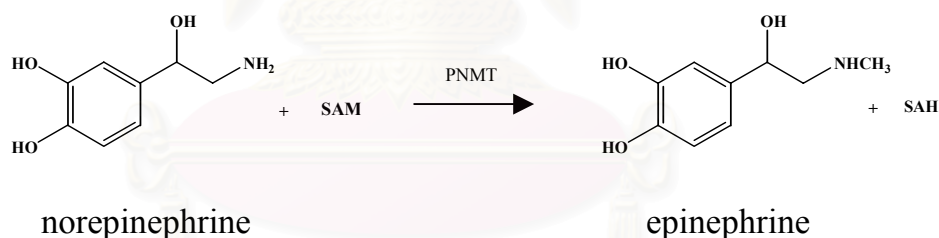
PNMT is located mainly in the adrenal medulla, but small quantities is also found in the brain of mammals (Saavedra *et al*, 1974), where it is localized in areas concerned with the control vital function such secretion of pituitary hormone (Crowley and Terry, 1981), heart rate and blood pressure. Reduction in the level of central epinephrine by PNMT inhibitors was initially believed to be the cause of this antihypertensive effect (Goldstein *et al*, 1982; Terry *et al*, 1981). Later, it was found that most of the widely-studied PNMT inhibitors were nonselective and had α_2-adrenoceptor binding affinity (Stolk *et al*, 1984; Ruffolo *et al*, 1984). Several means for inhibiting E biosynthesis seem possible

and most obviously such an action might be produced by inhibitors of the enzyme that are chemically related to the natural substrate, e.g., SAM, NE, SAH, and other compounds related to SAH and SAM inhibit PNMT. However, the majority PNMT inhibitors are structurally related to NE. It was observed that incorporation of the aminoalky side chain of certain β-phenylethylamine into a fused piperidine ring to give tetrahydroisoquinoline (THIQ) compound, that greatly enhances PNMT-inhibitory potency, and exhibits strong affinity for the α_2-adrenoceptor (Grunewal, 1999:118-134, 4351-4361). Thus tetrahydroisoquinoline compound has been modified to improve the PNMT-inhibitor activity based on the ideal to modify β-phenylethylamine, that the parent compound from which sympathomimetic drug are derived. The structure of β-phenylethylamine consists of a benzene ring with an ethylamine side chain. The substitution can be made on : 1) the terminal amino group, 2) the alpha- or beta-positions of the ethylamine side chain, and 3) the meta- and para-position of the aromatic ring (Delgado and Remeis, 1998:479-503), as illustrates in Figure 1.

β-phenylethylamine

N-tert-butylnorepinephrine

isoproterenol

metaproterenol
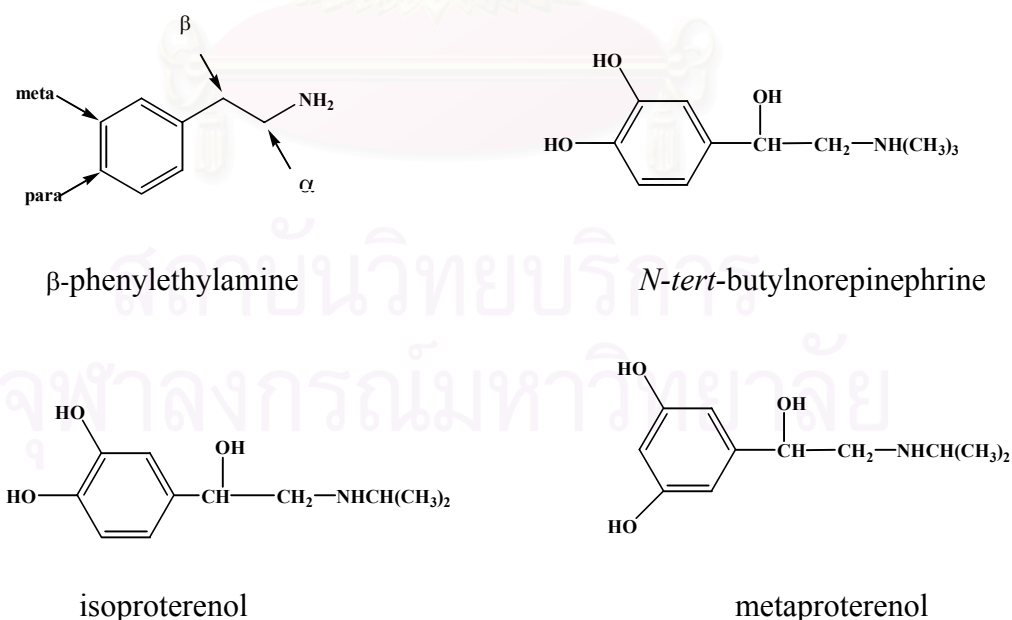
Figure 1 Structures of the phenylethylamines and some important catecholamines

Substitution on the terminal amino group : The substitution made on the amino group is important for direct agonistic activity. Both primary and secondary amines are found to be potent direct-acting agonist, but tertiary or quarternary amine trend to be poor direct agonist. The bulky of the nitrogen substitution increases the beta-receptor agonist acting but decreases the alpha-receptor agonist activity. In several instances, it has been shown the *N*-*tert*-butyl group enhances beta$_2$-selectivity. Large substituent on the amino group also protects the amino group from undergoing oxidative deamination by monoamine oxidase (MAO).

Substitution on the alpha- and beta-carbon of the ethylamine side chain : The substitution on the alpha-carbon increases the duration of action by making the compound resistant to metabolic deamination by MAO. Such compound often exhibits enhanced oral effectiveness and CNS activity. While at the beta-substitution, particularly the hydroxyl substitution may be important for storage of sympathomimetic amine in neural vesicle.

Substitution on the meta- and para-position of the aromatic ring : The aromatic ring are substituted at meta-and para-positon (catechol moiety) are maximal agonist activity at adrenergic receptors, and the substrate for catechol *O*-methyltransferase (COMT). But the absence of one or the other of these groups, particularly the hydroxyl at meta-position, without other substitutions on the ring may be dramatically reduced the potency of the drugs. Thus it can be replaced catechol moiety with resorcinol structure gave the drug metaproterenol. Since the resorcinol ring is not the substrate for COMT.

The two principle enzymes involved in adrenergic drug metabolism are monoamine oxidase (MAO) and catechol *O*-methyltransferase (COMT). Both of these enzymes are distributed throughout the body, with high concentration found in the liver and kidney. MAO is associated primarily with the outer membrane of the mitochondria, while COMT is found primarily in the

cytoplasm.   Neither MAO nor COMT exhibits a high degree of substrate specificity.

MAO oxidatively deaminate a variety of compound that contains an amino group attached to a terminal carbon.   The catecholamine metabolism indicate that in the adrenergic neuron of human brain and peripheral tissue NE is deamination oxidatively by MAO to give 3,4-dihydroxyphenyl glycolaldehyde (Figure 2).

Methylation by COMT occurs almost exclusively on the meta-hydroxyl group of catechol.   For example, the action of COMT upon NE and E give normetanephrine and metanephrin (Figure 2).   In fact, regardless of whether the first metabolism step is oxidation by MAO or methylation by COMT.
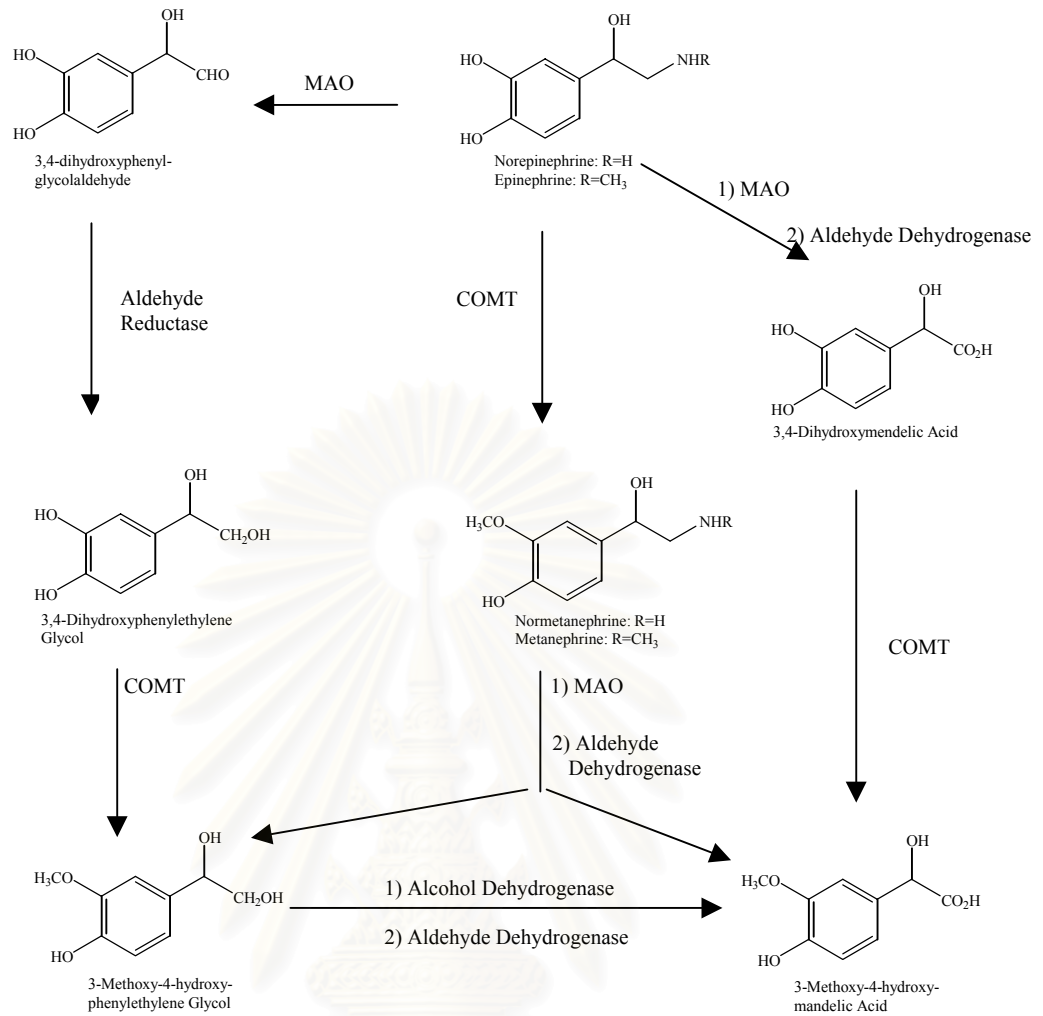
Figure 2 The metabolism of norepinephrine and epinephrine by MAO and COMT.

Design of the target compounds

To improve the activity of adrenergic drugs, the structures should be protected from the metabolism catalyzed by MAO or COMT. The substitution at alpha-position to the amino nitrogen or steric hindrance on the nitrogen atom can protect the MAO oxidation. Certainly the introduction of the methyl substitution was confirmed by the study of Bondinell, *et al* (1980), which involved the phenylethylamine that exhibits phenylethanolamine *N*-methyl-transferase (PNMT) inhibition in alpha-adrenergic receptors in the brain. The alpha-methylation on phenylethylamine improves the activity, and it increases blood brain barrier (BBB) penetration of the compound. Thus its alpha-methylation substituent refers to increase the lipophilicity. This result was agreed with the study of Grunewald, *et al* (1988:433-444, 824-830; 1999: 1982-1990), who studied the 1,2,3,4-tetrahydroisoquinoline derivatives. The investigation try to vary the substituents in 1,2,3,4-tetrahydroisoquinoline and demonstrated that the methyl-substituent on the C-3 position of 1,2,3,4-tetrahydroisoquinoline increases the activity to inhibite PNMT. The increasing in activity may due to the increasing of lipophilicity of this compound and hence increasing the BBB penetration.

The introduction of methyl on the C-3 position of 1,2,3,4-tetrahydro-isoquinoline causes the steric hindrance effect to metabolic deamination by MAO, and it can increase the lipophilicity of compound, which is necessary for the desired activity. Moreover, all these natural products have in common a methyl group at the C-3 position of 1,2,3,4-tetrahydroisoquinoline. In the target compounds the methyl substitution is remained at the C-3 position. Furthermore the pattern of substitution in aromatic ring is also necessary for the activity. The general pattern in ancistrotectorine have commonly meta-oxygenated at C-6 and C-8 positions, which is not a good substrate catalyzed by COMT. Therefore the target compounds can be retained the 6,8-disubstituent in aromatic ring.

All above results support the parent structure in this study is 3-methyl-1,2,3,4-tetrahydroioquinoline nucleus. The modification in the parent nucleus shall be made in the C-1 position and in nitrogen atom (Figure 3).
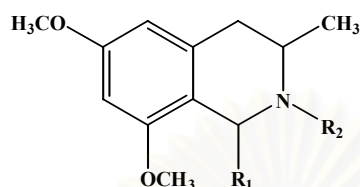
R$_1$: H, CH$_3$, CH$_2$OH, CH$_2$OMs, COOBu.

R$_2$: H, CH$_3$, -(CH$_3$)$_2$, CHO, benzyl group.

Figure 3 The chemical structures of target compounds

The synthetic approach for the studies

The 3-methyl-1,2,3,4-tetrahydroisoquinoline and derivatives are synthesized by the simple methods. In the study, the synthetic approach is divided into three major steps as follows.

1. To synthesize the starting material as *N*-benzylphenylethylamine (Scheme 1).

2. To cyclize the tetrahydroisoquinoline system through *N,O*-acetal intermediated using paraformaldehyde (Scheme 2).

3. To cyclize the tetrahydroisoquinoline system through *N,O*-acetal intermediated using butyl glyoxalate (Scheme 3).

Scheme 1 The synthetic procedures of *N*-benzylphenylethylamine
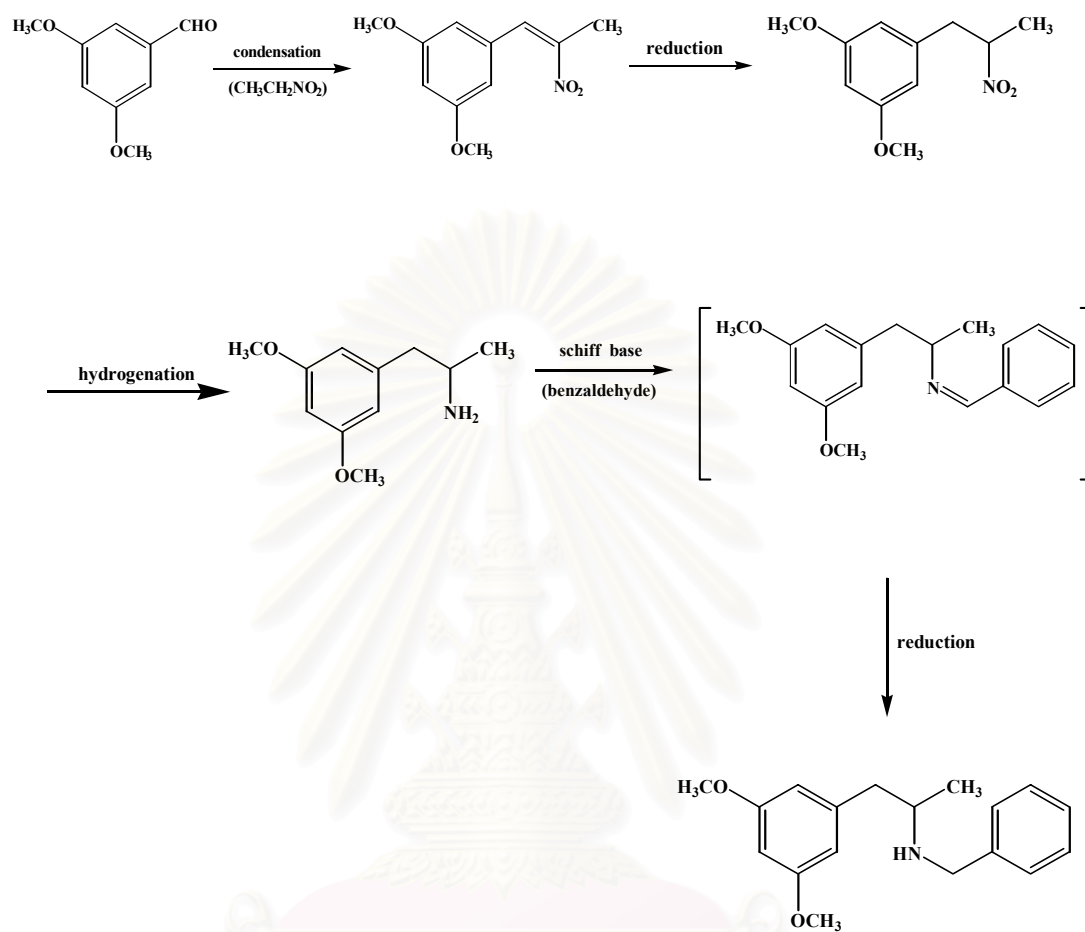
Scheme 2 The synthetic procedures for 1,2,3,4-tetrahydroisoquinoline through *N,O*-acetal intermediate with paraformaldehyde
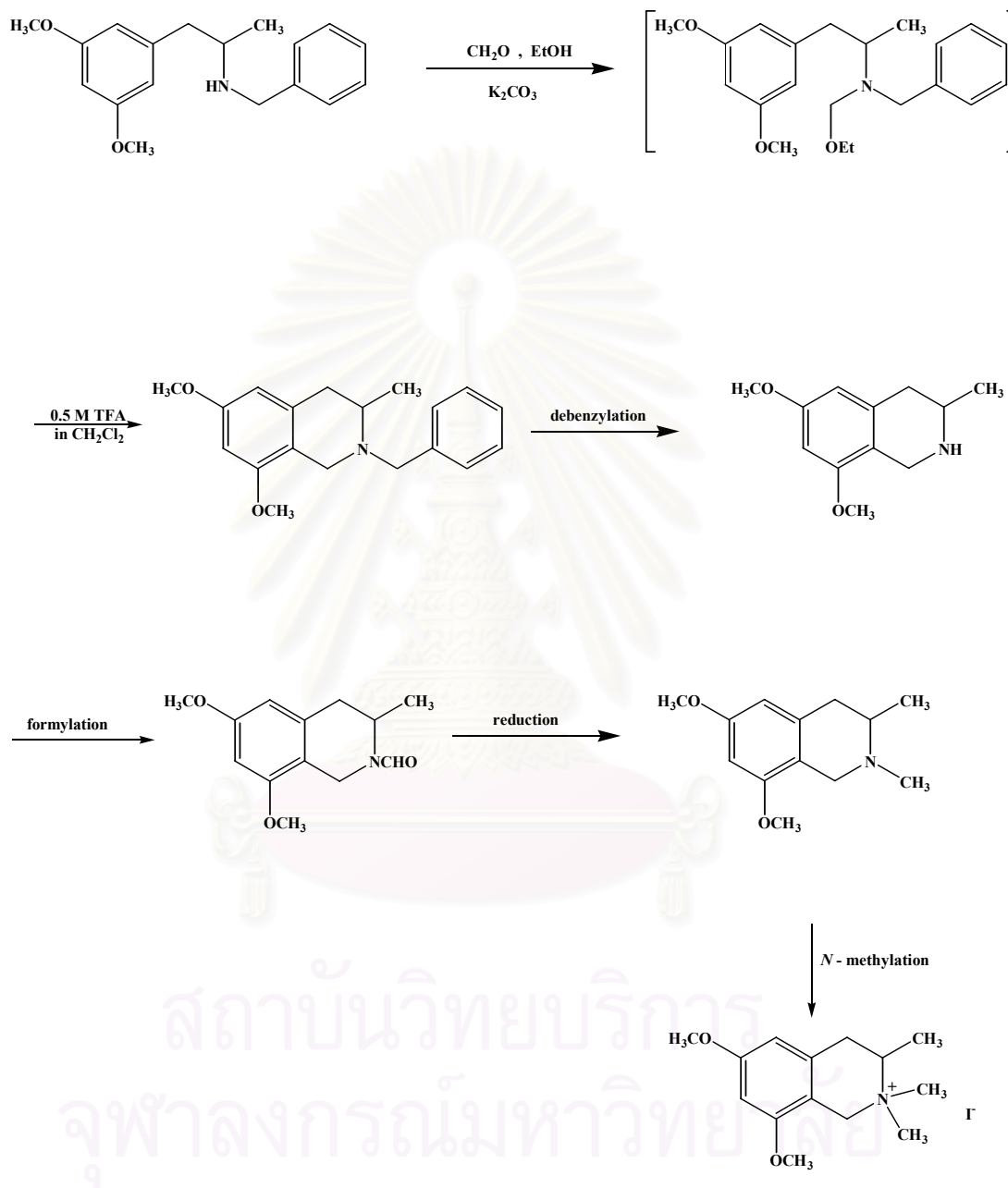
Scheme 3 The synthetic procedures for 1,2,3,4-tetrahydroisoquinoline through
N,O-acetal intermediate with butyl glyoxalate
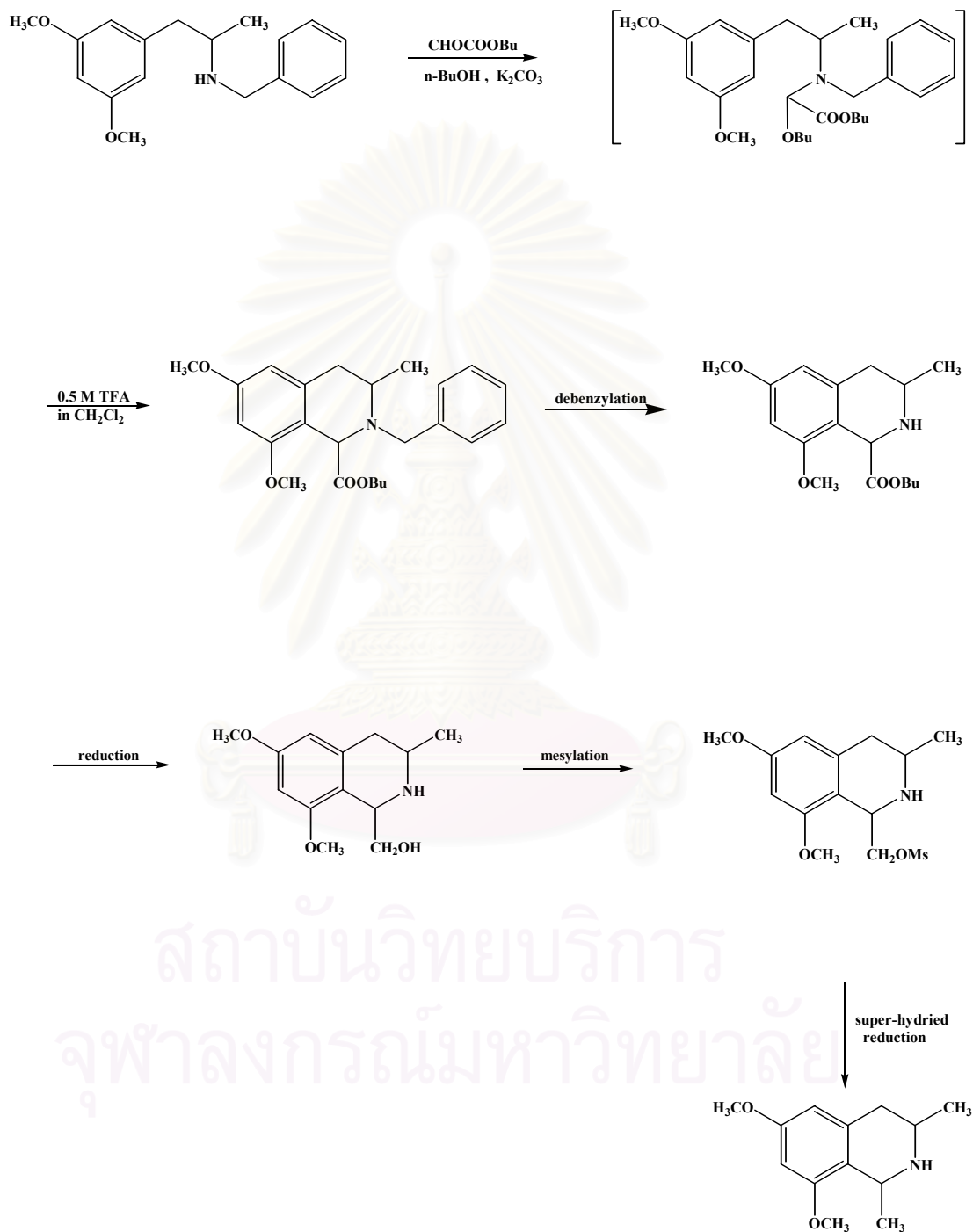
CHAPTER II

LITERLATURE   REVIEW

The adrenergic receptors (adrenoceptors) have been extensive studied. There are two major groups of receptors in mammalian tissue. Designated as α- and β-receptor, this hypothesis based on the differrent relative potencies of a series of adrenergic receptor agonist on various smooth muscle preparation. There are in turn subdivided into α_1, α_2, β_1, β_2, and β_3-receptor, based on their apparent drugs sensitivity (Delgado and Remers, 1998)

α-Adrenergic receptors of the CNS and in peripheral tissues affect a number of important physiological functions. In particular, α-receptors are involved in control of the cardiovascular system. For excample, constriction of vascular smooth muscle is mediated by both postjunctional α_1- and α_2-adrenergic receptors. In the heart, activation of α_1-receptor results in a selective inotropic response with little or no change in heart rate. In the brain, activation of postjunctional α_2-receptor reduces sympathetic outflow from the CNS, which in turn cause a lowering of blood pressure. The prototypical α_2-receptor is the presynaptic α-receptor found on the terminus of the sympathetic neuron. Interaction of this receptor with agonists such as NE and E results in inhibition of NE release from the neuron. Thus α_2-receptors play a role in the regulation of NE release. This receptor also mediates inhibition of acetylcholine release from parasympathetic nerve. Both α_1- and α_2-adrenergic receptors also play an important role in the regulation of a number of metabolic processes, such as insulin secretion and glycogenolysis.

β-Adrenergic receptors could be subdivided into β_1, β_2, and β_3 types. β_1-receptors are located mainly in heart, where mediate the positive inotropic and

chronotropic effects of the catecholamines, and found on the juxtaglomerular cells of the kidney, involved in increasing rennin secretion. β_2-receptors are located on smooth muscle through the body, involved in relaxation of the smooth muscle, producing such effects as bronchodilation and vasodilation. Moreover, they are also found in the liver, that promote glycogenesis. β_3-receptors are located on brown adipose tissue and involved in the stimulation of lipolysis. All three β-receptors are coupled to adenyl cyclase, which catalyzes the conversion of ATP to cAMP. None of these receptor is truly tissue-specific, because of many organs containing both α- and β-adrenoceptors, although usually one type predominates.

Tetrahydroisoquinoline (THIQ) has been received considerably attention in their biological activities. Some of them, such as 2-aminocarbonyl-1,2,3,4-tetrahydroisoquinolines are known as antiepileptics, repellants, and muscle relaxants (Venkov and Lukanov, 1989). Therefore, using ancistrotectorine as a lead molecule, the THIQ part may responsible for the pharmacological activity.

Structure-Activity Relationship (SAR) for Tetrahydroisoquinolines

To develop PNMT-inhibitor to adrenoceptors, Lam and Wellman (1980) have studied conformational restriction of various benzylamine through the incorporation of the side chain into a 1,2,3,4-THIQ, which results increasing inhibitory potency. However, these 1,2,3,4-THIQ ring systems still retain a high degree of flexibility. Grunewall and co-workers (1988) have studied influence of steric bulky on PNMT inhibition. In addition, 1-, 3-, and 4-methylsubstitution compounds were synthesized and substituted by methyl group in either benzylic position of THIQ result in as a PNMT inhibition activiity. The 3-methyl-THIQ (3, $K_i = 3.0$ μM) shows better activity as an inhibitor than when compare with THIQ (1, $K_i = 10.3$ μM), 1-methyl-THIQ (2, $K_i = 33.1$ μM), and 4-methyl-THIQ (4, $K_i = 70.1$ μM) (Figure 4).

1 (K_i = 10.3 μM)

2 (K_i = 33.1 μM)

3 (K_i = 3.0 μM)

4 (K_i = 70.1 μM).

5 (K_i = 174 μM)

6 (K_i>2000 μM)

7 (K_i > 2000 μM)

8 (K_i = 612 μM)

9 (K_i=612 μM)

10 (K_i = 52 μM)
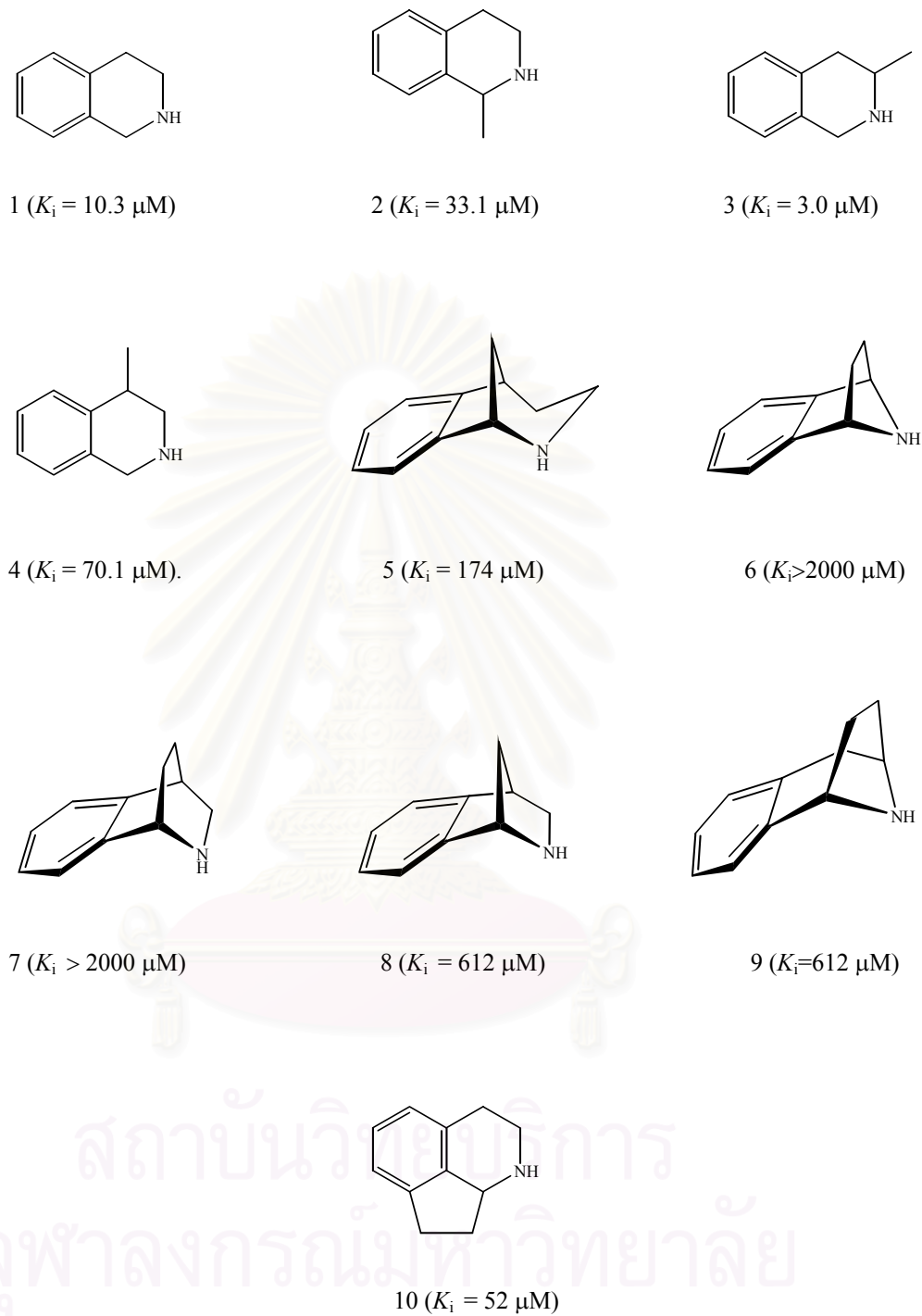
Figure 4   In vitro PNMT inhibitory activity exhibited by conformationally defined analogs of 1,2,3,4-tetrahydroisoquinolines

The possibility that methyl substitution of THIQ might induce conformation changes in the B ring. Therefore, full conformational restriction of B ring in analogs [5]-[10] were synthesized (Figure 4). The benzylamine analogs 5 (K_i = 174 μM), 6 (K_i > 2000 μM), 7 (K_i > 2000 μM), 8 (K_i = 612 μM), 9 (K_i = 153 μM), and 10 (K_i = 52 μM), each possessing a two-carbon bridge attached to both benzylic position incapable of competitive effectively with phenylethylamine or tetrahydroisoquinoline for the active site. Thus the introduction of bridging units across the B ring of THIQ results in dramatically reduced efficacy as an inhibitor of PNMT catalysis. The previous study found 3-substitution results in enhanced potency. Later, Grunewall and co-workers (1999) have synthesized and evaluated other 3-substituted THIQ analogues that vary in both steric and electronic character, as show in the Table 1.

Table 1 In vitro PNMT inhibitory activity exhibited by 3-substituted analogs of 1,2,3,4-tetrahydroisoquinoline
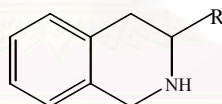
compounds	R	K_i ± SEM, μM
1	H	10.3 ± 0.86
3	CH_3	3.0 ± 0.19
11	CO_2H	> 2000
12	CO_2CH_3	69.5
13	CH_2OH	2.4 ± 0.24
14	$CONH_2$	40.5 ± 2.12
15	CH_2CH_3	23.9 ± 1.00

Extension of the methyl side chain in compound 3 (K_i = 3.0 µM), by a single methylene unit results in diminished potency for 3-ethyl-THIQ (15, K_i = 23.9 µM), suggesting that this zone for the active site is spatially compact. Since the carbonyl containing analogs 3-methoxycarbonyl-THIQ (12, K_i = 69.5 µM) and 3-aminocarbonyl-THIQ (14, K_i = 40.5µM) are much less capable of forming a strong enzyme-inhibitor dissociable complex compared to straight-chain derivatives possessing a similar steric component. The good activity of 3-hydroxymethyl-THIQ (13, K_i = 2.4 µM) as a PNMT inhibitor cannot be explained solely by steric tolerance for this side chain, but an active-site amino acid residue capable of specific e.g. hydrogen bonding interaction is located in closed proximity to the 3-position of bound THIQ.

Introduction of steric bulky groups around the 3-position of THIQ were found to be selective inhibitor of PNMT due to their decreased affinity for the α_2-adrenoceptor. This substitution on the 3-position should be sufficiently lipophilic to penetrate the BBB (Grunewal, 1999: 3315-3323, 3588-3601). While the substituents on aromatic ring of THIQs are potent inhibitor of PNMT. Furthermore the most of these compounds also exhibit strong affinity for the α_2-adrenoceptor.

Bondinell *et al* (1980) have synthesized the chloro-substututed, THIQ and concluded that the chlorine at the position-7 is optimal when compared to the position-5, -6, or-8 (Table 2) and the 7, 8-dichloro-substitution pattern resulted in maximum inhibition of PNMT, and result a decreasing in blood pressure and heart rate, due to the strong affinity for the α_2-adrenoceptor. These results indicated that aromatic substitution of THIQ can exhibit high PNMT inhibitor and high α_2-adrenoceptor activity.

Table 2 In vitro PNMT inhibitory activity exhibited by chloro-substituted analogs of 1,2,3,4-tetrahydroisoquinoline
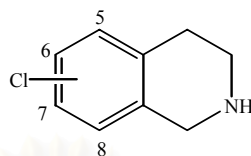
compounds	position of Cl substituted	in vitro PNMT inhibition (%)	
		10^{-4} M	10^{-6} M
1		73	3
16	5	81	6
17	6	81	19
18	7	98	60
19	8	96	52
20	5,6	93	17
21	5,7	95	24
22	5,8	89	15
23	6,7	98	43
24	6,8	76	6
25	7,8	98	97
26	5,7,8	97	73
27	6,7,8	96	86
28	5,6,7,8	95	74

The methyl substitution on position-1 of THIQ results in PNMT inhibition activity, but less active than that with substitution of position-3 of THIQ. Although, 1-benzyl-THIQ derivatives such trimetoquinol was also synthesized (He, 2000), and prove to be the β-adrenergic receptor agonist. Variation of the substituent in the aromatic ring A of trimetoquinol afford the β3-adrenergic receptor selectivity. While 1-benzylsubstituents of isoquinoline such papaverine is a potent inhibitor of phosphodiesterases (Walker, 1983).

Trimetoquinol   papaverine
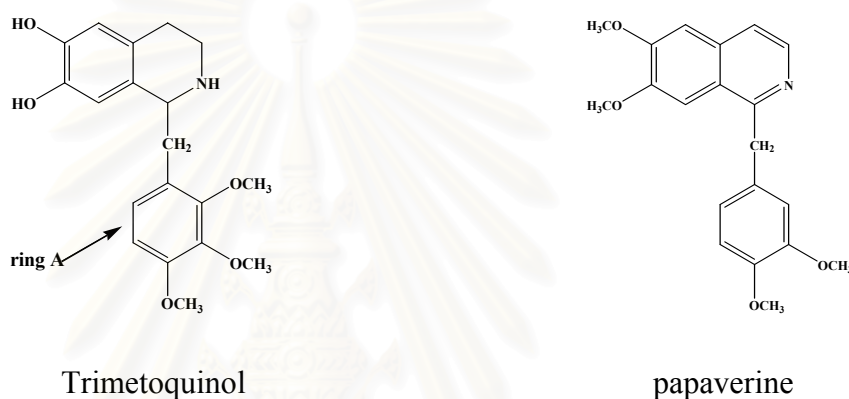
With all previously reports substitution at position-3 with lipophilic groups such as a methyl group result in increasing the activity and the compound could penetrate through BBB well. Therefore methyl-substitution at position-3 was designed and remained in the target compounds. While aromatic substitution in position-6 and -7 is necessary but subject to the metabolic degradation catalyst by for COMT. The modification as 6,8-disubstituent on aromatic ring could prevent COMT metabolism. Furthermore the variation 1-substituent have shown the variation of pharmacological activity and potent the activity.

General Method for the Preparation of Tetrahydroisoquinoline System

In general, the method for the synthesis of isoquinoline ring system can be classified systematically in five ways (Apsimon, 1977, vol.3) according to the mode of formation of the pyridine ring (Figure 5). The first type is ring closure between the benzene ring and the carbon atom, which forms the C_1-position of the resulting isoquinoline ring. The second type uses bond formation between the C-1 position and nitrogen atom. The third type uses cyclization by the combination of nitrogen atom with the C-3 position. The fourth type is due to the formation of isoquinoline ring by ring closure between the C-3 and C-4 position, and the fifth type necessitate ring closure between the benzene ring and C-4 position.

type 1   type 2   type 3

type 4   type 5
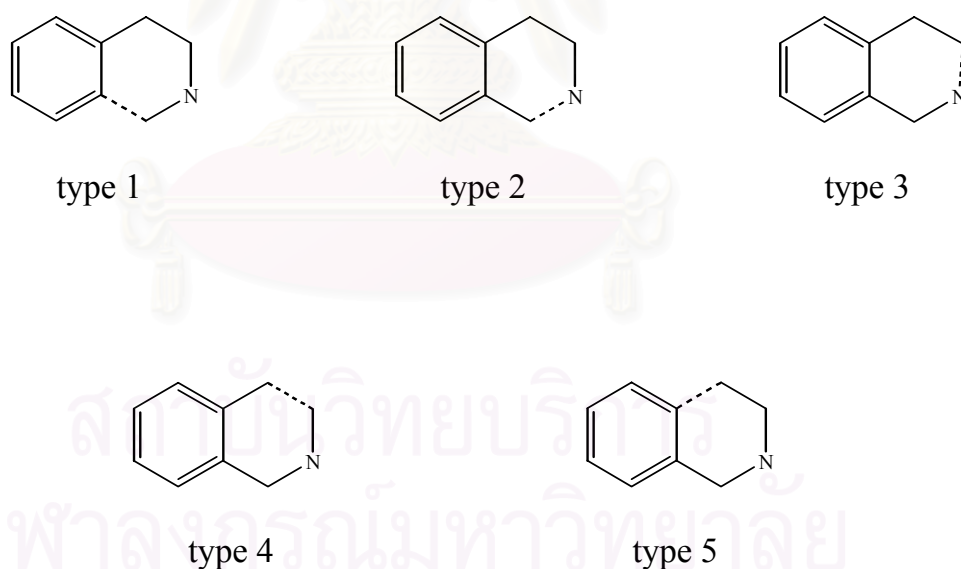
Figure 5 The general methods for the synthesis of isoquinoline ring system

Although all of these reaction types are known, the most popular reaction are the type 1 and 5. This investigation has been followed by type 1, the classical formation as the Bischer-Napieraski, the Pictet-Spengler, and the other reactions, especially the method of Kubo and co-workers (1987), which have been modified by conventional methods to give a mild and efficient methods as cyclized through *N,O*-acetal intermediate are described as follows.

1. The Bischler-Napieralski Reaction

The Bischler-Napieralski reaction consists in the cyclodehydration of β-phenylethylamide (amide compound) by heating to high temperatures with lewis acid such as phosphorus pentaoxide and phosphoryl chloride. In an inert solvent to give a 3,4-dihydroisoquinline which must be reduced to a 1,2,3,4-tetrahydroisoquinoline with sodium borohydride (Figure 9), but the yields are very poor under this high temperature condition.

amide
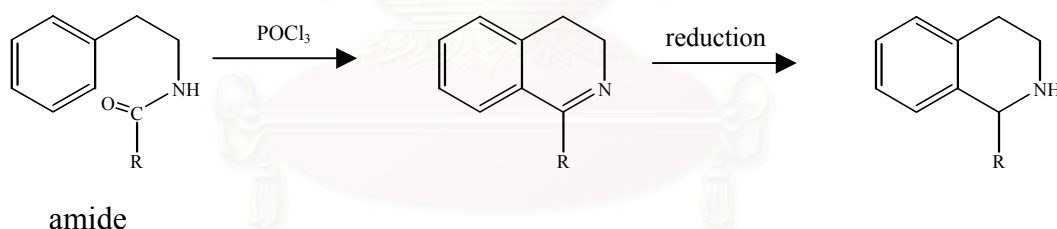
The modifications using lower temperatures and milder condensing agents have improved the reaction, and it has become the most frequently used method of preparing isoquinoline and tetrahydroisoquinoline derivatives.

The Bischler-Napieralski reaction involves an electrophilic attack upon an aromatic ring by a carbonium ion catalyze by an acid-catalyzed reaction. The reactivity of the aromatic nucleus depends on electron density at the cyclized position as shown in Figure 6.
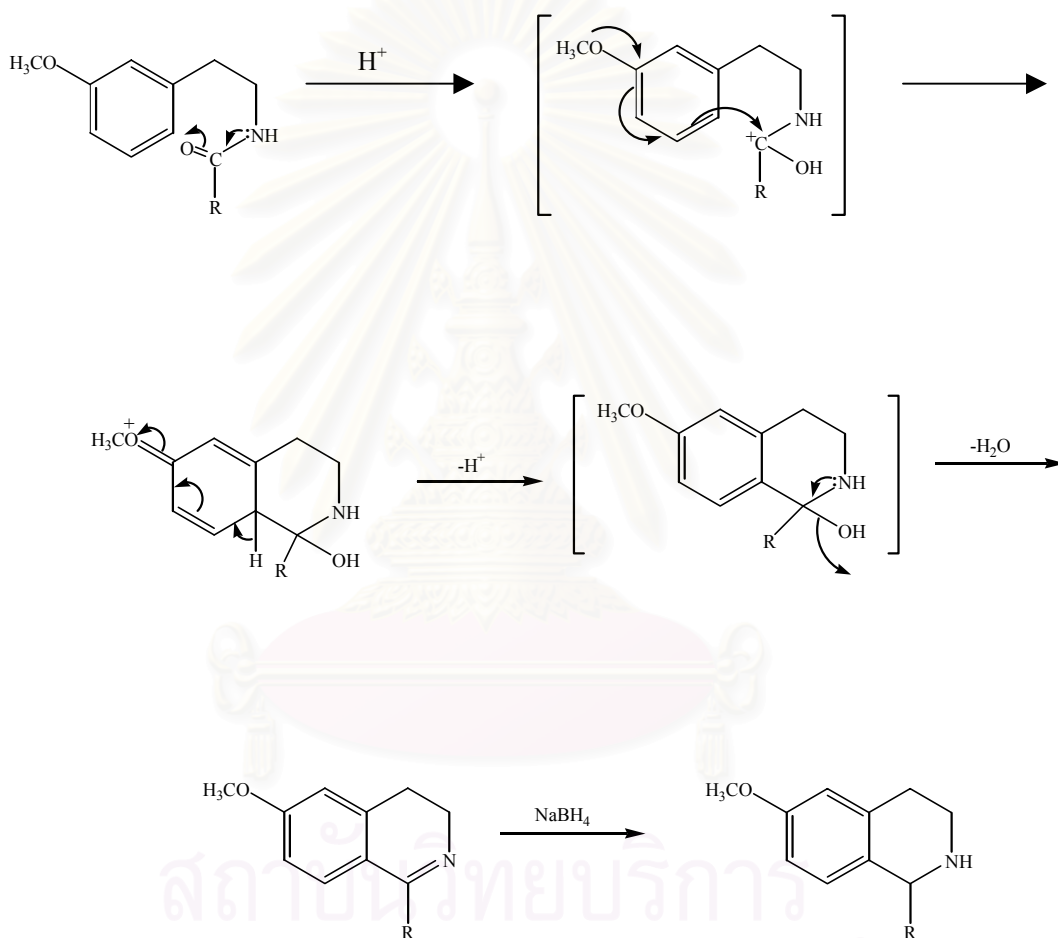
Figure 6 The proposed mechanism of Bischler-Napieralski cyclization

2. The Pictet-Spengler Reaction

The Pictet-Spengler reaction, which is one of the special cases of the Mannich reaction, consists in the condensation of a β-arylethylamine with a carbonyl compound to yield a 1,2,3,4-tetrahydroisoquinoline. Becker and Decker carried out the reaction two steps as the intermediate azomethine was often formed by schiff base reaction before fused ring by concentrated acid
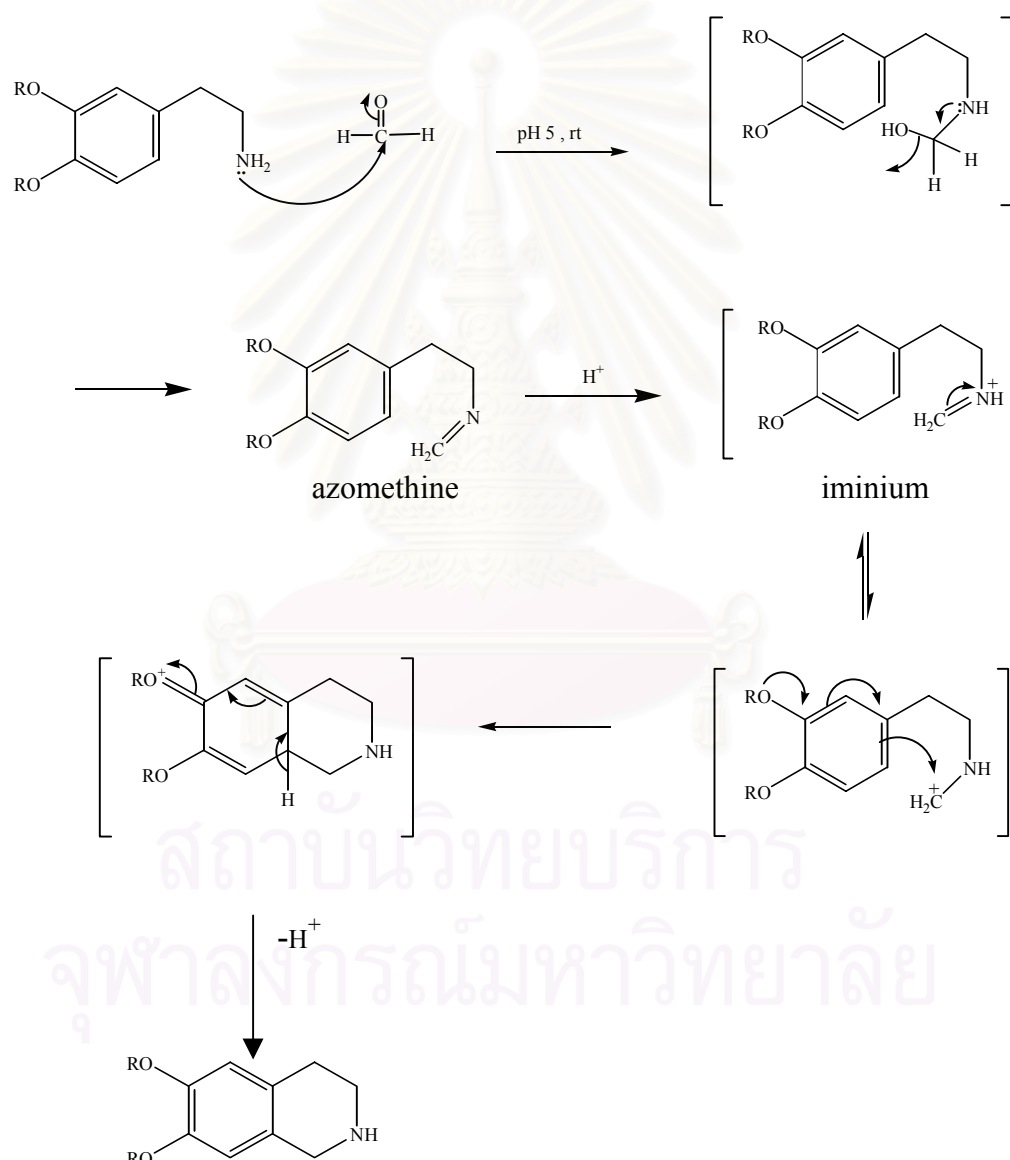
Figure 7 The proposed mechanism of Pictet-Spengler reaction

The electronic mechanism of the Pictet-Spengler reaction has not yet been investigation completely, but it is well known that schiff base is isolated as an intermediate in some case and then be cyclized by acid (Figure 7). This reaction also depends upon the great electron density at the cyclized position. Thus, the electron donating group would be existed at the para-position to the cyclized position in phenylethylamine was easily cyclized. Formaldehyde as carbonyl compound has been employed most frequently in the conventional Pictet-Spengler reaction. Generally the yield of this reaction is quite high.

3. Other synthetic reactions.

Several modifications of the synthesis have been developed with wider applicability. Very useful in this respect or iminium ions can prepared from N-oxide with sulphur dioxide, acetic anhydride, or trifluoro-acetic anhydride (Bather *et al*, 1978) (Figure 8).
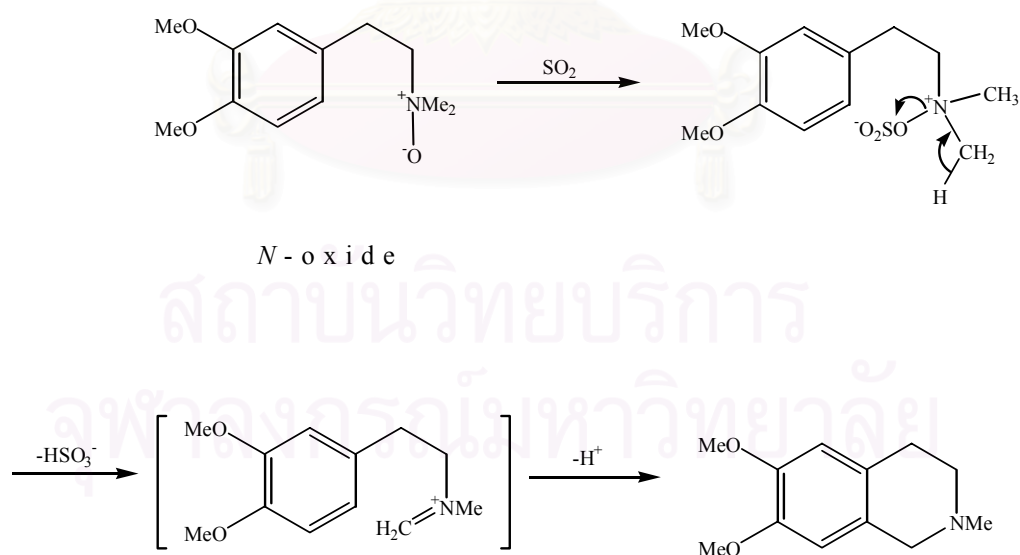
Figure 8 Synthesis of isoquinolines through *N*-acyliminium from *N*-oxide

Then one derived from a suitable constructed system should be able to undergo intermolecular electrophilic substitution to give a tetrahydroisoquinoline. Later, a various acyl chlorides such as sulfonyl chlorides (Lukanov *et al*, 1987), acetyl chloride (Venkov *et al*, 1989) were used to adducts with azomethines to give *N*-acyliminium before synthesized to tetrahydroisoquinoline (Figure 9). In addition to, carbonyl compounds were used to prepare *N*-acyliminium (Mollov *et al*, 1978; Lukanov *et al*, 1987; Venkov and Lukanov, 1992, 1996). Its found that the reaction can be carried out with the same results in an acyl chloride.
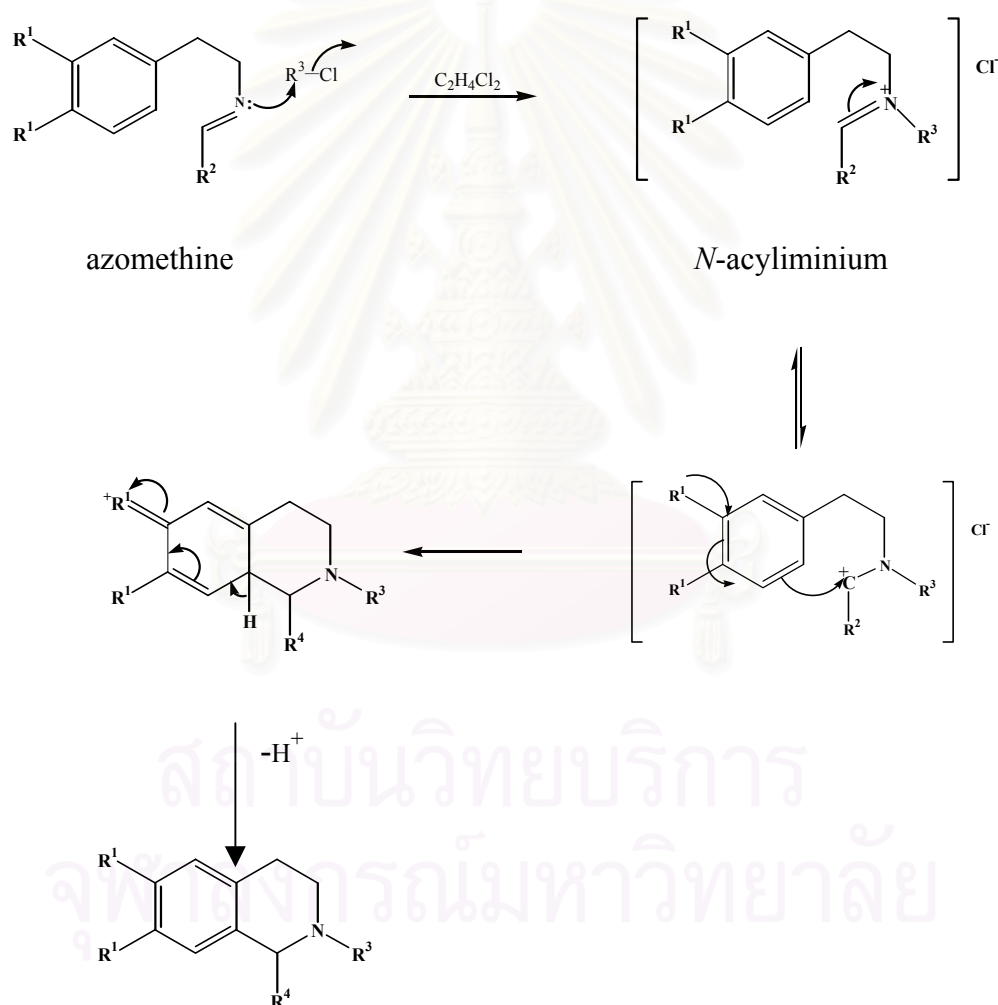
Figure 9 Synthesis of tetrahydroisoquinoline through *N*-acyliminium from azomethine

Kubo and co-workers (1987) reported the synthesis of 1,2,3,4-tetrahydroisoquinoline through *N,*O-acetal intermediate, the method is mild and efficient with application (Figure 10).
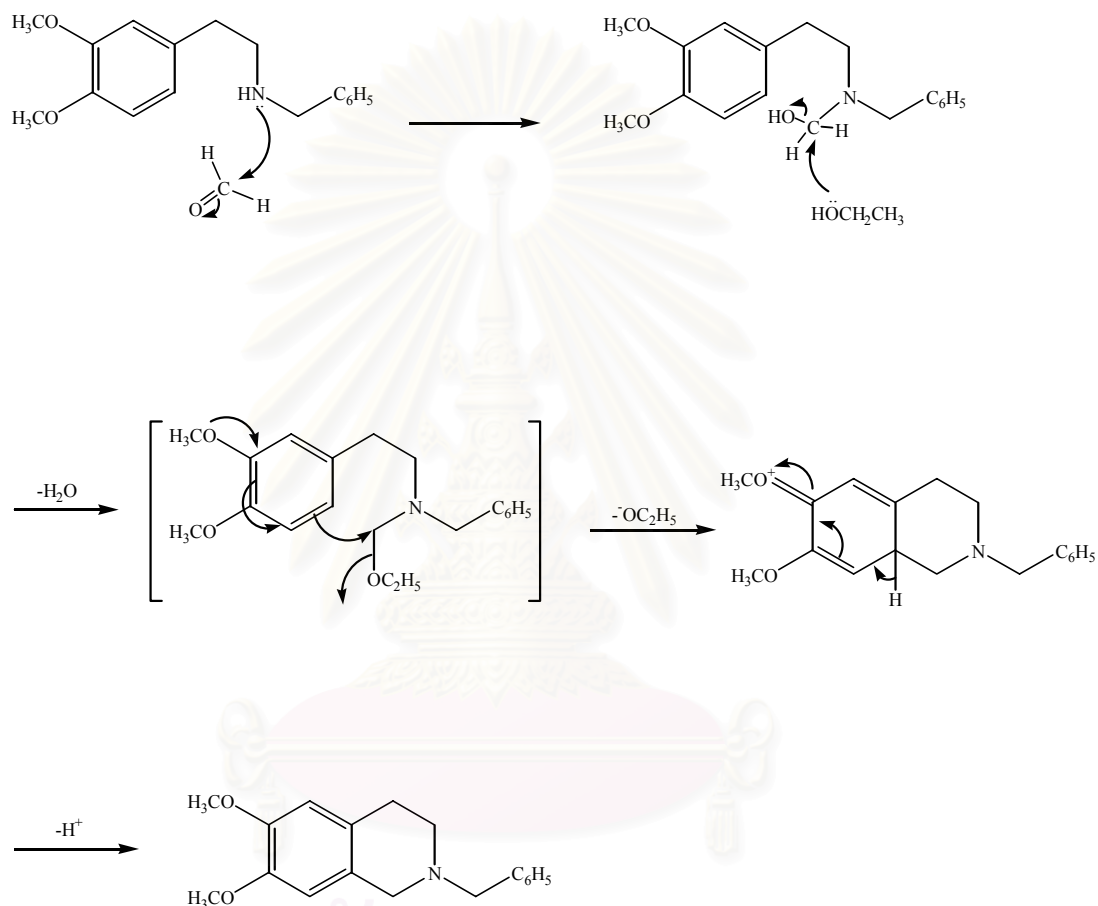
Figure 10 Synthesis of tetrahydroisoquinoline through *N,O*-acetal intermediate

General methods concerning the preparation of 3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives

1. Reduction of carbon-carbon double bonds

Catalytic hydrogenation : Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents can be catalytically hydrogenated. Catalytic hydrogenation on almost 99% known alkenes and hydrogen can be done at temperatures between 0 and 275 $^{\circ}$C (Morison and Boy, 1983). Many catalysts have been used for example, raney nickel, PtO_2, rhodium, ruthenium, palladium, and copper chromite. Hydrogenation in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures.

Metallic hydrides : Catalytic hydrogenation is most often used, double bond may be reduced by other reagent as well. Among these are sodium in methanol, chromous ion, zinc and acids, lithium and aliphatic amine. However metallic hydrides, such as lithium aluminium hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) do not in general reduced carbon-carbon double bond, although this can be done in special cases, where double bonds is polar.

2. Reaction of esters to alcohols

An esters can be reduced in two ways: a) by catalyst hydrogenation using molecular hydrogen, or b) by chemical reduction

Catalyst hydrogenation : Cleavage by hydrogen (Hydrogenolysis) of the ester requires more severe conditions than simple hydrogenation, high

pressures and elevated temperatures are requied. This reaction presents over catalyst such as copper chromite or palladium.

Chemical reduction : It is carried out by using of sodium metal and alcohol, or lithium aluminium hydride ($LiAlH_4$). $LiAlH_4$ is the most common reagent used to reduce an ester to an alcohol in an ether solvent, such as diethyl ether or tetrahydrofuran (THF). Anhydrous condition is required due to the very high reactivity of $LiAlH_4$ toward water. Generally, the working up for this reaction required addition of ethyl acetate or water to decompose excessive $LiAlH_4$. Heating of that reaction is usually sufficient to ignite the gaseous (Malkar and Komar, 1998 ; Guo and Sindelar, 1998). Increasing selective transformation of ester into alcohol was undergo the reaction below room temperature (Dalla and Catteau, 1999).

3. Reduction of nitro to amine

The nitro compounds can be reduced in two general ways: a) by catalytic hydrogenation using molecular hydrogen, or b) by chemical reduction, usually by a metal and acid.

Catalytic hydrogenation : hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with catalyst, such as nickel, or platinum, or palladium under hydrogenation gas. This method cannot be used when the molecule also contains some other easily hydrogenated group, such as carbon-carbon double bond.

Chemical reduction : This methods is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam distilled from the reaction mixture. The crude

amine may be contaminated with some unreduced nitro compounds, which can be separated by the basic properties of the amine; the amine is soluble in acid aqueous, which the nitro compound is not.

4. Schiff base

Schiff bases known as imines (Pine, 1987) are prepared from the reaction between primary amines and aldehydes or ketones to produce compounds possessing a carbon-nitrogen double bond. Imines are often not very stable, yet it may be important intermediates in some reactions.
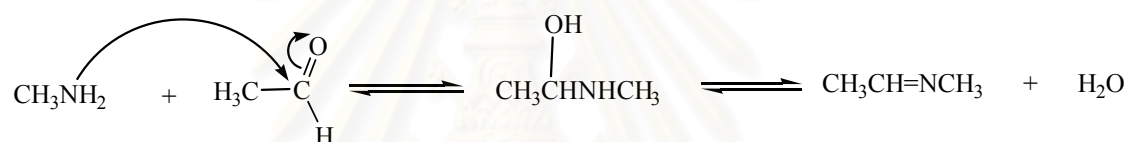
The reaction is more rapid at pH of 3.5 and slow at pH >5, the acidity of the medium increases the reaction rate. In the reaction, loss of water from the carbinolamine, an elimination reaction, is catalyzed by acid (Figure 11). Furthermore, dehydration is the rate-controlling step.
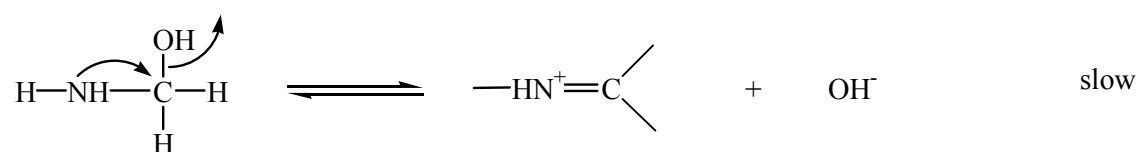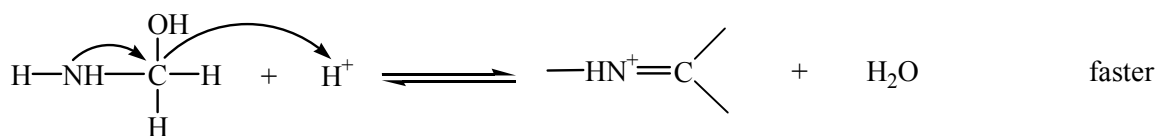
Figure 11 The effect of acid on dehydration

5. Oxidization of glycol to carbonyl groups

Glycol (1,2-diol) is oxidized with periodic acid (HIO_4) or lead tetraacetate by cleavage of carbon-carbon single bond between the hydroxy groups. Two carbonyl groups are formed in the process. The reaction has been formulated as proceeding thought cyclic ester, which undergo 1,2-elimination (Pine, 1987), illustrated in Figure 12.
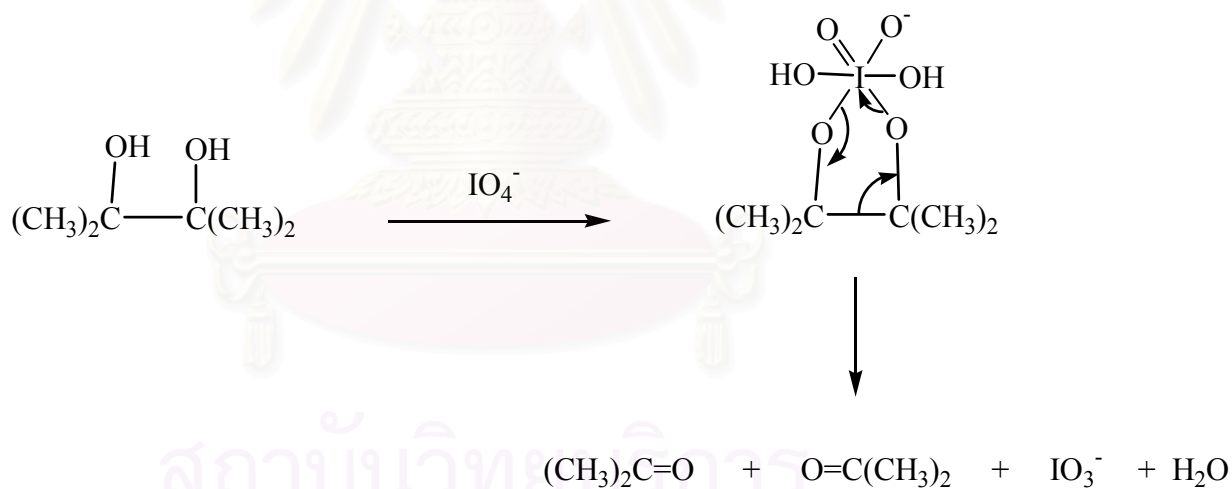
Figure 12 Oxidation of the glycol by periodic acid

CHAPTER III

EXPERIMENTS

Instruments

1. Melting Point Apparatus ; Buchi Capillary Melting Point Apparatus

2. Infrared Spectrophotometer ; Perkin Elmer Model 2000.

3. Nuclear Magnetic Resonance Spectrophotometer ; Bruker Spectrospin 300 (300 MHz).

4. Mass Spectrometer ; Platform II.

5. Elemental Analysis ; Perkin Elmer model 2000.

Chemicals

1. Acetic anhydride (BDH)

2. Benzaldehyde (Merck)

3. Benzene sulfonyl chloride (Merck)

4. Dibutyl L-(+)-tartrate (TCI)

5. 4-(Dimethylamino)pyridine (Fluka)

6. 3,5-Dimethoxybenzaldehyde (TCI)

7. Formic acid (Merck)

8. Lithium aluminium hydride (Fluka)

9. Methane sulfonyl chloride (Merck)

10. Methyl iodide (BDH)

11. Nitroethane (TCI)

12. 10 % Palladium on activated charcoal (TCI)

13. Paraformaldehyde (Merck)

14. Periodic acid (Fluka)

15. Sodium borohydried (Fluka)

16. Trifuoroacetic acid (Fluka)

General Procedures for Synthesis of 3-Methyl-1,2,3,4-tetrahydroiso-quinoline Derivatives

I. Procedures for Synthesis of *N*-benzyl-2-(3,5-dimethoxypenyl)-1-methylethylamine, the starting material

1. 3,5-dimethoxy-β-nitrostyrene (CU-19-01)

Ammonium acetate (9.29 g, 120.5 mmol) was added to a stirred solution of 3,5-dimethoxybenzaldehyde (20.0 g, 120.5 mmol) in nitroethane (50 ml) at room temperature. The mixture was refluxed for 2 h, then poured into water (100 ml) and extracted with ethyl acetate (3×100 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The remaining yellow solid was recrystallized from MeOH to afford prisms of products. Yield: 26.37 g. (98%); m.p. 84-86 ^{0}C.

IR	1649	cm^{-1}	(v_s C=C, aliphatic)
(KBr)	1519	cm^{-1}	(v_{as} NO_2)
	1321-1310	cm^{-1}	(v_s NO_2)
	1210	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1157	cm^{-1}	(v_{as} C-<u>O-C</u>)
	1060	cm^{-1}	(v_s C=<u>C-O</u>-C)
	(Figure 13)		

^{1}H -NMR	2.54	ppm	(s, 3H, 1-CH$_3$)
(CDCl$_3$/TMS)	3.84	ppm	(s, 6H, 3$^/$ and 5$^/$-OCH$_3$)
	6.54	ppm	(1H, H-4$^/$)
	6.56	ppm	(2H, H-2$^/$ and H-6$^/$)
	8.02	ppm	(s, 1H, H-2)
	(Figure 14)		

EIMS	223 (M$^+$), 177 (57.76%), 119 (46.78%), 103(59.47%), 91
	(100.00%), 77 (71.85%), 63 (61.13%)
	(Figure 15)

2. 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)

A stirred solution of 3,5-dimethoxy-β-nitrostyrene (0.723 g, 3.24 mmol), silica gel (6.0 g) in the mixtures of CHCl$_3$ (35 ml) and IPA (11 ml) was cooled in ice-water, and sodium borohydride (0.491 g, 13.0 mmol) was added over 1 h. The reaction was stirred at room temperature for 1 h. Glacial acetic acid was slowly added to the stirred reaction. Then silica gel was eliminated by filtration and washed with chloroform (100 ml). The combined filtrates were washed with 5 % sodium bicarbonate (3×100 ml) and water (3×100 ml), dried, and concentrated under reduced pressure to give the yellow oil of products. Yield: 5.01 g (99%).

IR	1550	cm^{-1}	(v_{as} NO$_2$)
(Neat)	1353-1322	cm^{-1}	(v_s NO$_2$)
	1205	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1153	cm^{-1}	(v_{as} C-<u>O-C</u>)
	1065	cm^{-1}	(v_s C=<u>C</u>-O-C)
	(Figure 16)		

¹H -NMR	1.52	ppm	(d, J=6.5 Hz, 3H, 1-CH$_3$)
(CDCl$_3$/TMS)	2.91	ppm	(dd, J=13.7, 6.7 Hz, 1H, H-2)
	3.25	ppm	(dd, J=13.7, 7.3 Hz, 1H, H-2)
	3.75	ppm	(s, 6H, 3′ and 5′-OCH$_3$)
	4.77	ppm	(m, 1H, H-1)
	6.30	ppm	(s, 2H, H-2′ and H-6′)
	6.34	ppm	(s, 1H, H-4′)

(Figures 17, 18)

EIMS   225 (M$^+$), 178 (6.72%), 151 (16.04%), 91 (31.34%), 85
(68.28%), 83 (82.09%), 57 (67.16%), 55 (88.06%), 50 (100%)
(Figure 19)

3. 2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-03)

A solution of 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroehane (4.220 g, 18.76 mmol) in ethanol (10 ml) was hydrogenated over 10 % Pd/C (0.34 g, 5 % mmol of starting material) under slightly pressure of hydrogen gas. The catalyst was removed by filtration and washed with ethanol (100-200 ml). The combined filtrates were evaporated to give the yellow oily residues. The resulting residues were dissolved in 100 ml of benzene and extracted   with 1 N HCl (3×100 ml). The acidic aqueous portion was basified and adjusted to pH = 9-10 with ammonium solution, and then extracted with chloroform (3× 100 ml) and washed with water (3×100 ml). The combined extracts were dried and evaporated to afford pale yellow oil of products. Yield: 3.07g. (84%).

IR	1596	cm^{-1}	(ν C=C, aromatic)
(Neat)	1205	cm^{-1}	(ν_{as} C=<u>C-O</u>-C)
	1152	cm^{-1}	(ν_{as} C-<u>O-C</u>)
	1058	cm^{-1}	(ν_s C=<u>C-O</u>-C)
	(Figure 20)		

^{1}H -NMR	1.12	ppm	(d, J=6.3 Hz, 3H, 1-CH$_3$)
(CDCl$_3$/TMS)	1.67	ppm	(s, 1H, NH)
	2.44	ppm	(dd, J=13.1, 8.3 Hz, 1H, H-2)
	2.66	ppm	(dd, J=13.1, 5.1 Hz, 1H, H-2)
	3.16	ppm	(m, 1H, H-1)
	3.77	ppm	(s, 6H, 3$^/$ and 5$^/$-OCH$_3$)
	6.34	ppm	(m, 3H, H-2$^/$, H-4$^/$ and H-6$^/$)
	(Figures 21, 22)		

EIMS	192 (5.2%), 152 (2.24%), 149 (7.29%), 91 (25.93%), 85
	(73.03%), 83 (92.97%), 55 (66.09%), 50 (100%)
	(Figure 23)

4. *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine

(CU-19-04)

Benzaldehyde (7.77 g, 73.35 mmol) was added to a solution of 2-(3,5-dimethoxyphenyl)-1-methylethylamine (2.86 g, 14.67 mmol) in benzene (100 ml). The mixture was refluxed under a Dean-Stark separator. The solvent was removed under reduced pressure to give the intermediate Schiff base yellowish oil. This was dissolved in EtOH (100 ml) and NaBH$_4$ (1.67 g, 44.0 mmol) was added in one portion with stirring. The mixture was stirred at the

room temperature for overnight. The excess $NaBH_4$ was decomposed with glacial acetic acid, evaporated under reduced pressure to give the resulting residues. This was diluted with ethyl acetate (100 ml) and extracted with 1 N HCl (3×100 ml). The collecting aqueous fractions were basified and adjusted to pH = 9-10 with ammonia solution. The basic aqueous fraction was extracted with chloroform (3×100 ml), washed with water (3×100 ml), dried, and concentrated under reduced pressure to give the yellow oil of products. Yield: 2.14 g. (75%).

IR	3296	cm^{-1}	(v N-H)
(Neat)	1596	cm^{-1}	(v C=C, aromatic)
	1445-1432	cm^{-1}	(v O-CH$_3$)
	1205	cm^{-1}	(v_{as} C=$\underline{C}$-$\underline{O}$-C)
	1152	cm^{-1}	(v_{as} C-$\underline{O}$-C)
	1054	cm^{-1}	(v_s C=$\underline{C}$-$\underline{O}$-C)
	(Figure 24)		

^{1}H -NMR	1.09	ppm	(d, J=6.2 Hz, 3H, 1-CH$_3$)
(CDCl$_3$/TMS)	1.75	ppm	(s, 1H, NH)
	2.57	ppm	(dd, J=13.2, 6.2 Hz, 1H, H-2)
	2.67	ppm	(dd, J=13.3, 7.4 Hz, 1H, H-2)
	2.93	ppm	(m, 1H, H-1)
	3.69	ppm	(d, J=13.2 Hz, 1H, N-CH$_2$Ph)
	3.74	ppm	(s, 6H, 3$'$ and 5$'$-OCH$_3$)
	3.80	ppm	(d, J=13.3 Hz, 1H, N-CH$_2$Ph)
	6.30	ppm	(s, 3H, H-2$'$ and H-4$'$ and H-6$'$)
	7.18-7.34	ppm	(5H, aromatic)
	(Figures 25, 26)		

EIMS   285(M$^+$), 283 (7.76%), 151 (36.41%), 134 (85.35%), 91 (100%), 83(61.32%), 77 (57.54%), 65 (63.41%)
(Figure 27)

II. The Procedures for Cyclization of *N*-benzyl-2-(3,5-dimethoxy-phenyl)-1-methylethylamine to the Tetrahydroisoquinoline with Para-formaldehyde

1. 2-Benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydro-isoquinoline (CU-19-05)

A solution of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethyl-amine (1.00 g, 3.5 mmol) and potassium carbonate (1.94 g, 14.0 mmol) in ethanol (25 ml) was stirred for 10 min at room temperature. Paraformaldehyde (0.16 g, 5.2 mmol) was then added in one portion, the mixture was stirred overnight at room temperature, then filtered. The filtrate was evaporated under reduced pressure to give the residue *N,O*-acetal which was used without purification. To the *N,O*-acetal was added 0.5 M TFA in CH_2Cl_2 (70 μl, 3.5 mmol) **(Note 1)**. This mixture was stirred at 0 ^oC for 1 h, then diluted with cool water (100 ml) and extracted with chloroform (3×100 ml). The combined extracts were washed with water, dried, and evaporated to dryness. The residue was chromatographed on silica gel eluting with 1% of MeOH in CH_3Cl_3 to give products. Yield: 0.95 g (91%).

Anal. calcd. for $C_{19}H_{23}NO_2$ C,76.767; H,7.806; N,4.716

    Found   C,76.558; H,7.617; N,4.746

IR	2961	cm^{-1}	(v C-H, aromatic)
(Neat)	1602	cm^{-1}	(v C=C, aromatic)
	1205	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1147	cm^{-1}	(v_{as} C-<u>O-C</u>)
	1051	cm^{-1}	(v_s C=<u>C-O</u>-C)
	(Figure 28)		

^{1}H -NMR	1.07	ppm	(d, J = 6.4 Hz, 3H, 3-CH$_3$)
(CDCl$_3$/TMS)	2.51	ppm	(dd, J = 16.2, 4.7 Hz, 1H, H-4)
	2.95	ppm	(dd, J = 16.4, 4.8 Hz, 1H, H-4)
	3.05	ppm	(m, 1H, H-3)
	3.57	ppm	(s, 2H, N-CH$_2$Ph)
	3.58	ppm	(d, J = 13.3, Hz, 1H, H-1)
	3.68	ppm	(s, 3H, 6- or 8-OCH$_3$)
	3.74	ppm	(s, 3H, 8- or 6-OCH$_3$)
	3.80	ppm	(d, J = 13.3 Hz, 1H, H-1)
	6.21	ppm	(s, 1H, H-5 or H-7)
	6.23	ppm	(s, 1H, H-7 or H-5)
	7.28	ppm	(5H, aromatic)
	(Figures 29, 30)		

COSY   (Figure 31)

^{13}C-NMR	13.75	ppm	(3-CH$_3$)
(CDCl$_3$/TMS)	36.01	ppm	(C-4)
	46.29	ppm	(N-CH$_2$Ph)
	50.89	ppm	(C-3)
	55.24	ppm	(OCH$_3$)
	56.08	ppm	(OCH$_3$)
	57.71	ppm	(C-1)
	97.64	ppm	(C-7)
	104.27	ppm	(C-5)
	115.68	ppm	(C-q)
	126.74	ppm	(C-4$^/$)
	128.5	ppm	(C-2$^/$ and C-6$^/$)
	129.5	ppm	(C-3$^/$ and C-5$^/$)
	135.59	ppm	(C-q)
	139.53	ppm	(C-q)

157.014	ppm	(C-q)
158.72	ppm	(C-q)

(Figure 32)

DEPT   (Figure 33)

COLOC   (Figure 34)

MS   297 (M^+), 282 (100%), 206 (3.75%), 190 (4.25%), 164 (52.32%), 91 (9.91%)

(Figure 35)

Note 1

A bisisoquinoline was obtained when the *N,O*-acetal intermediate was treated with excess TFA (2 ml), as the main product (44% yield).

2. 5,5$^/$-Bis(methylene)-2-benzyl-6,8-dimehtoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline

^{1}H-NMR	1.06	ppm	(6H, 3-CH$_3$ and 3$^/$-CH$_3$)
(CDCl$_3$/TMS)	2.45	ppm	(2H, H-4 and H-4$^/$)
	2.72	ppm	(2H, H-4 and H-4$^/$)
	2.95	ppm	(2H, H-3 and H-3$^/$)
	3.33-3.98	ppm	(8H, H-1 and H-1$^/$ and N-CH$_2$Ph and N$^/$-CH$_2$Ph)
	3.70	ppm	(s, 6H, 6-and 6$^/$-OCH$_3$ or 8-and 8$^/$-OCH$_3$)
	3.71	ppm	(s, 6H, 8-and 8$^/$-OCH$_3$ or 6-and 6$^/$-OCH$_3$)

3.92	ppm	(s, 2H, 5-CH$_2$-5$^/$)
6.28	ppm	(s, 2H, H-7 and H-7$^/$)
7.12-7.36	ppm	(m, 10H, aromatic)

(Figure 36)

COSY   (Figure 37)

^{13}C-NMR	15.13	ppm	(3-CH$_3$)
(CDCl$_3$/TMS)	15.67	ppm	(3-CH$_3$)
	29.69	ppm	(5-CH$_2$-5$^/$)
	32.93	ppm	(C-4)
	33.13	ppm	(C-4)
	47.19	ppm	(N-CH$_2$Ph)
	47.40	ppm	(N-CH$_2$Ph)
	51.46	ppm	(C-3)
	51.75	ppm	(C-3)
	55.15	ppm	(OCH$_3$)
	56.12	ppm	(OCH$_3$)
	57.29	ppm	(C-1)
	93.15	ppm	(C-7)
	115.34	ppm	(C-5)
	119.99	ppm	(C-8a)
	126.70	ppm	(C-4$^/$)
	128.16	ppm	(C-2$^/$, C-6$^/$)
	128.95	ppm	(C-3$^/$, C-5$^/$)
	135.27	ppm	(C-4a)
	139.53	ppm	(C-1$^/$)
	154.66	ppm	(C-8)
	156.48	ppm	(C-6)

(Figure 38)

DEPT   (Figure 39)

COLOC   (Figure 40)

MS   607(M⁺+1),307(17.86%),289,(12.19%),154(100%), 136(62.63%)

              (Figure 41)

3. 6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline

(CU-19-06)

The solution of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.93 g, 3.1 mmol) in ethanol (30 ml) was hydrogenated with 10 % Pd/C (0.15 g, 5 % mmol of starting material), to afford the yellow oil of products. Yield: 0.45 g (70%).

IR	3286	cm⁻¹	(v N-H)
(Neat)	1606	cm⁻¹	(v C=C, aromatic)
	1206	cm⁻¹	(v_{as} C=<u>C-O</u>-C)
	1150	cm⁻¹	(v_s C-<u>O-C</u>)
	(Figure 42)		

¹H -NMR	1.18	ppm	(d, J=6.1 Hz, 3H, 3-CH₃)
(CDCl₃/TMS)	1.68	ppm	(s, 1H, NH)
	2.33	ppm	(dd, J=16.9, 11.4 Hz, 1H, H-4)
	2.85	ppm	(m, 1H, H-4)
	2.90	ppm	(m, 1H, H-3)
	3.70	ppm	(d, J=6.4,1H, H-1)
	3.77	ppm	(s, 3H, 6- and 8-OCH₃)
	3.79	ppm	(s, 3H, 8- and 6-OCH₃)
	4.04	ppm	(d, J=16.3 Hz, 1H, H-1)
	6.30	ppm	(2H, H-5 and H-7)
	(Figure 43)		

4. 6,8-Dimethoxy-2-formyl-3-methyl-1,2,3,4-tetrahydroiso-quinoline (CU-19-07)

A solution of 6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroiso-quinoline (0.30 g, 1.45 mmol) in formic acid (2.67 g, 58.00 mmol; 40 molar eq) and acetic anhydride (1.47 g, 14.49 mmol; 10 molar eq) was heated at 70 ^{o}C for 1 h (Shinohura *et al*, 1997). Then, the cool solution was diluted with chloroform, washed with the cool water (3×100 ml), dried, and concentrated under reduced pressure to give the yellow residues. The residues were chromatographed on a silica gel eluting with Hexane : EtOAc (1:1). Yield: 0.204 g (60 %).

IR	3418	cm^{-1}	(overtone C=O, amide)
(Neat)	1661	cm^{-1}	(v C=O, amide)
	1597	cm^{-1}	(v C=C, aromatic)
	1213	cm^{-1}	(v_{as} C=$\underline{C}$-$\underline{O}$-C)
	1118	cm^{-1}	(v_s C-$\underline{O}$-$\underline{C}$)
	(Figure 44)		

^{1}H -NMR	1.18	ppm	(3H, 3-CH$_3$)
(CDCl$_3$/TMS)	2.58	ppm	(m, 2H, H-4)
	3.80	ppm	(6H, 6- and 8- OCH$_3$)
	4.10	ppm	(1H, H-1)
	4.20	ppm	(1H, H-1)
	4.45	ppm	(1H, H-3)
	6.34	ppm	(2H, H-5 and H-7)
	8.12	ppm	(s, 1H, NCHO)
	(Figure 45)		

5.   6,8-Dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-08)

A solution of 6,8-dimethoxy-2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline in dry THF (20 ml) was stirred at 0 ^{O}C on an ice-water bath. LiAlH$_4$ (0.125 g, 3.30 mmol) was added as one portion over 30 min. The solution was refluxed for 2 h. The stirred reaction was added with ethyl acetate, insoluble material was filtered off. The solvent was concentrated to give a yield of products. Yield: 0.142 g (78%).

IR	3378	cm^{-1}	(v C-N)
(Neat)	1606	cm^{-1}	(v C=C, aromatic)
	1211	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1149	cm^{-1}	(v_{as} C-<u>O-C</u>)
	(Figure 46)		

^{1}H -NMR	1.14	ppm	(d, J=5.7 Hz, 3H, 3-CH$_3$)
(CDCl$_3$/TMS)	2.47	ppm	(s, 3H, N-CH$_3$)
	2.62	ppm	(m, 2H, H-4)
	2.78	ppm	(m, 1H, H-3)
	3.78	ppm	(s, 6H, 6- and 8-OCH$_3$)
	3.82	ppm	(overlapped, 2H, H-1)
	6.22	ppm	(s, 1H, H-5 or H-7)
	6.26	ppm	(s, 1H, H-7 or H-5)
	(Figure 47)		

6. 6,8-Dimethoxy-2,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-09)

A). A solution of 6,8-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (50 mg, 0.22 mmol), MeI (19 µl, 0.30 mmol) in dry THF (10 ml) was heated at 80°C for 10 min (Kametani *et al*, 1968). Then the mixture reaction was evaporated to give a light brown solid (hygroscopic). Yield : 65.7 mg (80%).

B). A solution of 6,8-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (50 mg, 0.22 mmol), MeI (19 µl, 0.30 mmol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature for 96 h (Bringmann *et al*, 2000). The mixture reaction was concentrated to give a light brown solid (hygroscopic). Yield : 64 mg (78%).

IR	1606	cm^{-1}	(v C=C, aromatic)
	1204	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1151	cm^{-1}	(v_{s} C-<u>O-C</u>)
	(Figure 48)		
^{1}H-NMR	1.55	ppm	(d, J=6.46 Hz, 3H, 3-CH_3)
(CDCl$_3$/TMS)	2.91	ppm	(dd, J=18.44, 8.84 Hz, 1H, H-4)
	3.20	ppm	(s, 3H, N^{+}-CH_3)
	3.25	ppm	(dd, J=18.70, 4.8 Hz, 1H, H-4)
	3.58	ppm	(s, 3H, N^{+}-CH_3)
	3.80	ppm	(s, 6H, 6- and 8-OCH_3)
	4.41	ppm	(m, 1H, H-3)
	4.52	ppm	(d, J= 5.60 Hz, H-1)
	4.65	ppm	(d, J=15.7 Hz, H-1)
	6.31	ppm	(s, 1H, H-5 or H-7)
	6.34	ppm	(s, 1H, H-7 or H-5)
	(Figure 49)		

III. **The Procedures for Cyclization of *N*-benzyl-2-(3,5-dimetho-xyphenyl)-1-methylethylamine to the Tetrahydroisoquinoline with Butyl glyoxalate**

1. Butyl glyoxalate

To a solution of dibutyl-L(+)-tartrate (19.06 g, 72.74 mmol) in dry ether (150 ml) cooled in an ice water-bath, was added (16.58 g, 72.74 mmol) of periodic acid (HIO_4^-) in a small portions over 1 hour under nitrogen gas with stirring. The milky reaction mixture was vigorous stirred at room temperature until the ether layer became almost clear and a white solid separated. The ether phase was decanted, dried (Na_2SO_4), and distilled in a short-path-distillation set to give the clear butyl glyoxalate (Kelly, 1972). Yield 27.5 g (72%).

2. Butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahy-droisoquinoline-1-carboxylate (CU-19-10)

A mixture solution of *N*-benzyl-2-(3,5- dimethoxyphenyl)-1-methylethylamine (1.99 g ,7.0 mmol), butyl glyoxalate (9.10 g, 70.0 mmol), K_2CO_3 (4.83 g, 35 mmol) in n-butanol (10 ml) was stirred overnight at room temperature, then filtered. The filtrate was evaporated under reduced pressure to give the *N,O*-acetal. 0.5 M TFA in CH_2Cl_2 (0.168 ml) was added to the *N,O*-acetal (**Note 2**). This mixture was stirred in ice water-bath for 1 hour. The reaction was poured into a cool water (100 ml) and extracted with CH_2Cl_2 (3×100 ml). The combined extracts were concentrated under reduced pressure to give the residue of products. This residue was chromatographed on a silica gel eluting with hexane:EtOAc (5:1) and recrystallized with hexane to give a pale yellow to white prisims. Yield : 2.52g (91%), m.p. 81-83 ^{0}C.

IR	3330	cm^{-1}	(overtone C=O)
(Neat)	1735	cm^{-1}	(v C=O, ester)
	1596	cm^{-1}	(v C=C, aromatic)
	1261	cm^{-1}	(v_{as} C=$\underline{C}$-$\underline{O}$-C)
	1193	cm^{-1}	(v_{as} C-$\underline{O}$-C)
	1172-1148	cm-1	(v_s C-$\underline{O}$-C)

(Figure 50)

Anal. cal. for $C_{24}H_{31}NO_4$: C, 72.611; H, 7.871; N, 3.528

Found   :   C,72.523;, H,7.802; N, 3.522

^{1}H-NMR	0.92	ppm	(t, J=7.3 Hz, 3H, H-4$^/$)
(CDCl$_3$)	1.17	ppm	(d, J=6.6 Hz, 3H, 3-CH$_3$)
	1.34	ppm	(m, 2H, H-3$^/$)
	1.56	ppm	(m, 2H, H-2$^/$)
	2.62	ppm	(dd, J=16.6,9.3 Hz, 1H, H-4)
	2.74	ppm	(dd, J=16.5,4.4 Hz, 1H, H-4)
	3.46	ppm	(m, 1H, H-3)
	3.58	ppm	(d, J=14.5 Hz, 1H, N-CH$_2$Ph)
	3.67	ppm	(s, 3H, 6- or 8-OCH$_3$)
	3.79	ppm	(s, 3H, 8- or 6-OCH$_3$)
	3.89	ppm	(d, J=14.5 Hz, 1H, N-CH$_2$Ph)
	4.08	ppm	(m, 2H, H-1$^/$)
	4.41	ppm	(s, 1H, H-1)
	6.27	ppm	(s, 2H, H-5, H-7)
	7.2-7.5	ppm	(5H, aromatic-H)

(Figures 51, 52)

^{13}C-NMR	13.66	ppm	(C-4$^{/}$)
(CDCl$_3$)	17.88	ppm	(3-CH$_3$)
	19.03	ppm	(C-3$^{/}$)
	30.71	ppm	(C-2$^{/}$)
	33.31	ppm	(C-4)
	48.61	ppm	(N-CH$_2$Ph)
	51.19	ppm	(C-3)
	55.15	ppm	(6- or 8-OCH$_3$)
	55.26	ppm	(8- or 6-OCH$_3$)
	59.94	ppm	(C-1)
	64.20	ppm	(C-1$^{/}$)
	96.16	ppm	(C-5 or C-7)
	104.33	ppm	(C-7 or C-5)
	126.62-128.38	ppm	(aromatic-C)
	137.44	ppm	(8a-C)
	140.10	ppm	(4a-C)
	158.21	ppm	(C-6 or C-8)
	159.49	ppm	(C-8 or C-6)
	172.94	ppm	(carbonyl ester)
	(Figures 53, 54)		

DEPT	(Figure 54)
COSY	(Figure 55)
ROESY	(Figure 56)
EIMS	398(M$^+$+1), 396 (2.80%), 296 (99.50%), 204 (63.01%), 190(73.42%), 175 (39.52%), 146 (46.09%), 91 (100%), 57 (83.78%)
	(Figure 57)

Note 2

When the *N,O*-acetal intermediate was treated with excess TFA (2ml), two diasteriomeric isomer (A and B) of butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate were obtained.

A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate

^{1}H-NMR	0.88	ppm	(6H, 2H-4$^/$)
(CDCl$_3$)	1.20	ppm	(d, J=6.6 Hz, 3H, 3-CH$_3$)
	1.33	ppm	(4H, 2H-3$^/$)
	1.58	ppm	(4H, 2H-2$^/$)
	2.60	ppm	(dd, J=16.5,9.8 Hz, 1H, H-4)
	2.85	ppm	(dd, J=16.5, 4.2 Hz, 1H, H-4)
	3.45	ppm	(d, J=7.5 Hz, 1H, N-CH$_2$Ph)
	3.69	ppm	(s, 3H, 6- or 8-OCH$_3$)
	3.79	ppm	(s, 3H, 8- or 6-OCH$_3$)
	3.90	ppm	(d, J=14.6 Hz, 1H, N-CH$_2$Ph)
	4.10	ppm	(m,1H, H-3)
	4.20	ppm	(m, 2H, H-1$^/$)
	4.44	ppm	(s, 1H, H-1)
	5.36	ppm	(d, J=5.3 Hz, 1H, 5-CH)
	6.29	ppm	(s, 1H, H-7)
	7.20-7.48	ppm	(5H, aromatic-H)
	(Figure 58)		

^{13}C-NMR	13.78	ppm	(C-4)
(CDCl$_3$)	18.62	ppm	(3-CH$_3$)
	19.21	ppm	(C-3$^{/}$ or C-3$''$)
	29.83	ppm	(C-4+ C-2$^{/}$+C-2$^{//}$+C-3$^{/}$ or C-3$^{//}$)
	30.70	ppm	(C-4+ C-2$^{/}$+C-2$^{//}$+C-3$^{/}$ or C-3$^{//}$)
	30.87	ppm	(C-4+ C-2$^{/}$+C-2$^{//}$+C-3$^{/}$ or C-3$^{//}$)
	48.72	ppm	(C-3)
	55.24	ppm	(8- or 6-OCH$_3$)
	55.77	ppm	(6- or 8-OCH$_3$)
	60.31	ppm	(C-1)
	64.2	ppm	(C-1$^{/}$,C-1$^{//}$)
	65.39	ppm	(C-1$^{/}$,C-1$^{//}$)
	66.75	ppm	(5-CH)
	93.14	ppm	(C-7)
	113.84	ppm	(8a)
	117.32	ppm	(4a)
	126.54-128.27	ppm	(aromatic-C)
	136.59	ppm	(C-1)
	139.84	ppm	(C-5)
	157.41	ppm	(C-6 or 8)
	158	ppm	(C-8 or 6)
	172.49	ppm	(-COO)
	174.15	ppm	(-COO)
	(Figure 59)		
DEPT	(Figure 60)		
COSY	(Figure 61)		
MS	528 (M^{+}+1), 426 (13.90%), 307 (22.88%), 289 (11.11), 154 (100%), 136 (68.29%), 107 (21.05%), 91(19.98%)		
	(Figure 62)		

B : **butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate**

^{1}H-NMR	0.88	ppm	(m, 6H, 2H-4$^/$)
(CDCl$_3$)	1.25	ppm	(d, J=8 Hz, 3H, 3-CH$_3$)
	1.33	ppm	(4H, 2H-3$^/$)
	1.58	ppm	(4H, 2H-2$^/$)
	2.67	ppm	(dd, J=16.5, 9.8 Hz, 1H, H-4)
	2.75	ppm	(dd, J=16.4, 4.5 Hz, 1H, H-4)
	3.51	ppm	(overlapped, 1H, N-CH$_2$Ph)
	3.69	ppm	(s, 3H, 6- or 8-OCH$_3$)
	3.79	ppm	(s, 3H, 8- or 6-OCH$_3$)
	3.90	ppm	(d, J=14.45 Hz, 1H, N-CH$_2$Ph)
	4.10	ppm	(m, 1H, H-3)
	4.20	ppm	(m, 2H, H-1$^/$)
	4.44	ppm	(s,1H, H-1)
	5.36	ppm	(s, 1H, 5-CH)
	6.29	ppm	(s, 1H, H-7)
	7.20-7.48	ppm	(5H, aromatic-H)
	(Figure 63)		
^{13}C-NMR	13.79	ppm	(C-4)
(CDCl$_3$)	18.97	ppm	(3-CH$_3$)
	19.18	ppm	(C-3$^/$ or C-3$''$)
	29.80	ppm	(C-4+ C-2$^/$+C-2$^{//}$+C-3$^/$ or C-3$^{//}$)
	30.83	ppm	(C-4+ C-2$^/$+C-2$^{//}$+C-3$^/$ or C-3$^{//}$)
	30.92	ppm	(C-4+ C-2$^/$+C-2$^{//}$+C-3$^/$ or C-3$^{//}$)
	48.73	ppm	(C-3)
	55.24	ppm	(8- or 6-OCH$_3$)
	55.70	ppm	(6- or 8-OCH$_3$)
	60.30	ppm	(C-1)

64.26	ppm	(C-1$'$,C-1$''$)
65.29	ppm	(C-1$'$,C-1$''$)
66.93	ppm	(5-CH)
92.89	ppm	(C-7)
103.92	ppm	(8a)
117.12	ppm	(4a)
126.54-129.47	ppm	(aromatic-C)
136.59	ppm	(C-1)
139.81	ppm	(C-5)
157.38	ppm	(C-6 or 8)
158.08	ppm	(C-8 or 6)
172.34	ppm	(-COO)
174.15	ppm	(-COO)

(Figure 64)

DEPT   (Figure 65)

COSY   (Figure 66)

4.   Butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylate (CU-19-11)

A solution of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (0.10 g, 025 mmol), in ethanol 30 ml was hydrogenated with 10 % Pd/C (0.025 g). Then catalyst was filtrated, evaporated to give residue of products. This residue was diluted with CH_2Cl_2 (10 ml) and washed with water (3x100ml). The solvent was evaporated to give the product.   Yield : 71 mg (91%).

IR	3324	cm^{-1}	(overtone C=O)
(Neat)	1732	cm^{-1}	(v C=O, ester)
	1602	cm^{-1}	(v C=C, aromatic)
	1362-1050	cm^{-1}	(v_{as} C=$\underline{C}$-$\underline{O}$-C ; v_s C-$\underline{O}$-C)
	(Figure 67)		

^{1}H-NMR	0.91	ppm	(t, J=7.35 Hz, 3H, H-4$^/$)
(CDCl$_3$)	1.18	ppm	(d, J=6.18 Hz, 3H, 3-CH$_3$)
	1.32	ppm	(m, 2H, H-3$^/$)
	1.61	ppm	(m, 2H, H-2$^/$)
	2.05	ppm	(s, H, NH)
	2.47	ppm	(dd, J=16.2,10.8 Hz, 1H, H-4)
	2.73	ppm	(dd, J=16.3,3.6 Hz, 1H, H-4)
	3.09	ppm	(m, 1H, H-3)
	3.74	ppm	(s, 3H, 6- or 8-OCH$_3$)
	3.78	ppm	(s, 3H, 8- or 6-OCH$_3$)
	4.12	ppm	(m, 2H, H-1$^/$)
	4.72	ppm	(s, 1H, H-1)
	6.24	ppm	(s, 2H, H-5 or H-7)
	6.28	ppm	(s, 2H, H-7 or H-5)
	(Figures 68, 69)		
COSY	(Figure 70)		

5. 6,8-Dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-12).

A solution of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahy-droisoquinoline (0.15 g, 0.49 mmol) in dry THF (10 ml) cooled on an ice water. LiAlH$_4$ (0.058 g, 1.52 mmol) was added a small portion of over 1 hour in the cool stirring. Then the mixture reaction was heated to reflux for 1-2 h. The reaction mixture was poured into water (50 ml) and then was extracted with ether (3x50 ml). The ethereal fractions was extracted 1 N HCl (3x50 ml) and the acidic aqueous was basified to pH 9-10 with ammonia. This aqueous fraction was extracted with CH$_2$Cl$_2$ (3×100 ml), dried, and concentrated under reduced pressure to afford the products. Yield : 77 mg (85%).

IR	3324	cm^{-1}	(v O-H)
(Neat)	1602	cm^{-1}	(v C=C, aromatic)
	1206	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1172-1148	cm^{-1}	(v_s C-<u>O-C</u>)
	1087-1050	cm^{-1}	(v_s C=C-<u>O-C</u>)
	(Figure 71)		
^{1}H-NMR	1.19	ppm	(d, J=6.2 Hz, 3H, 3-CH$_3$)
(CDCl$_3$)	2.37	ppm	(dd, J=16.5, 5.5 Hz, 1H, H-4)
	2.58	ppm	(s, 2H, NH and OH)
	2.72	ppm	(dd, J=16.7, 3.4 Hz, 1H, H-4)
	3.09	ppm	(m, 1H, H-3)
	3.35	ppm	(t, J=10.2 Hz,1-CH$_2$)
	3.74	ppm	(s, 6H, 6- and 8-OCH$_3$)
	3.85	ppm	(dd, J=10.3, 4.1 Hz, 1-CH$_2$)
	4.15	ppm	(dd, J=10.9, 4.1 Hz, H-1)
	6.25	ppm	(s, 2H, H-5 or H-7)
	6.29	ppm	(s, 2H, H-7 or H-5)
	(Figures 72, 73)		

COSY   (Figure 74)

6.   2-Benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahy-droisoquinoline (CU-19-13).

　　　　　To a solution of butyl-2-benzyl-3-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (0.18 g, 0.45 mmol), LiAlH$_4$ (0.068 g, 1.8 mmol) in THF (25 ml) was heated at 80 ^{0}C. The reaction mixture was poured into water (50 ml) and then was extracted with ether (3x50 ml). The ethereal fractions was extracted 1 N HCl   (3x50 ml)   and the acidic aqueous was basified to pH 9-10 with ammonia. This aqueous fraction was extracted with CH$_2$Cl$_2$ (3×100 ml), dried, and concentrated under reduced pressure to give a product. Yield :0.14 g (90%).

IR	3436	cm^{-1}	(v O-H)
(Neat)	1606	cm^{-1}	(v C=C, aromatic)
	1212	cm^{-1}	(v_{as} C=<u>C-O</u>-C)
	1148	cm^{-1}	(v_s C-<u>O-C</u>)
	1070	cm^{-1}	(v_s C=<u>C-O</u>-C)
	(Figure 75)		

^{1}H-NMR	1.34	ppm	(d, J=6.6 Hz, 3H, 3-CH$_3$)
(CDCl$_3$)	2.55	ppm	(dd, J=17.0, 4.4 Hz, 1H, H-4)
	2.73	ppm	(dd, J=17.0, 11.5 Hz, 1H , H-4)
	3.21	ppm	(d, J=13.4 Hz, 1H, N-CH$_2$Ph)
	3.38	ppm	(t, J=10.1,1H, 1-CH$_2$)
	3.43	ppm	(m, 1H, H-3)
	3.69	ppm	(s, 3H, 6-or 8-OCH$_3$)
	3.75	ppm	(overlapped,1H, 1-CH$_2$)
	3.78	ppm	(s, 3H, 8-or 6-OCH$_3$)

3.95	ppm	(d, 1H, J=13.4 Hz, N-CH$_2$Ph)
3.98	ppm	(dd, J=9.8, 5.0,1H, H-1)
6.24	ppm	(s, 2H, H-5 or H-7)
6.29	ppm	(s, 2H, H-7 or H-5)
7.28-7.40	ppm	(5H, aromatic)

(Figures 76, 77)

COSY   (Figure 78)

^{13}C-NMR
(CDCl$_3$)

19.36	ppm	(3-CH$_3$)
31.33	ppm	(C-4)
45.65	ppm	(C-3)
48.97	ppm	(N-CH$_2$Ph)
55.07	ppm	(6- or 8-OCH$_3$)
55.18	ppm	(8- or 6-OCH$_3$)
57.20	ppm	(C-1)
60.64	ppm	(1-CH$_2$)
96.50	ppm	(C-7)
104.22	ppm	(C-5)
126.62-128.38	ppm	(aromatic-C)
137.44	ppm	(8a-C)
140.11	ppm	(4a-C)
158.22	ppm	(C-6 or C-8)
159.50	ppm	(C-8 or C-6)

(Figures 79, 80)

DEPT   (Figure 80)

COLOC   (Figure 81)

Attempt to Prepare the Mesylate compounds

Several methods have been tried to prepare the mesylate without success as follows.

A). MsCl (0.057 g, 0.5 mmol) was added to a stirred solution of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.06 g, 0.5 mmol), Et$_3$N (0.030 g, 0.3 mmol) in dry CH$_2$Cl$_2$ (10ml). The reaction mixtures were at room temperature, overnight.

B). A solution of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.025g, 0.076 mmol), K$_2$CO$_3$ (0.0105 g, 0.076 mmol) in DMF (30 ml) was added with MsCl (0.0087 g, 0.076 mmol). The reaction mixtures were stirred at room temperature, overnight.

C). MsCl (0.057 g, 0.5 mmol) was added to a stirred solution of *N*-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroiso-quinoline (0.06 g, 0.5 mmol), Et$_3$N (0.030 g, 0.3 mmol) in dry CH$_2$Cl$_2$ (10ml). The reaction mixtures were at room temperature for overnight.

D). MsCl (7.79 mg, 0.068 mmol) was added to a stirred solution of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.016 g, 0.068 mmol), 11.8 M NaOH (86 μl, 0.068 mmol) in DMF (15 ml). The resulting solution was stirred at 60-70 ^{o}C for 5 h.

E). NaH (50% oil dispersion, washed with dry hexane three time, 0.015 g,0.6116 mmol) was added to a stirred solution of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.10 g, 0.306 mmol) in dry THF (15 ml) under ice-water. MsCl (0.088 g, 0.765 mmol) was added dropwise to it over 1 h. The resulting solution was stirred at room temperature for overnight.

F). A solution of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (10 mg, 0.03mmol), Et$_3$N (6 mg, 0.06 mmol), 4-dimethylaminopyridine (DMAP) (1.37 mg, 0.003 mmol) in toluene (4 ml) was cooled with ice-water. MsCl (5.13 mg, 0.045 mmol) was added dropwise over 2 h. The reaction mixture was stirred at room temperature for overnight.
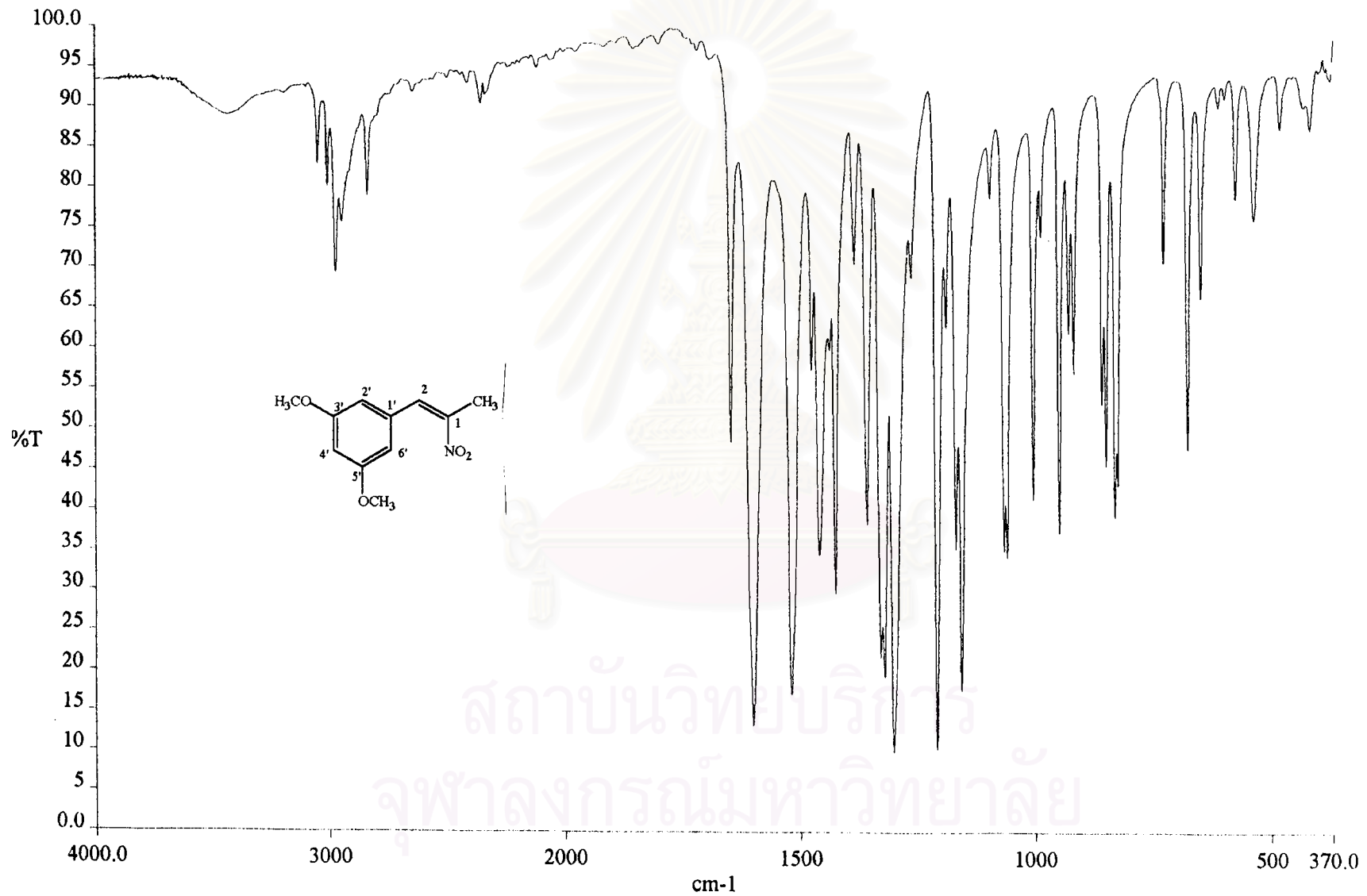
Figure 13 The IR spectrum (KBr) of 3,5-dimethoxyphenyl-β-nitrostyrene (CU-19-01)
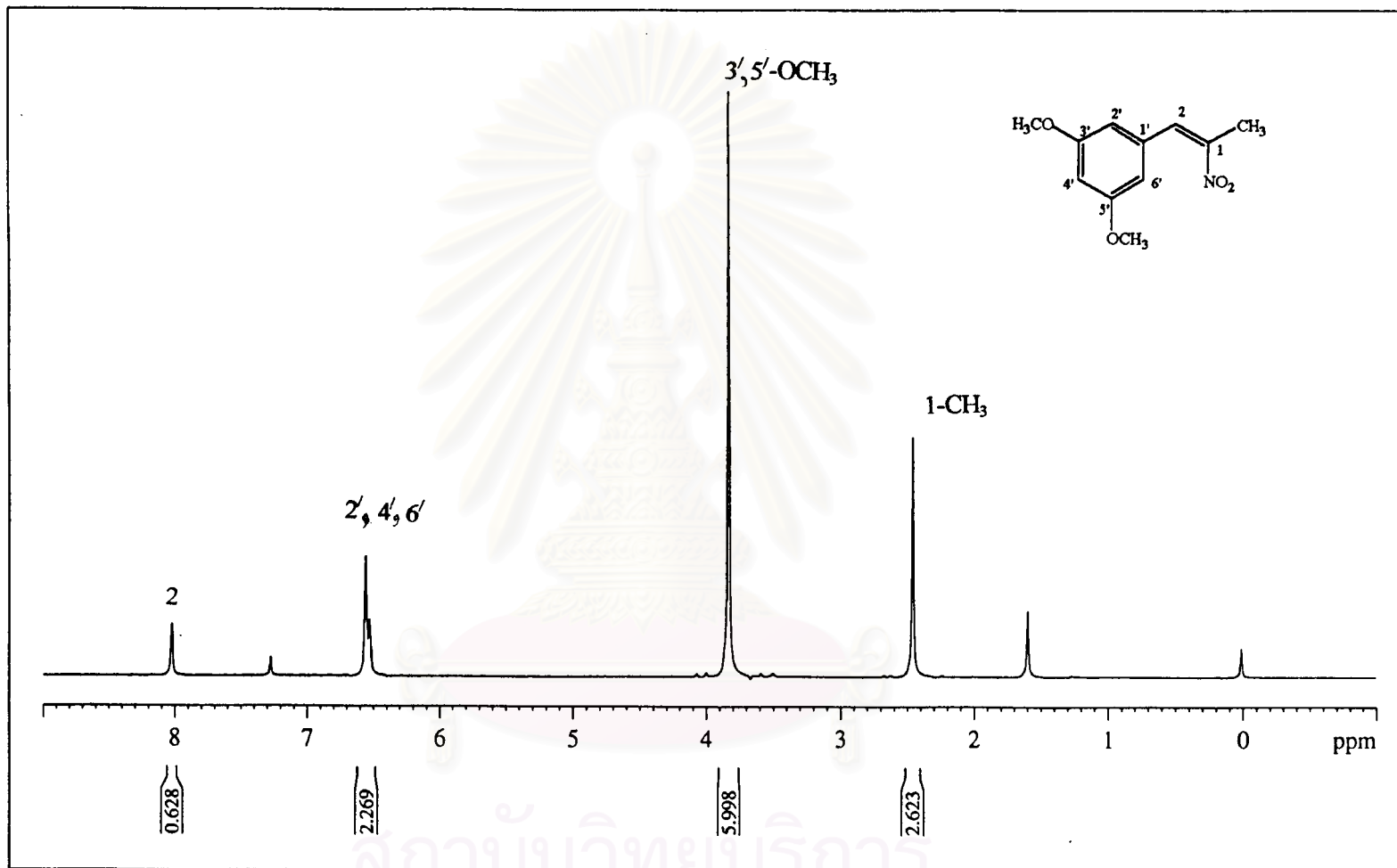
Figure 14 The 300 MHz ^{1}H-NMR spectrum of 3,5-dimethoxyphenyl-β-nitrostyrene (CU-19-01)
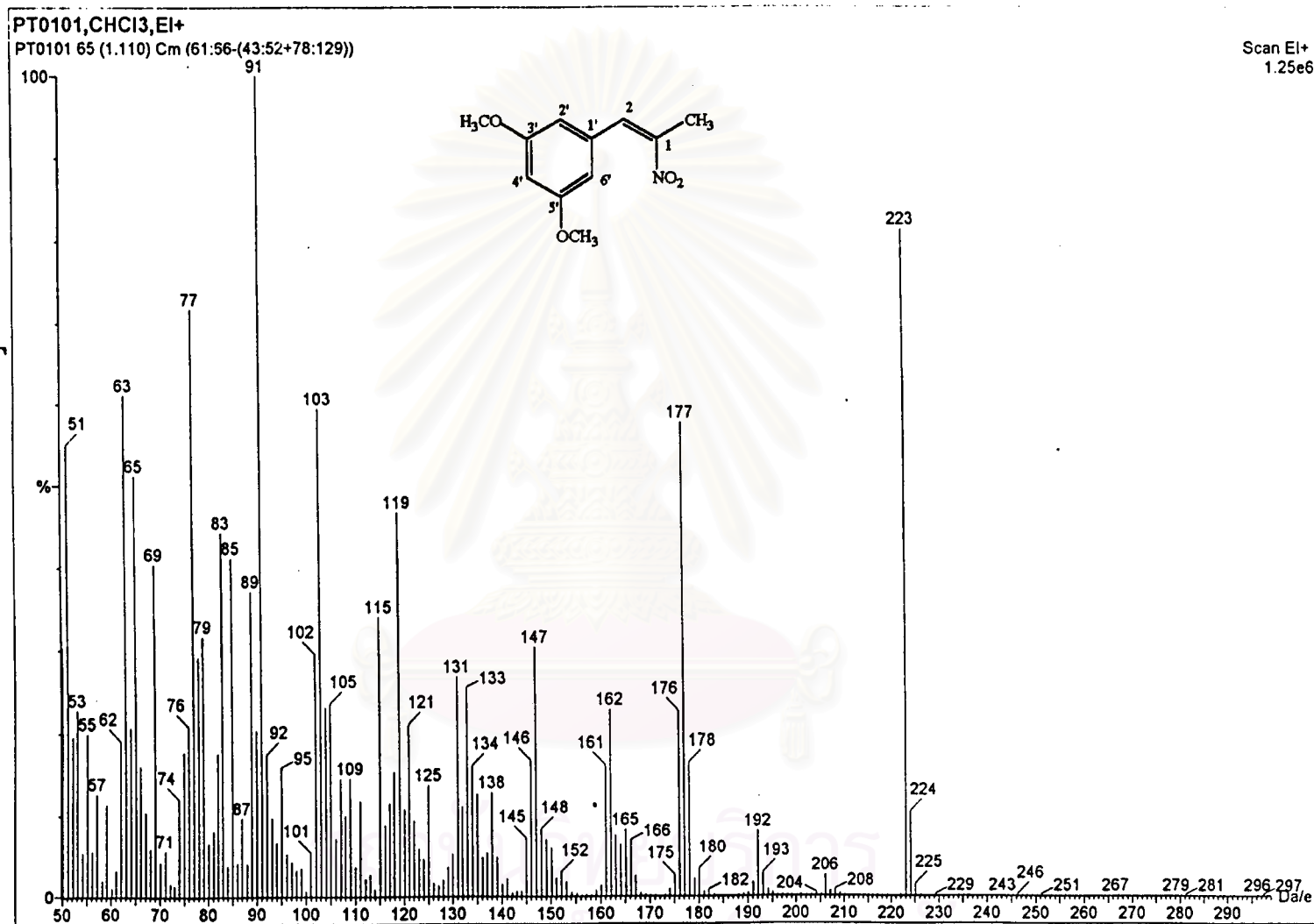
Figure 15 The electron impact mass spectrum of 3,5-dimethoxyphenyl-β-nitrostyrene (CU-19-01)
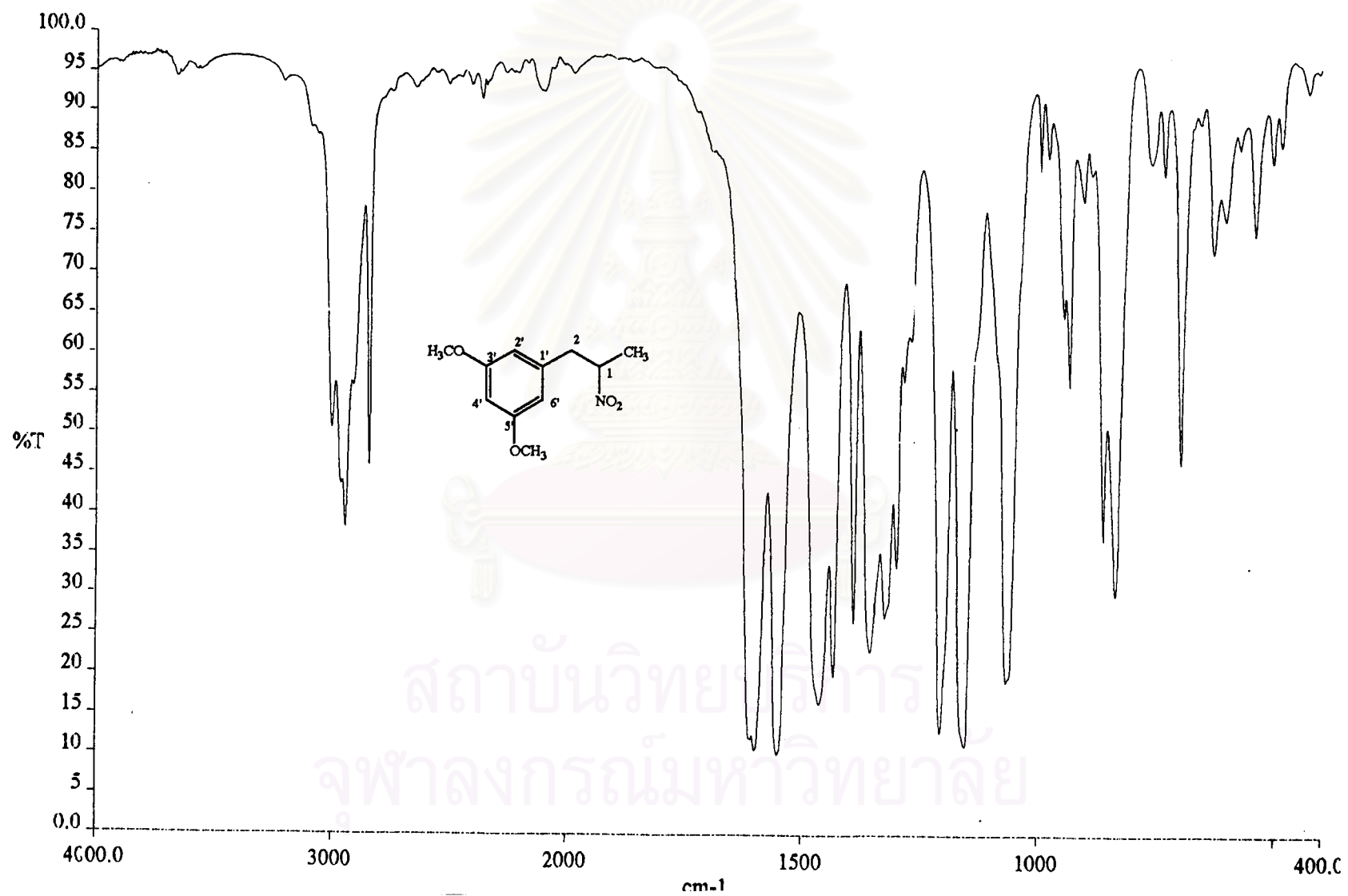
Figure 16 The IR spectrum (Neat) of 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)
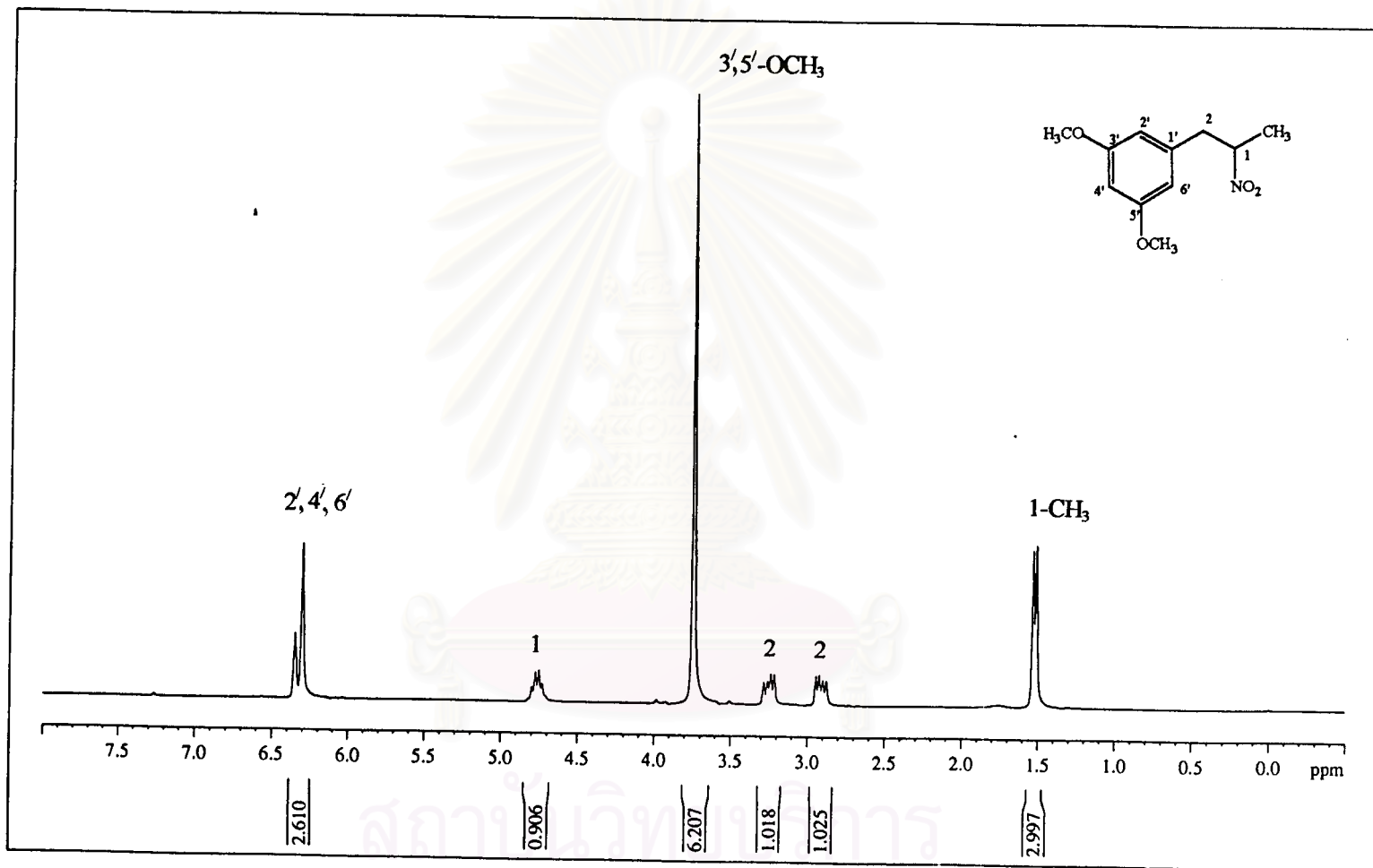
Figure 17 The 300 MHz ^{1}H-NMR spectrum of 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)
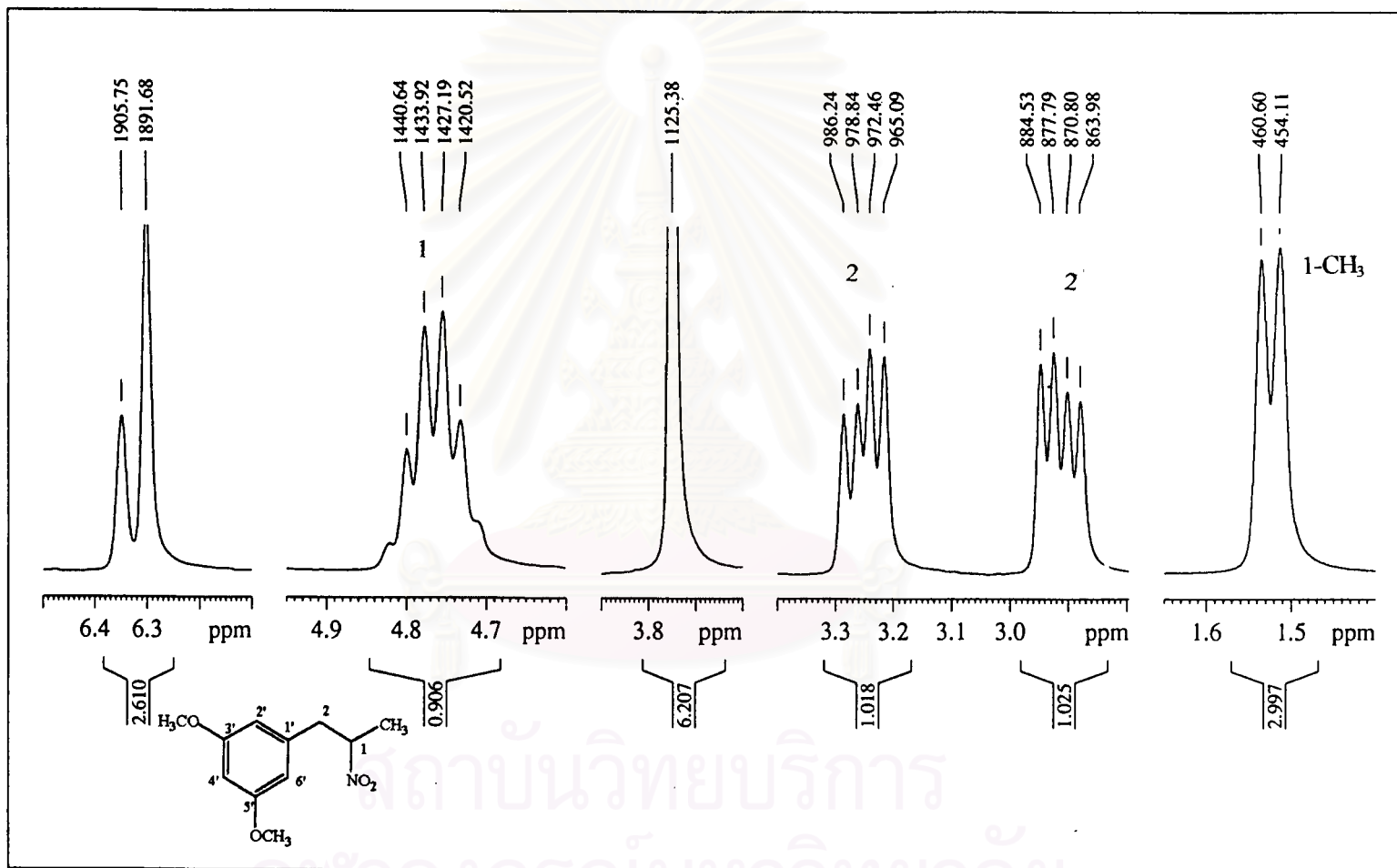
Figure 18 The 300 MHz ^{1}H-NMR spectrum of 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02) (Enlarged scale)
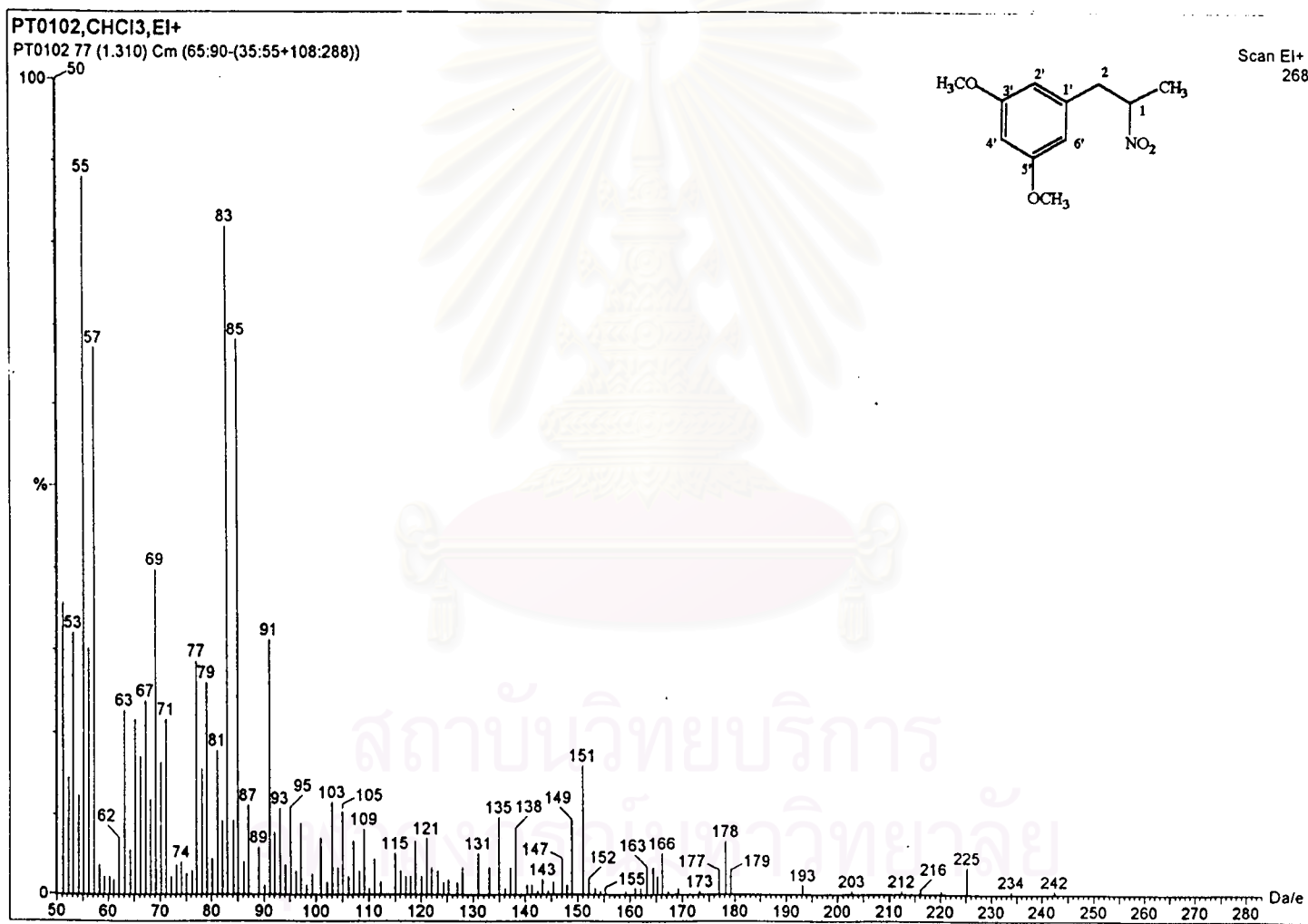
Figure 19 The electron impact mass spectrum of 2-(3,5-dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)
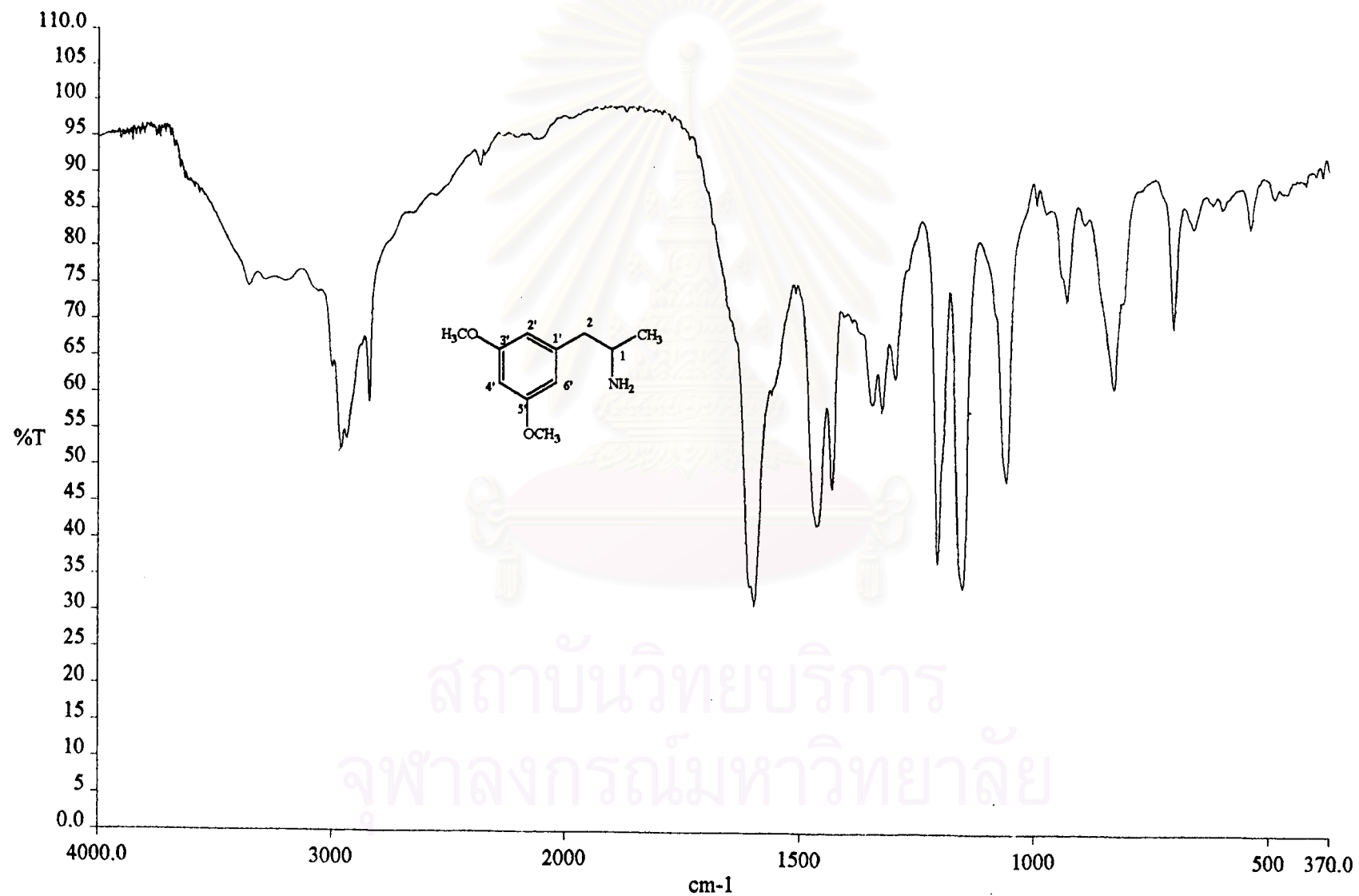
Figure 20 The IR spectrum (Neat) of 2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-03)
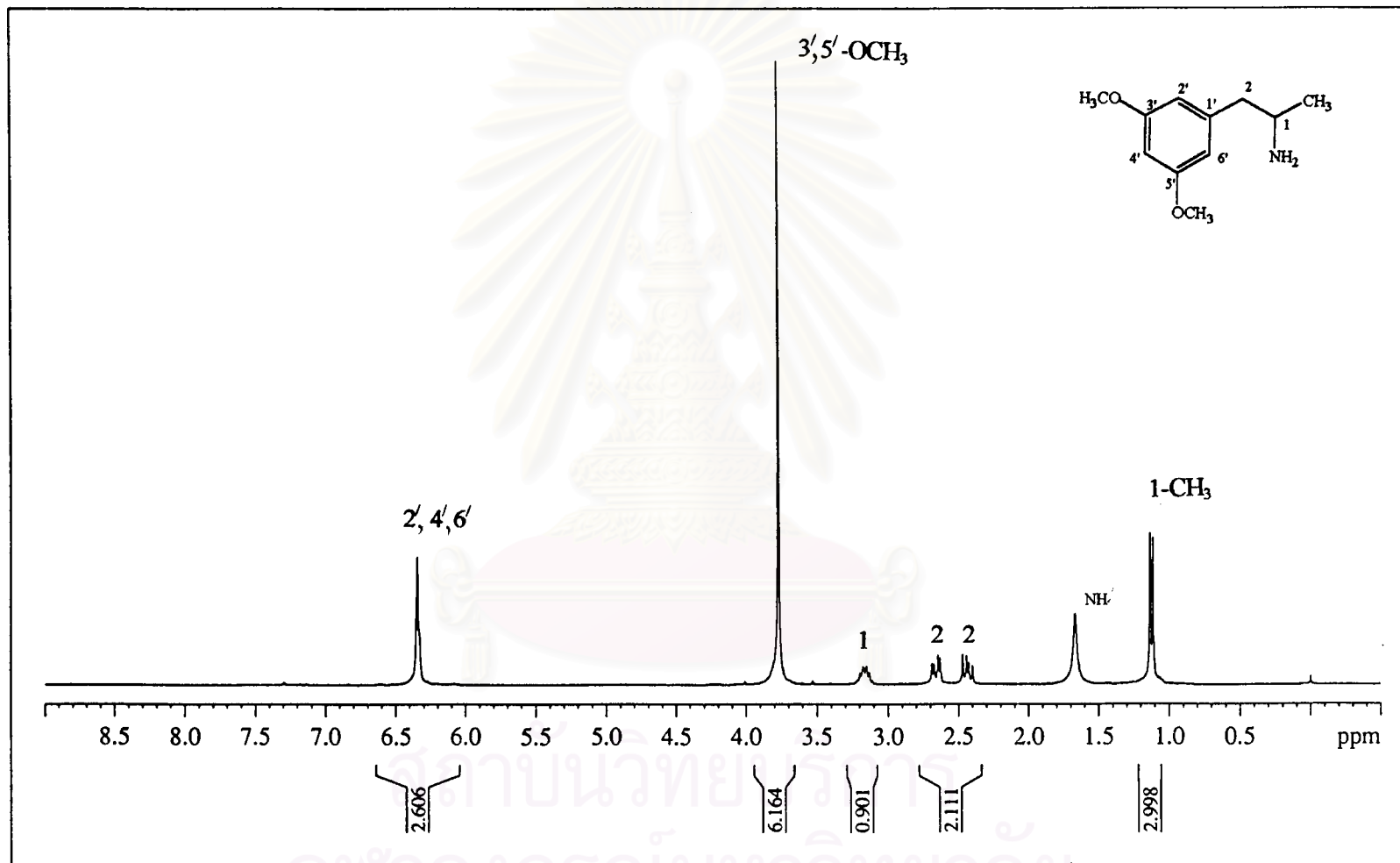
Figure 21 The 300 MHz ^{1}H-NMR spectrum of 2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-03)
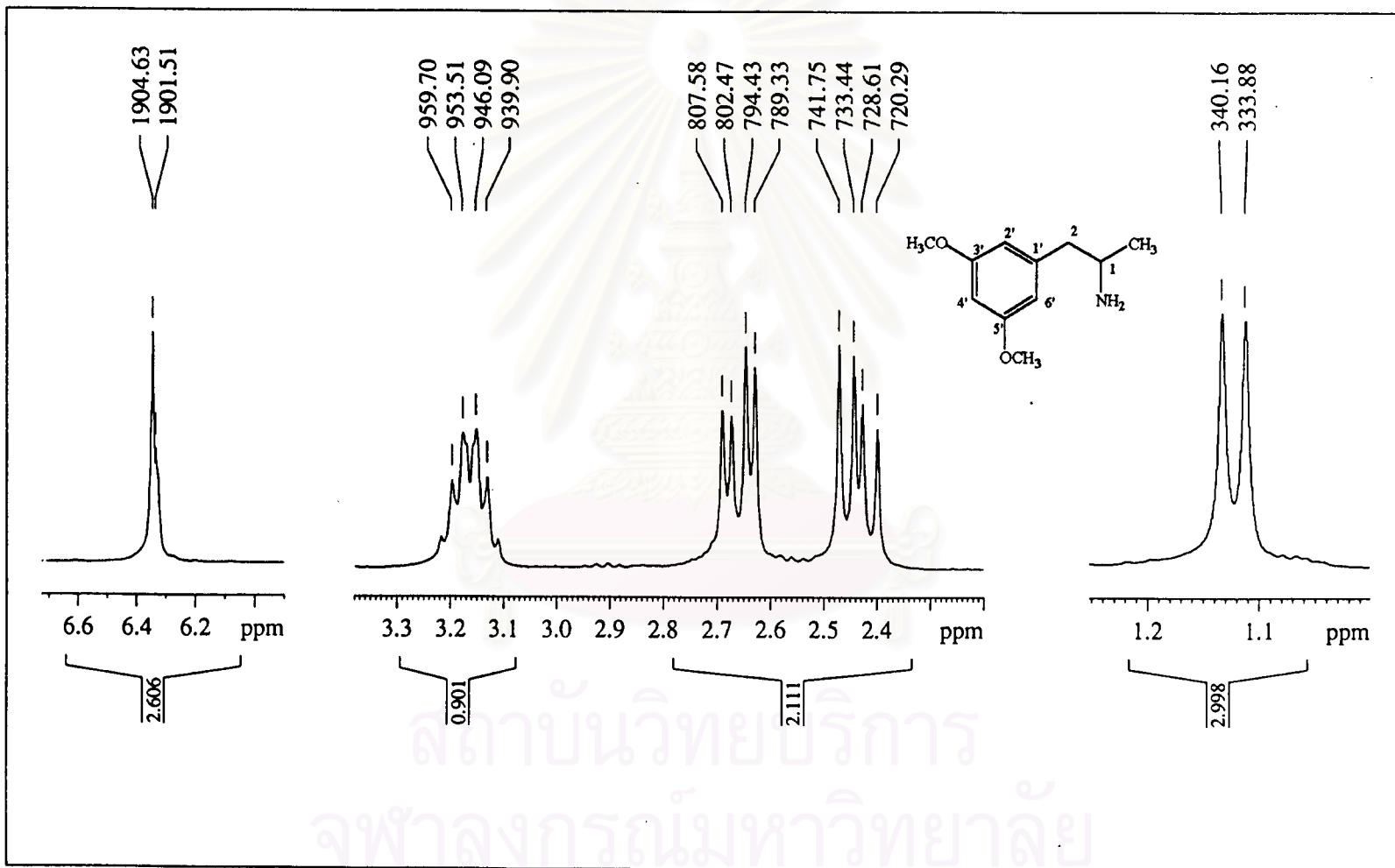
Figure 22 The 300 MHz ¹H-NMR spectrum of 2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-03)
(Enlarged scale)
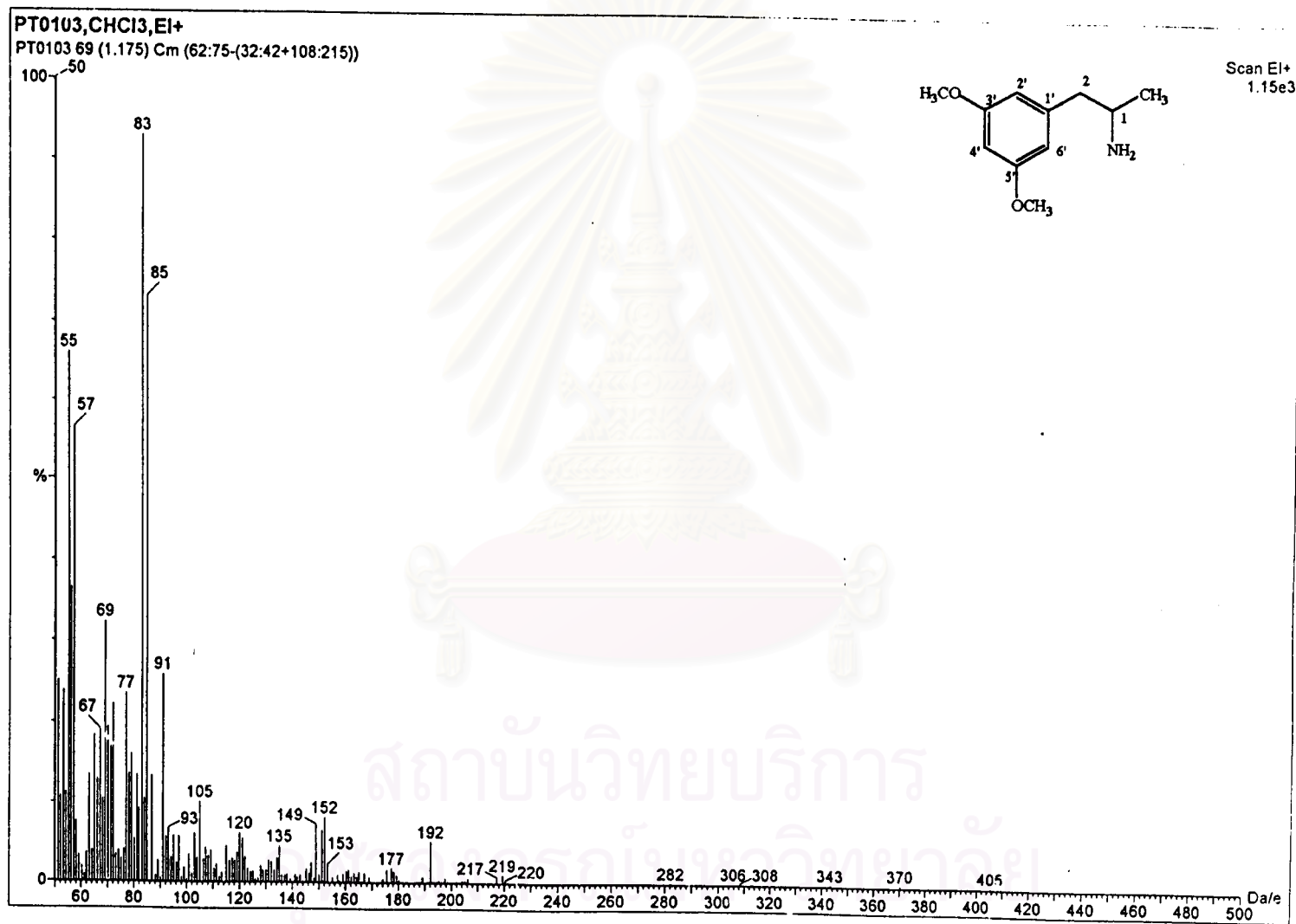
Figure 23 The electron impact mass spectrum of 2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-03)
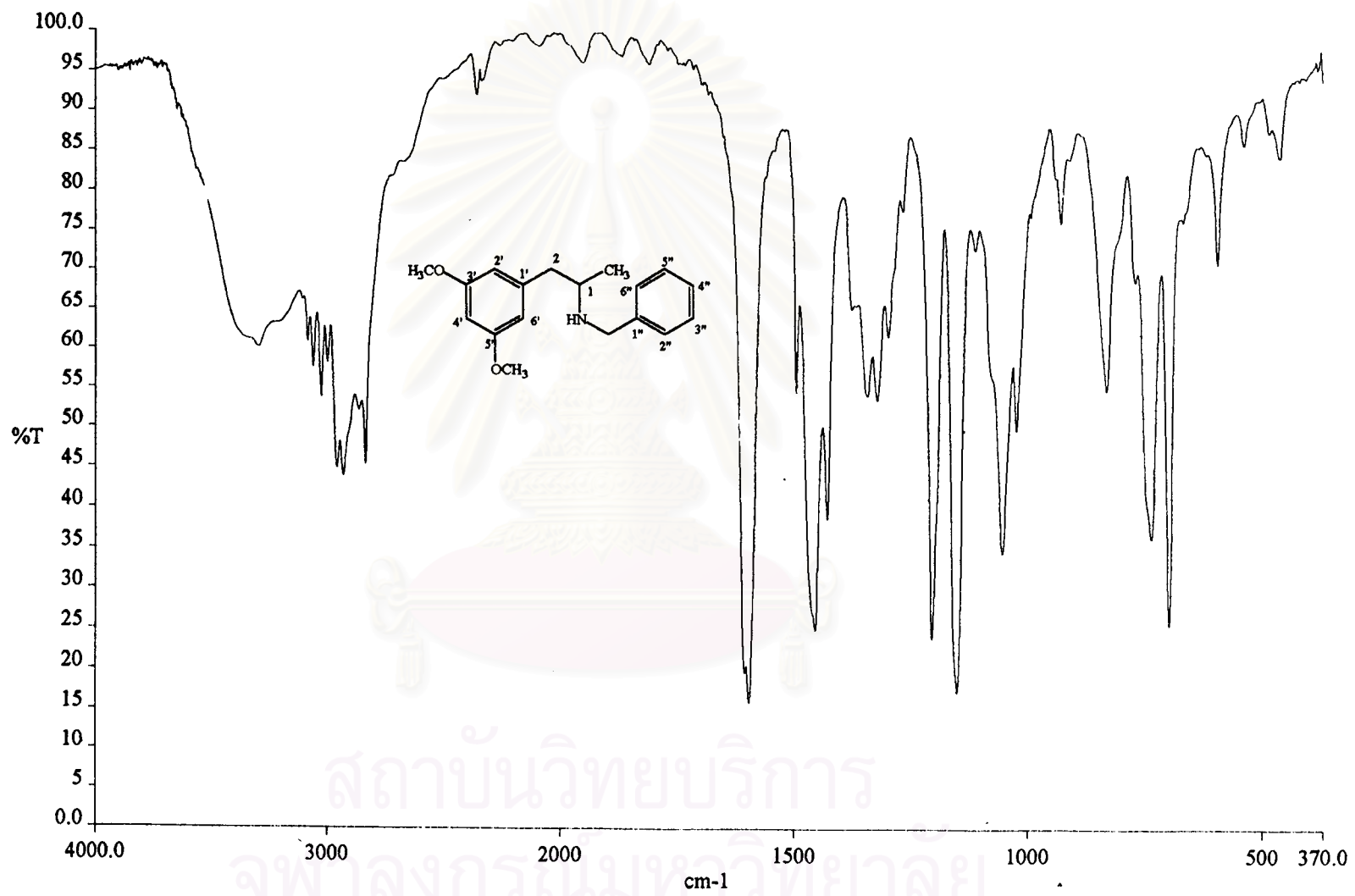
Figure 24 The IR spectrum (Neat) of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-04)
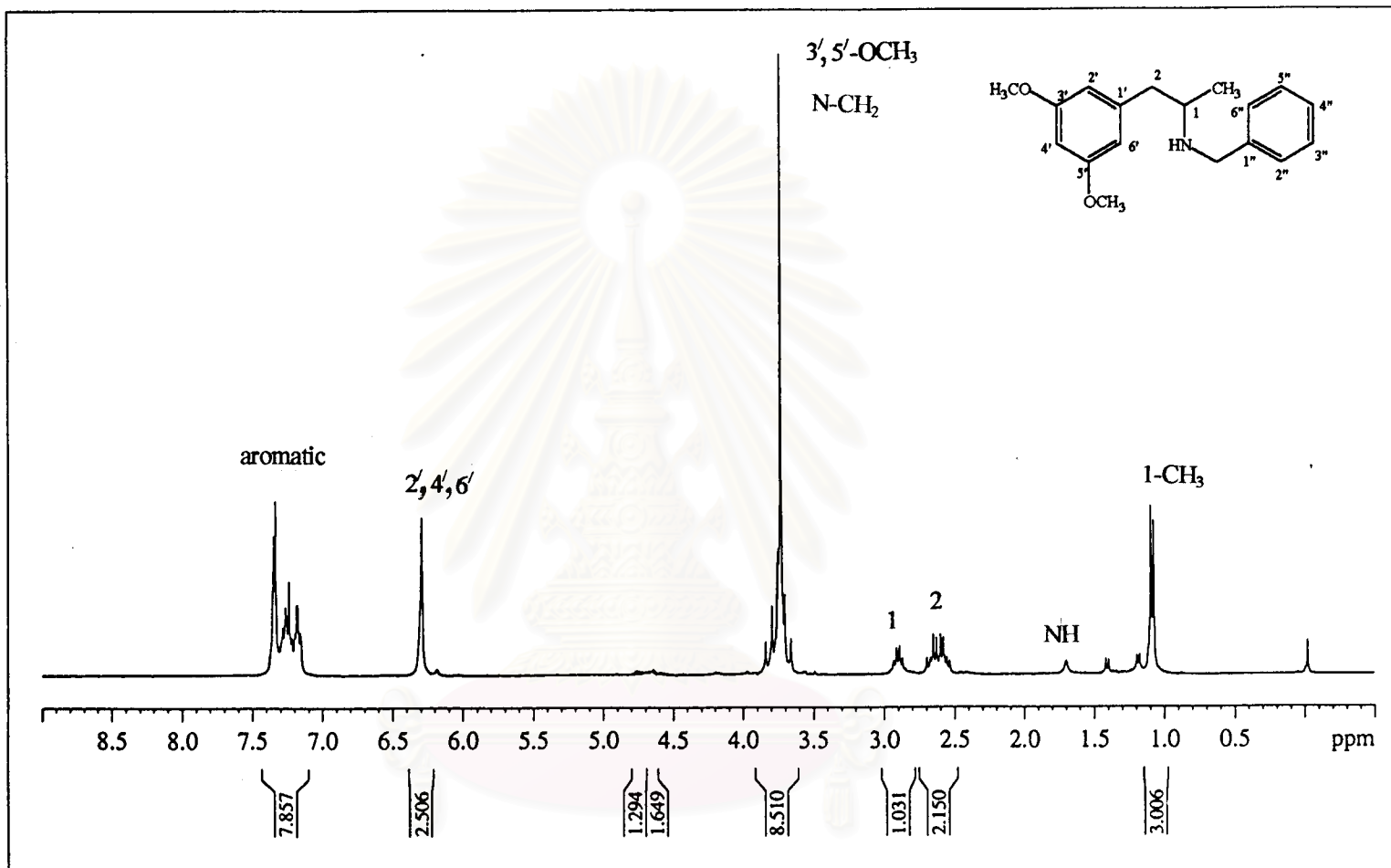
Figure 25 The 300 MHz ^{1}H-NMR spectrum of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-04)
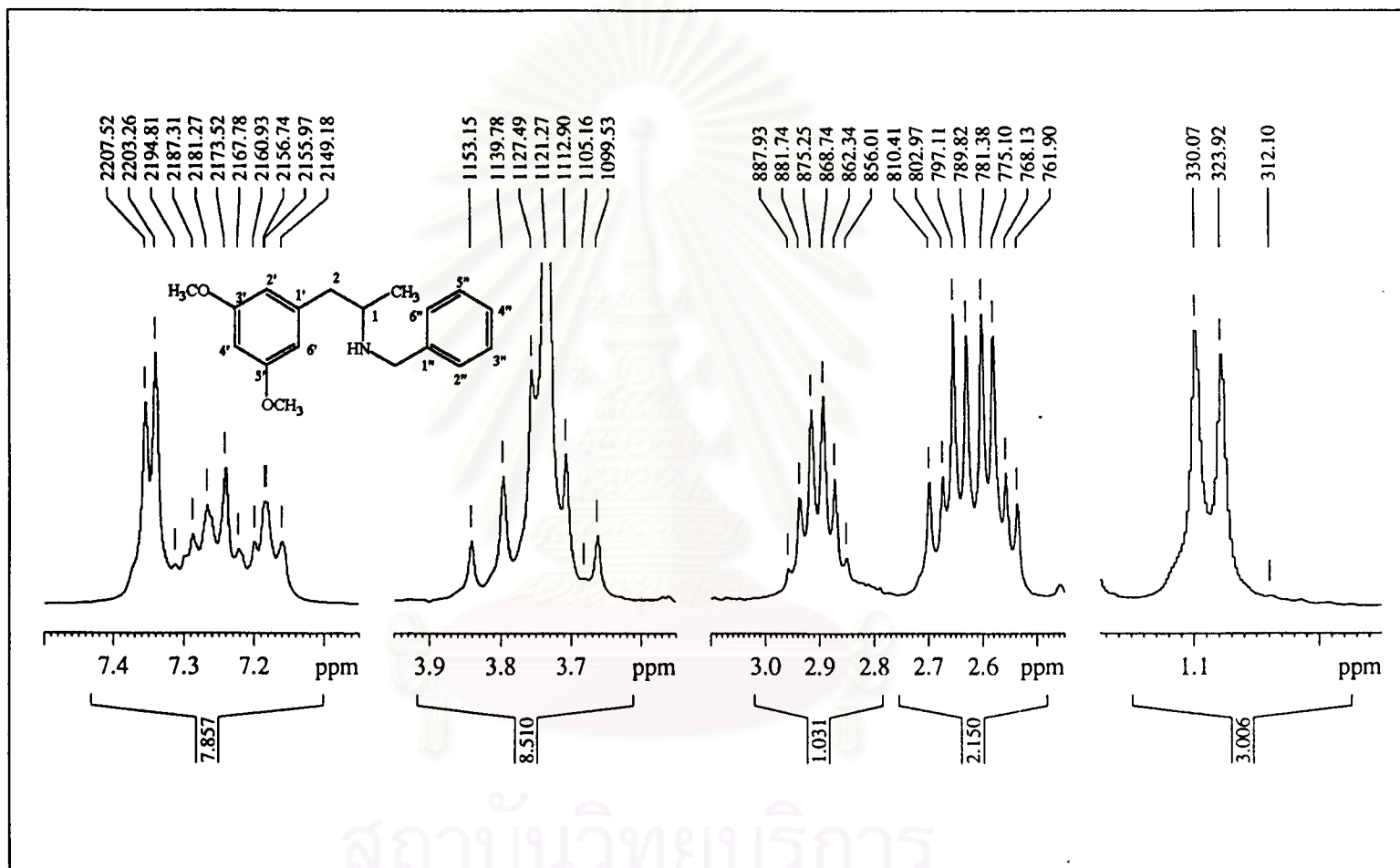
Figure 26 The 300 MHz ^{1}H-NMR spectrum of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-04)
(Enlarged scale)

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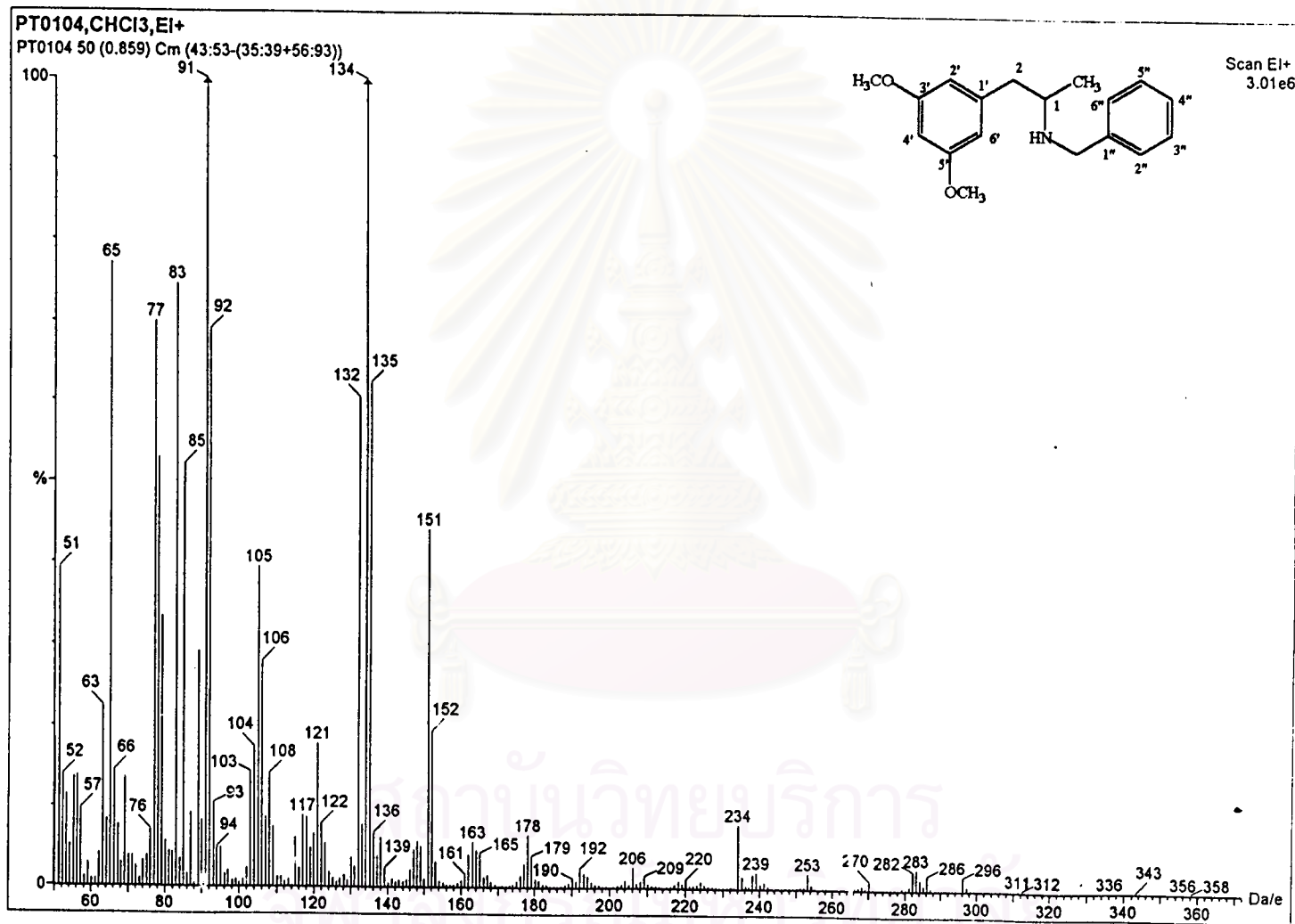
Figure 27 The electron impact mass spectrum of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-04)
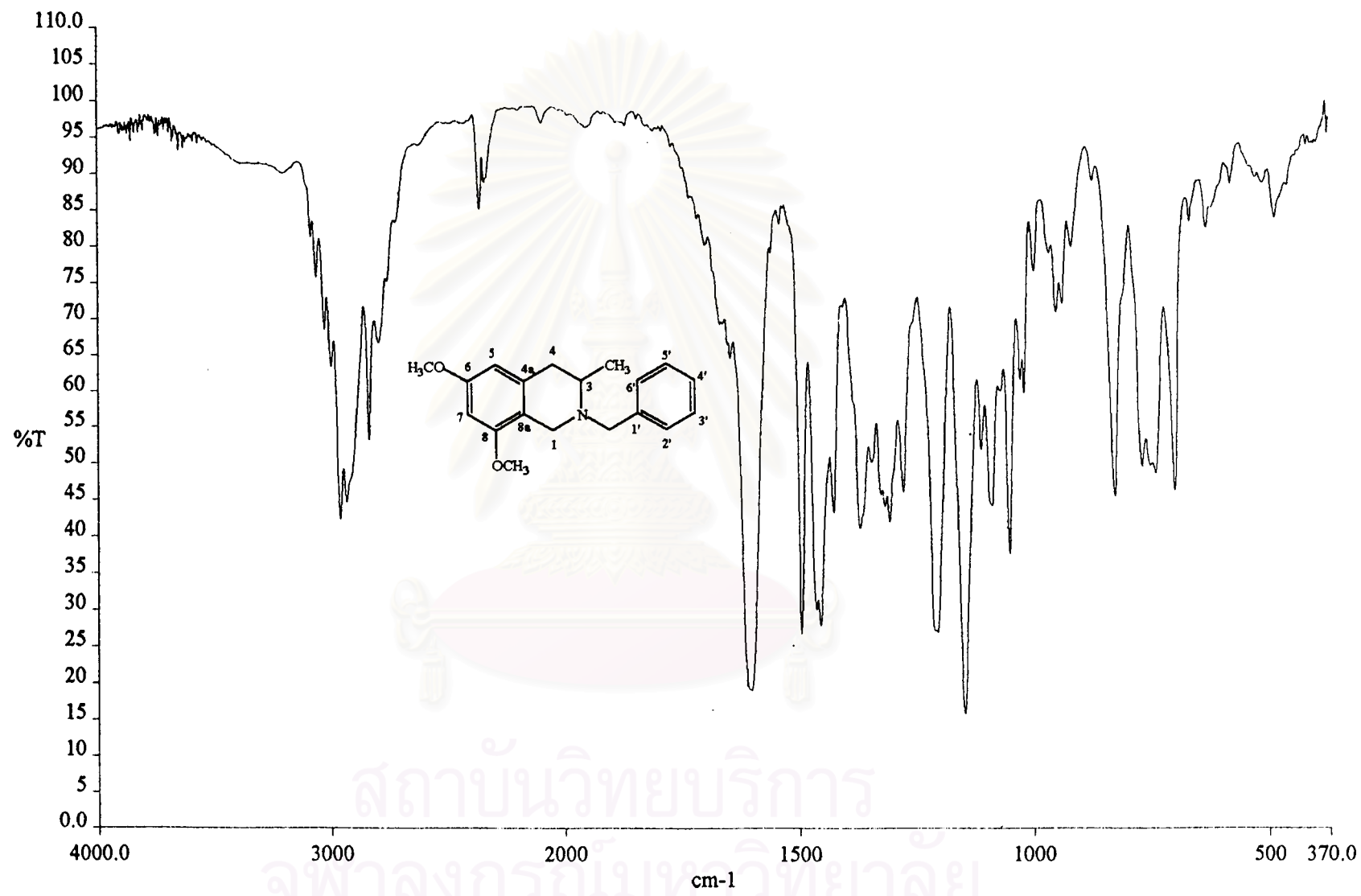
Figure 28 The IR spectrum (Neat) of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)
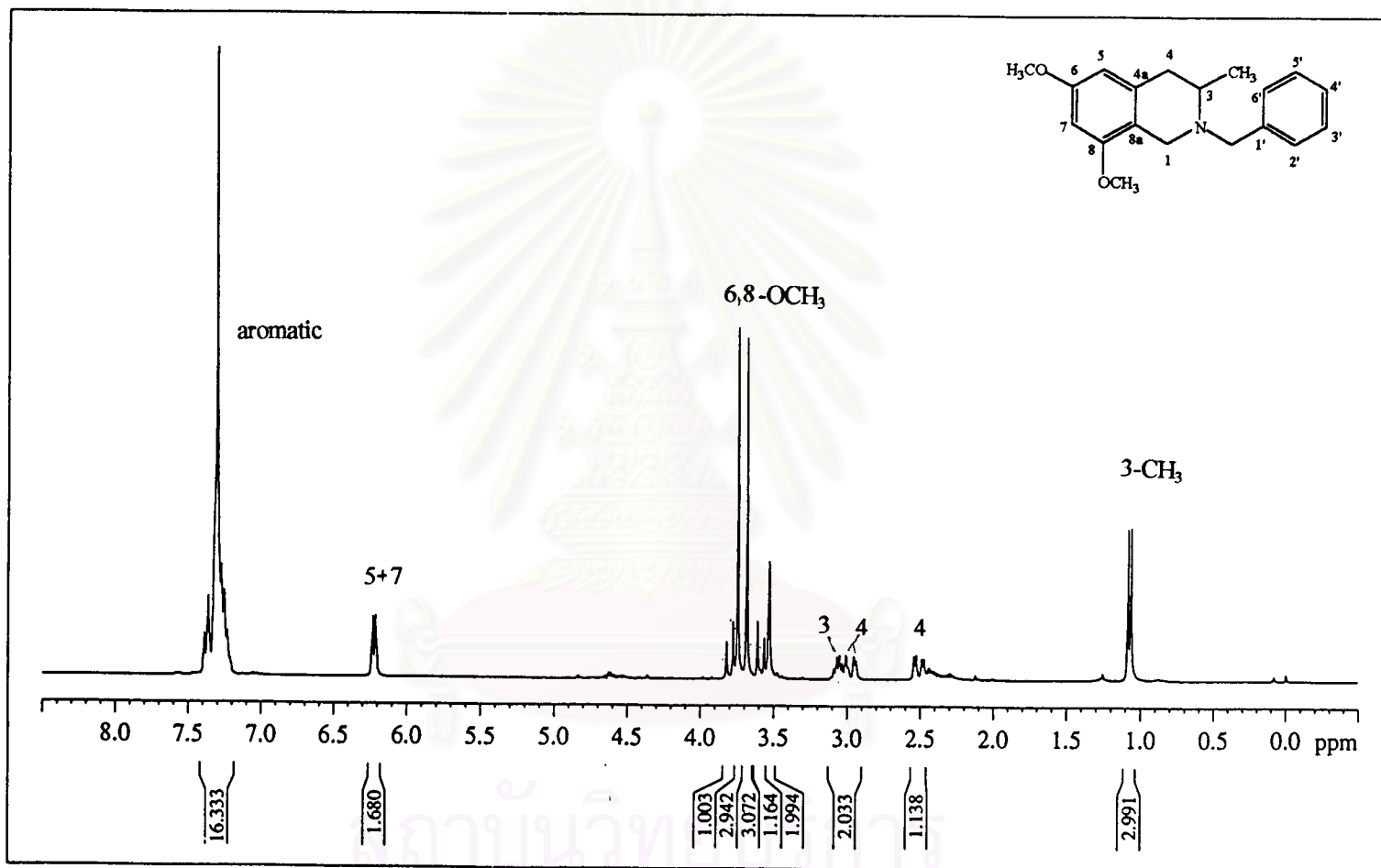
Figure 29 The 300 MHz ^{1}H-NMR spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)
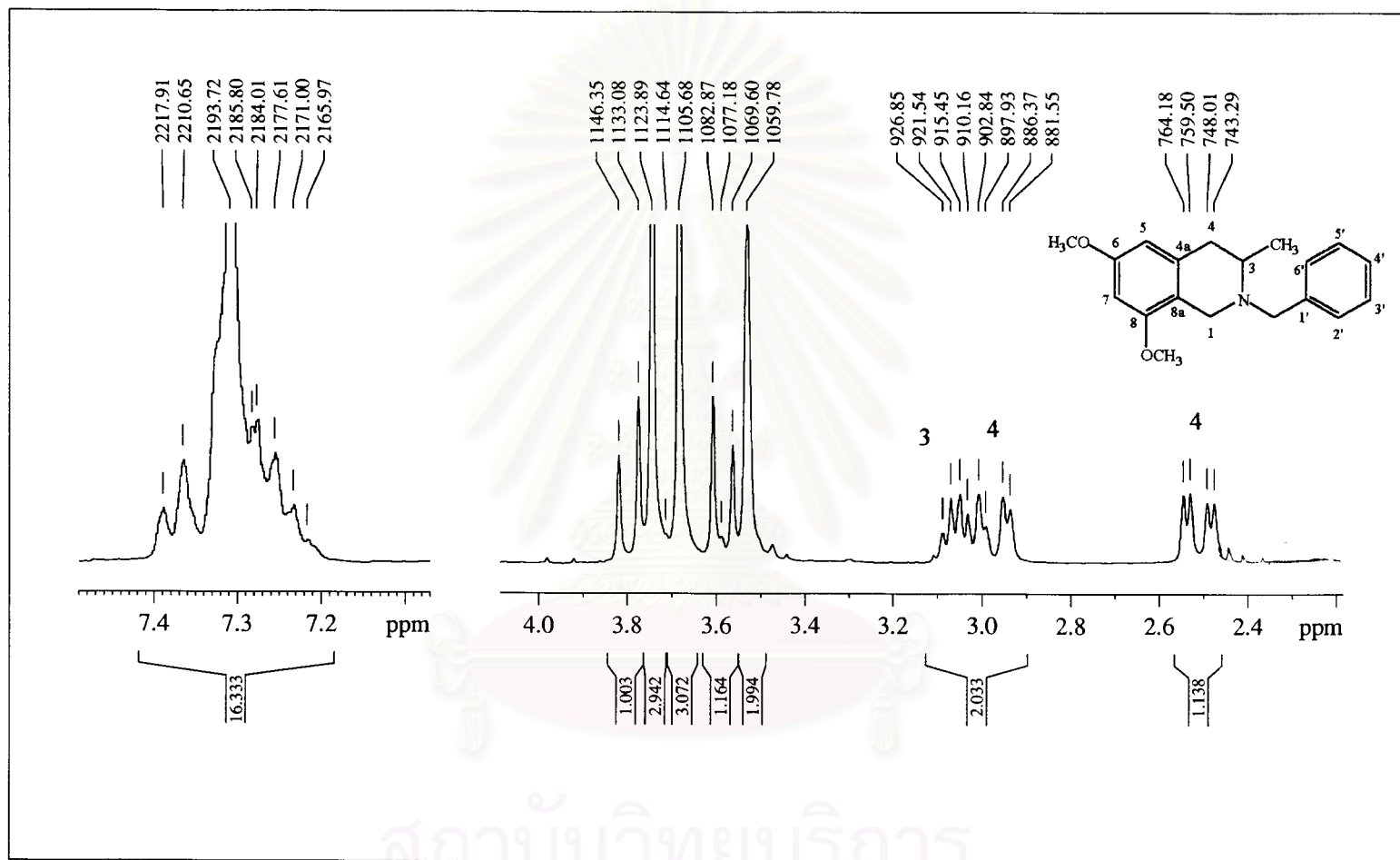
Figure 30 The 300 MHz ^{1}H-NMR spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05) (Enlarged scale)
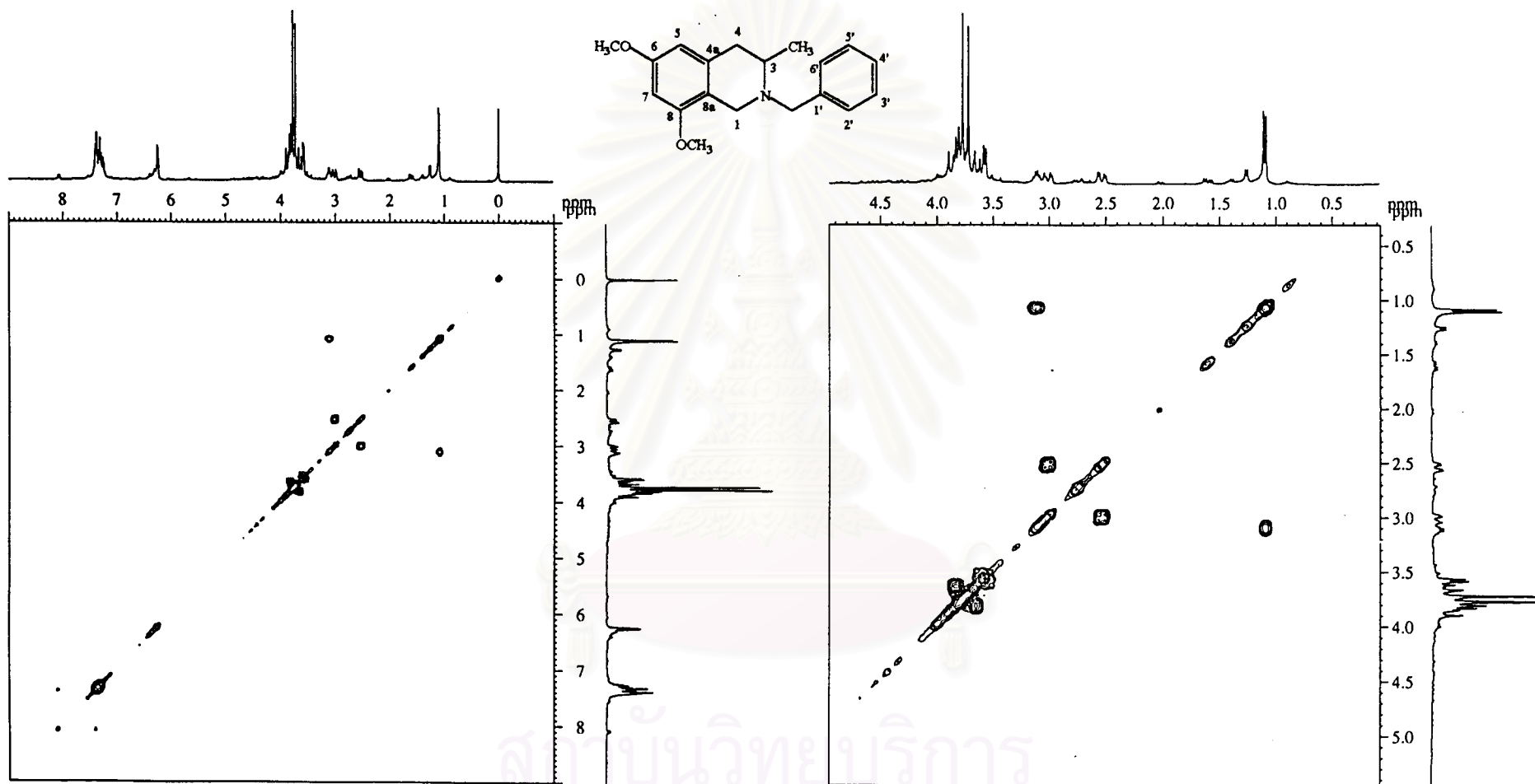
Figure 31 The 300 MHz COSY spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)

Figure 32 The 75 MHz ^{13}C-NMR spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)
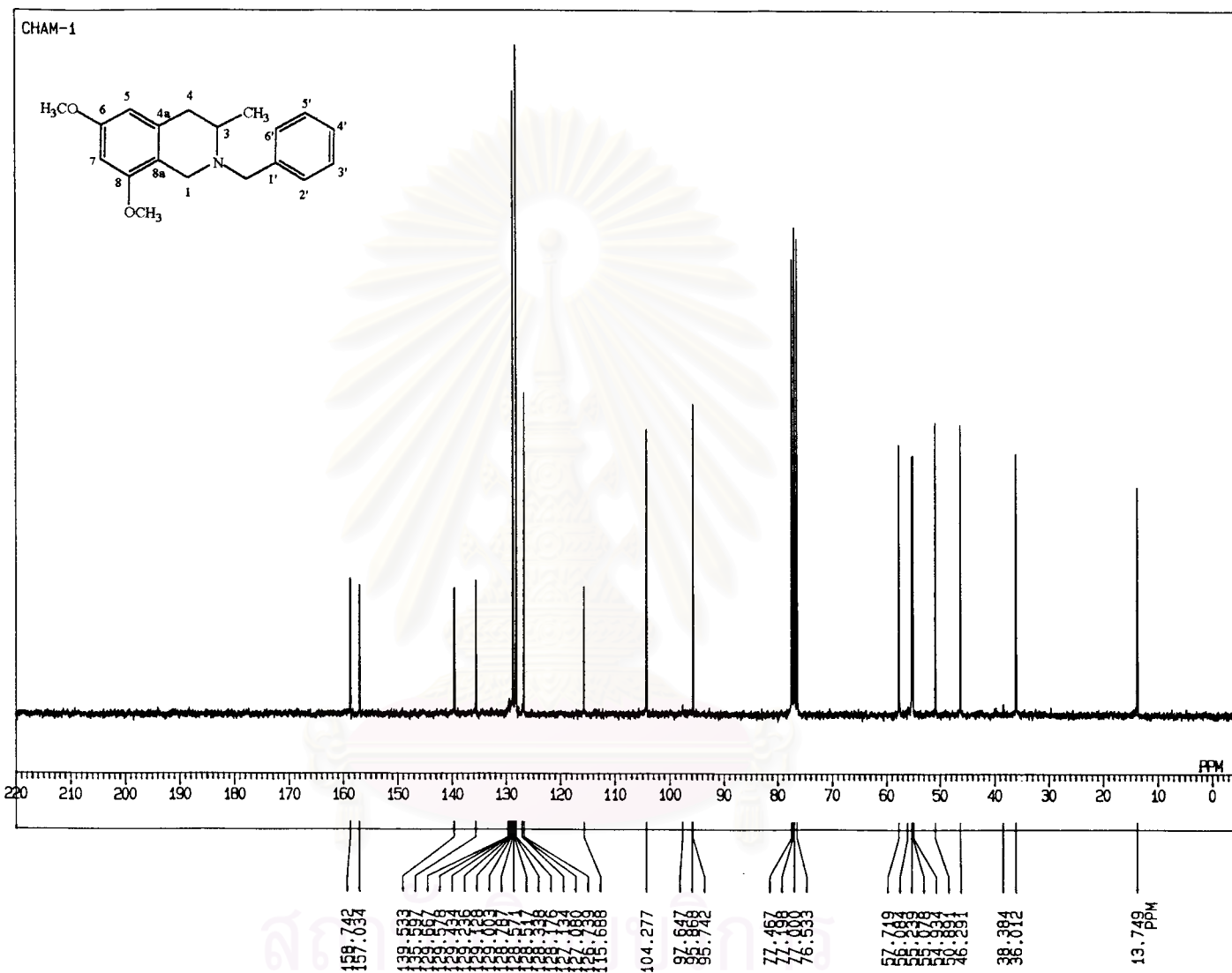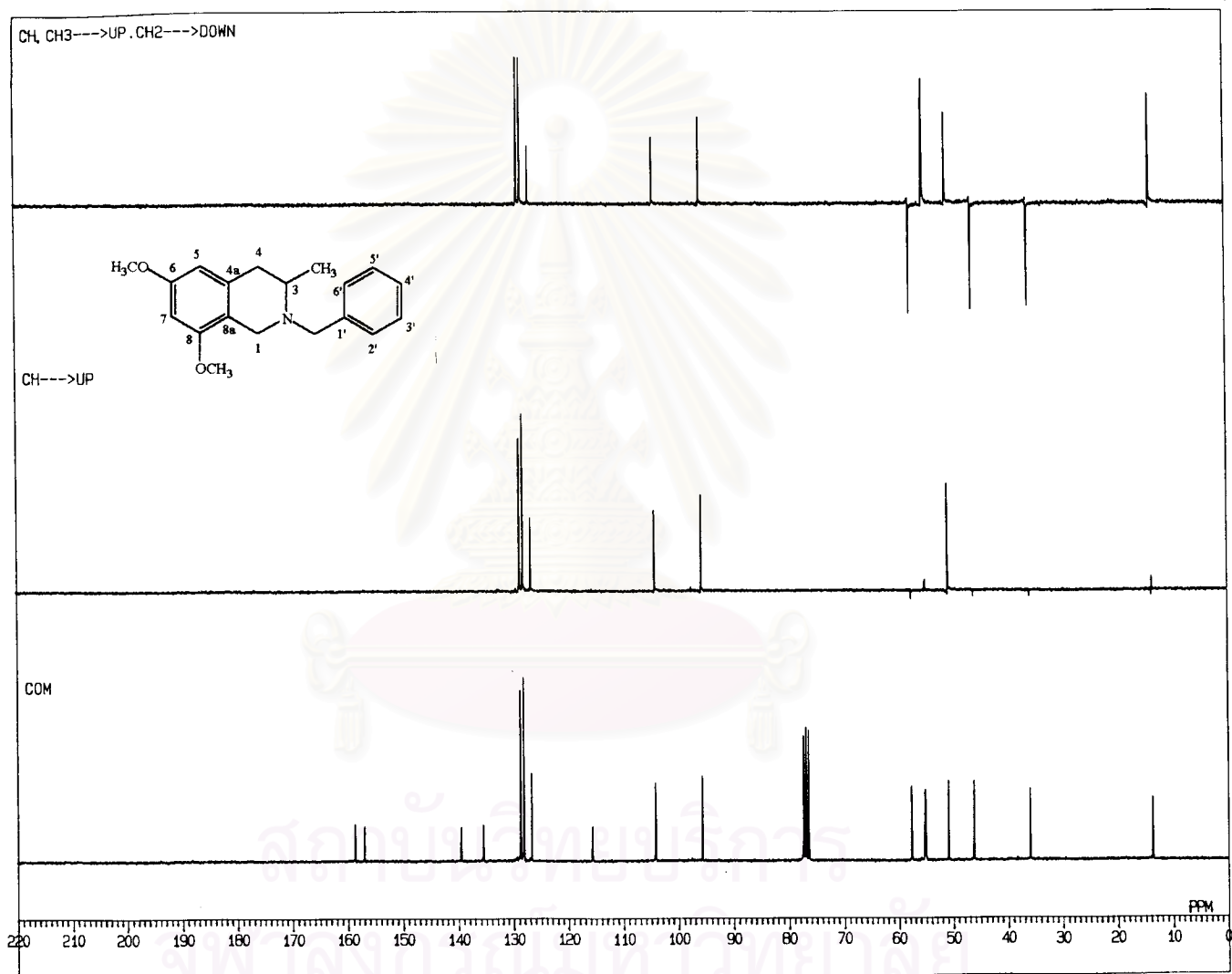
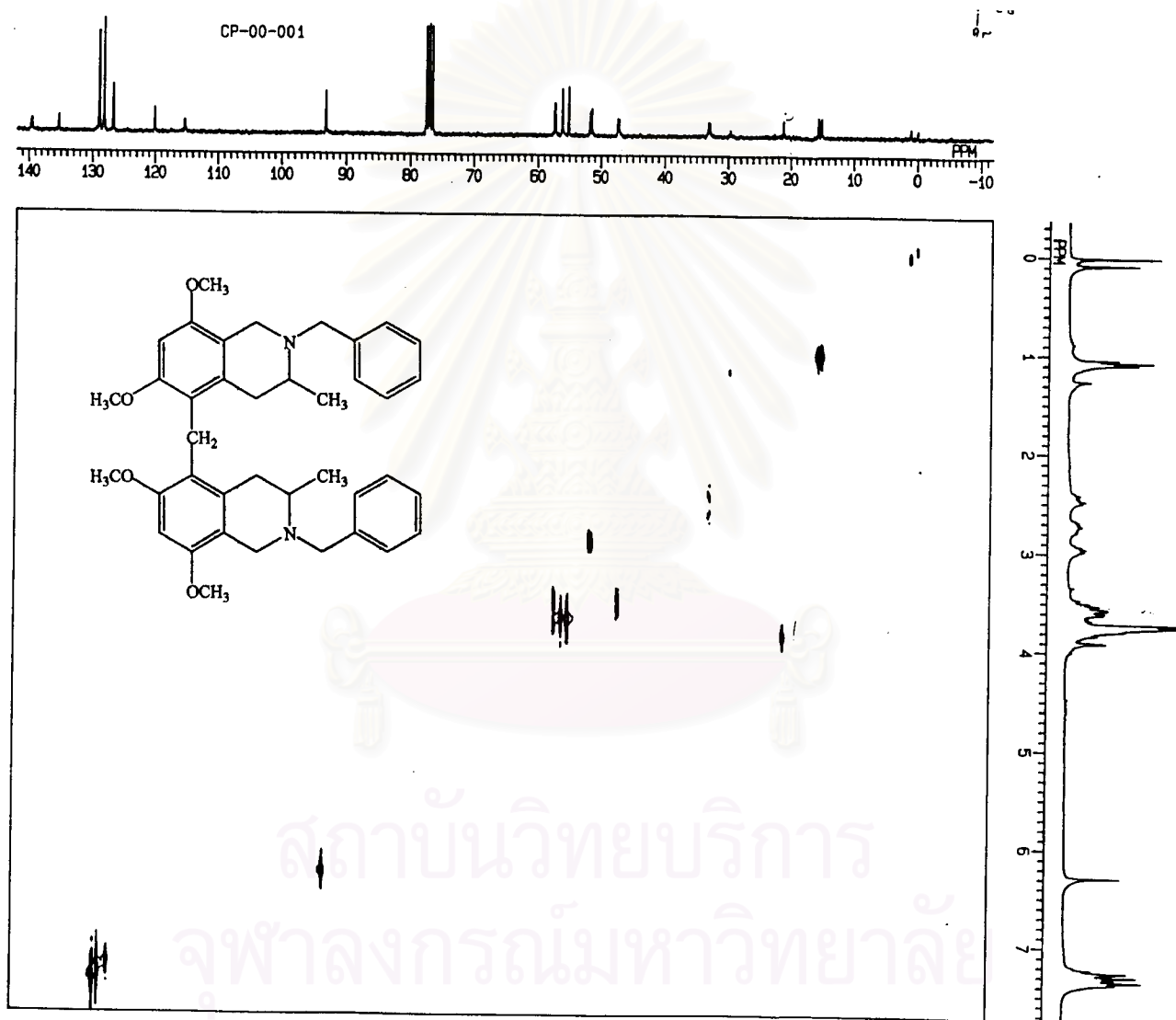Figure 33 The 75 MHz DEPT 135 spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)

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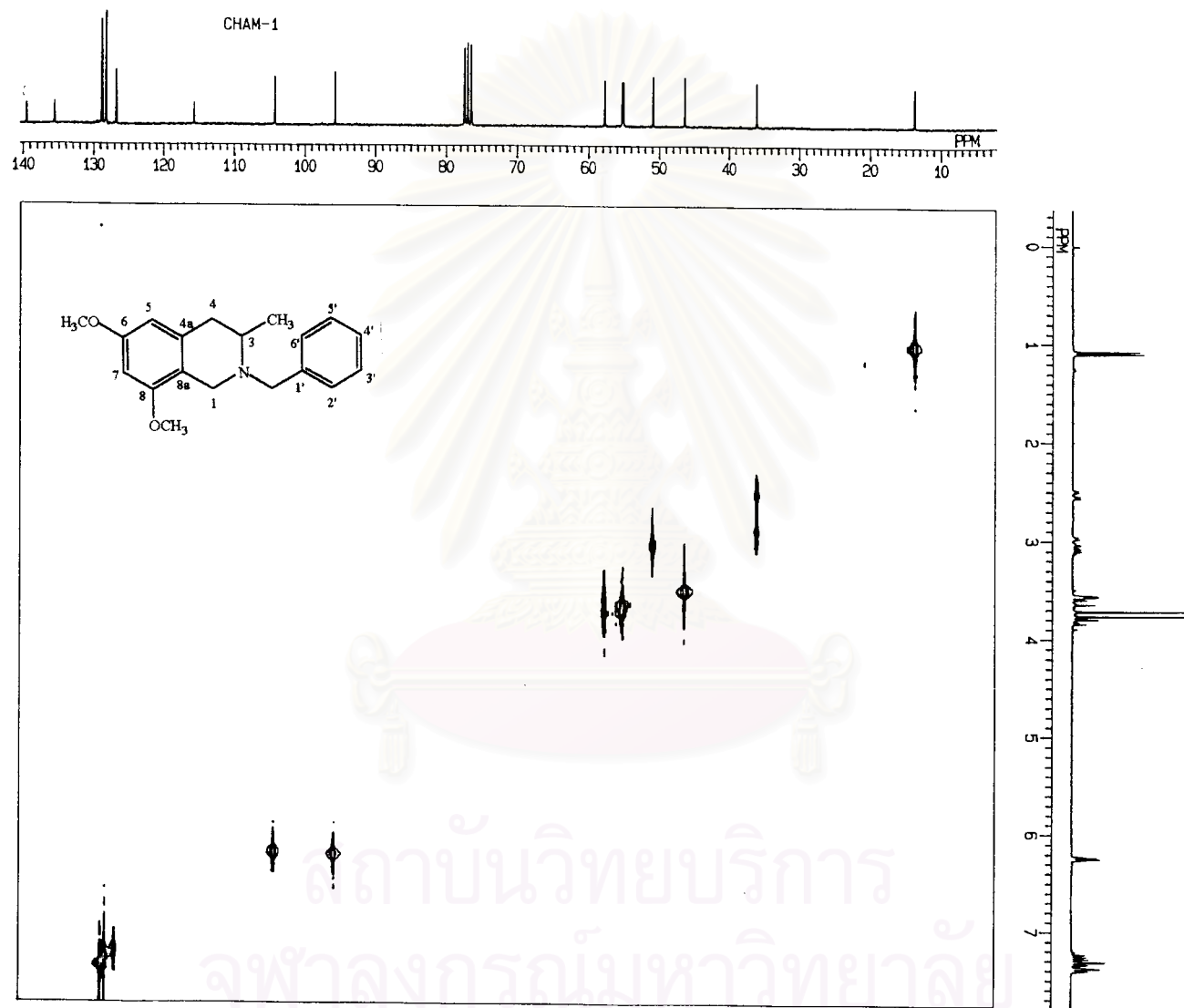
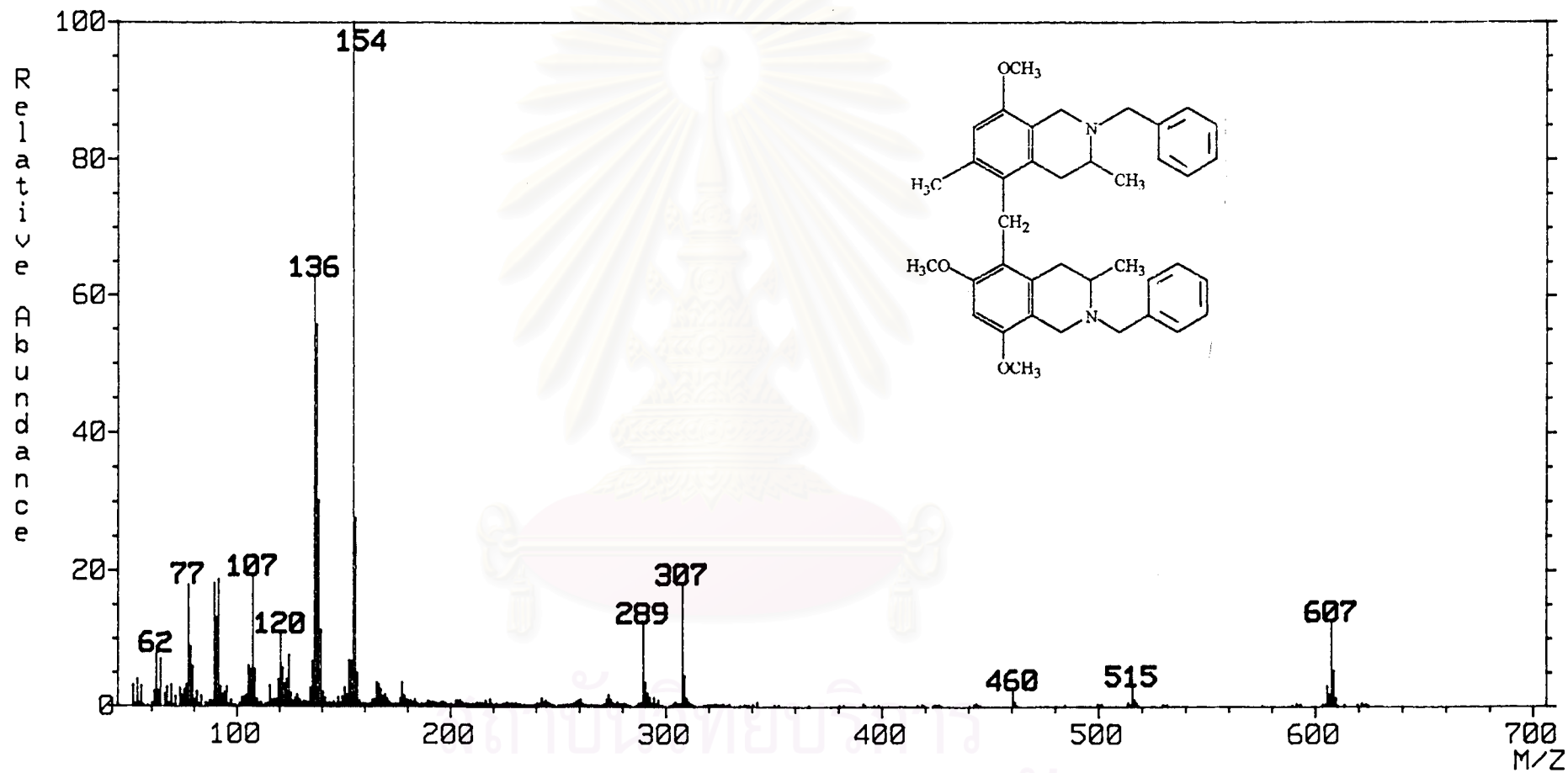Figure 34 The COLOC spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)
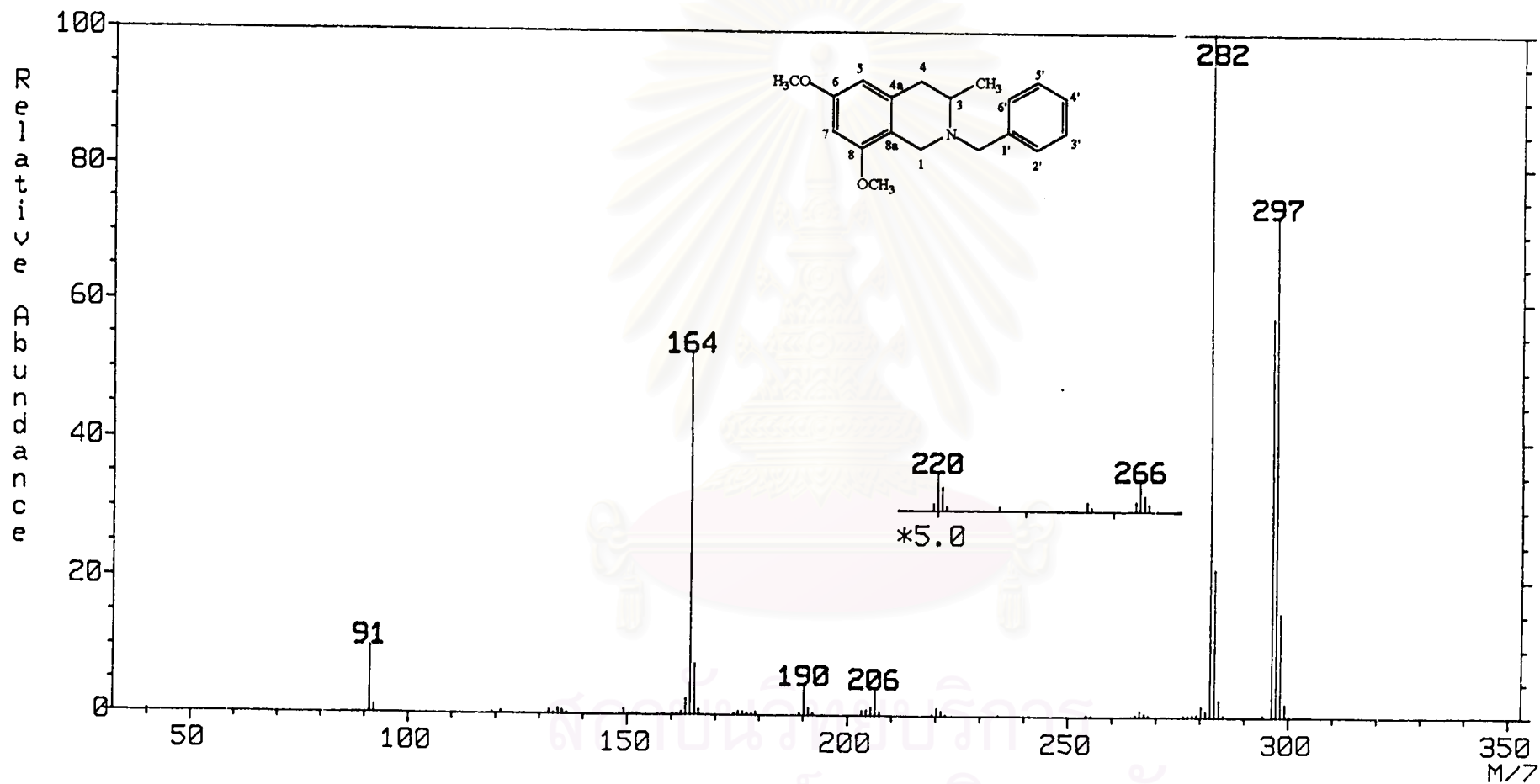
Figure 35 The electron impact mass spectrum of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)
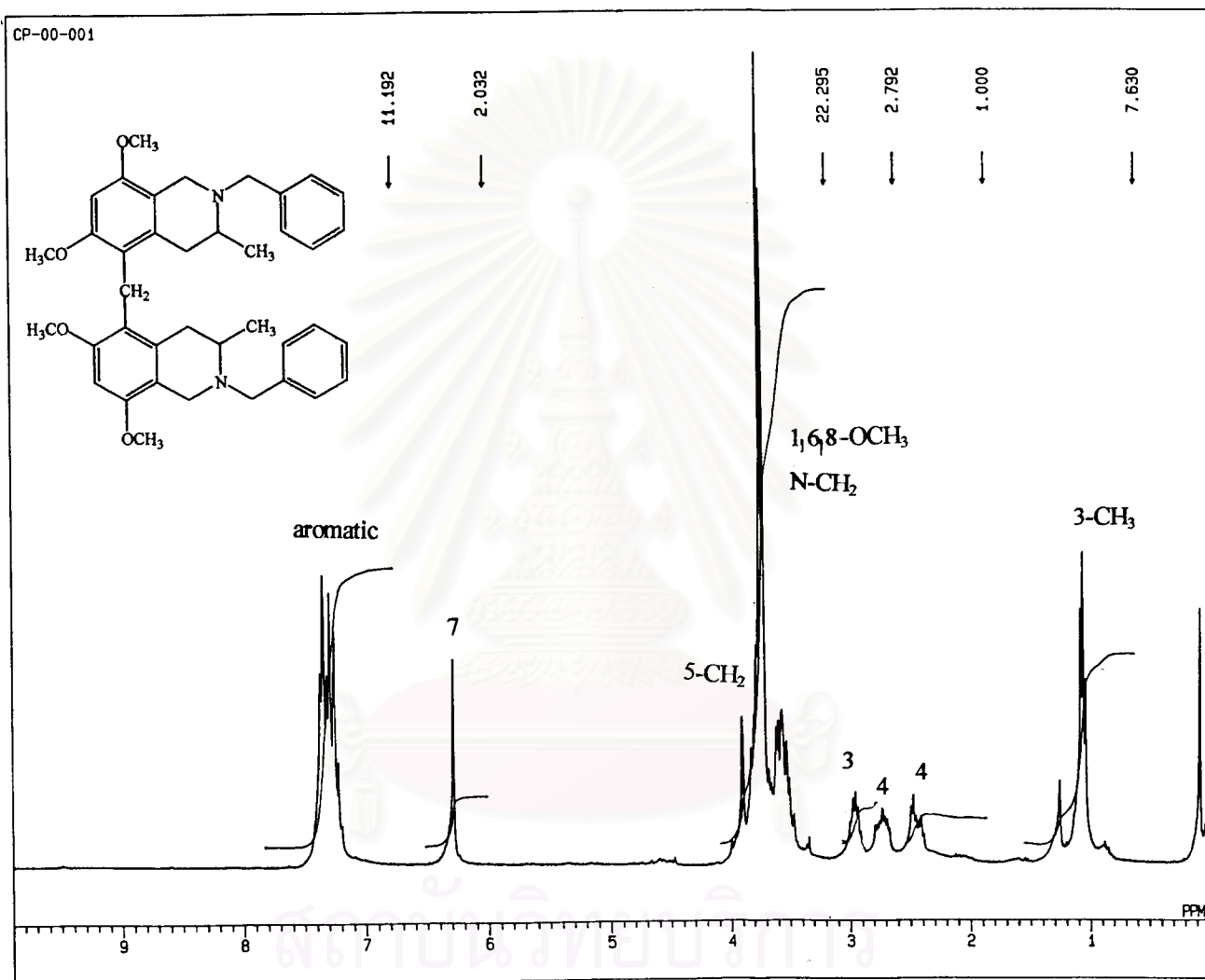
Figure 36 The 300 MHz ^{1}H-NMR spectrum of 5,5′-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline
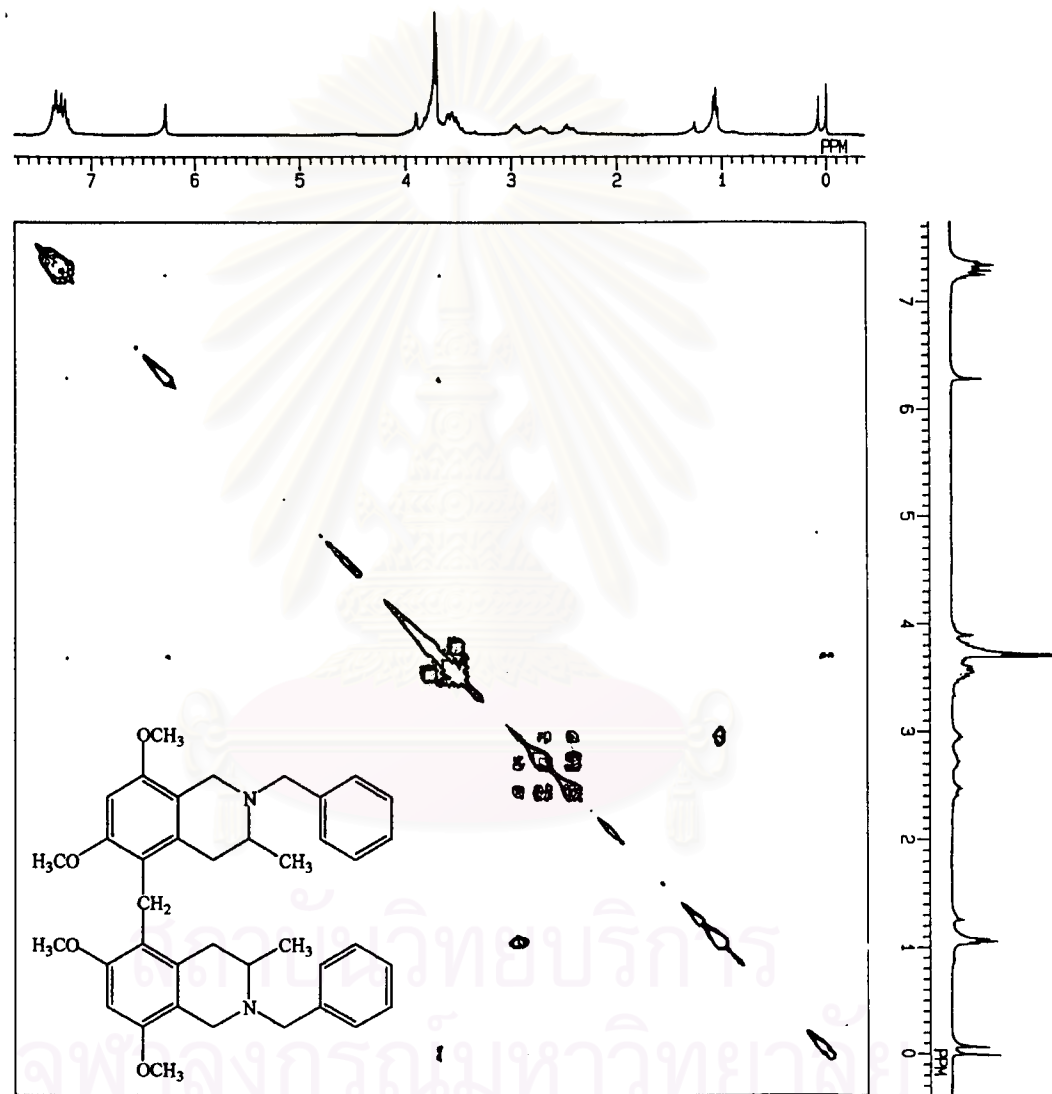
Figure 37 The 300 MHz COSY spectrum of 5,5′-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline
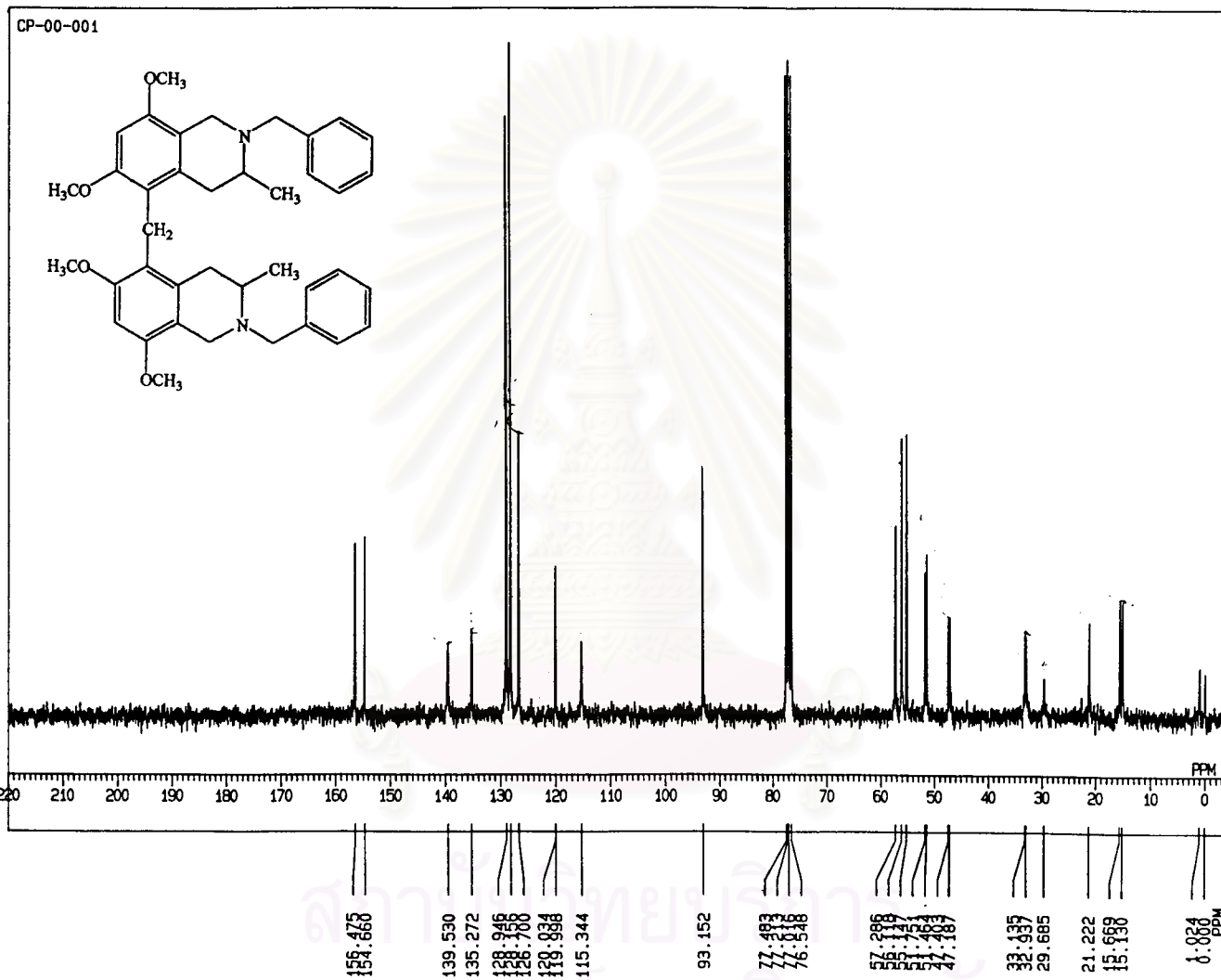
Figure 38 The 75 MHz ^{13}C-NMR spectrum of 5,5'-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline
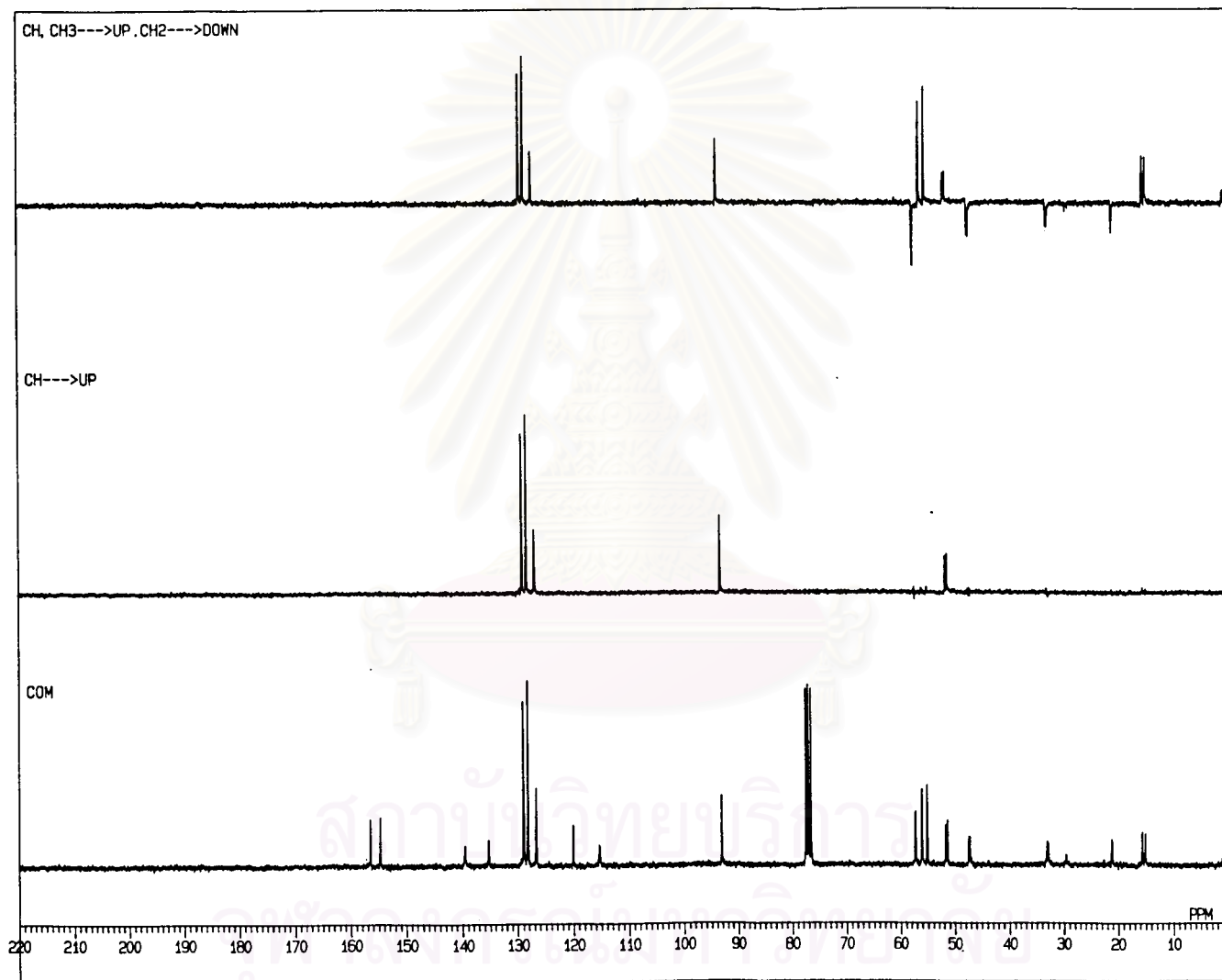
Figure 39 The 75 MHz DEPT 135 spectrum of 5,5′-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline

Figure 40 The COLOG spectrum of 5,5′-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline

Figure 41 The Mass spectrum of 5,5′-bis(methylene)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline
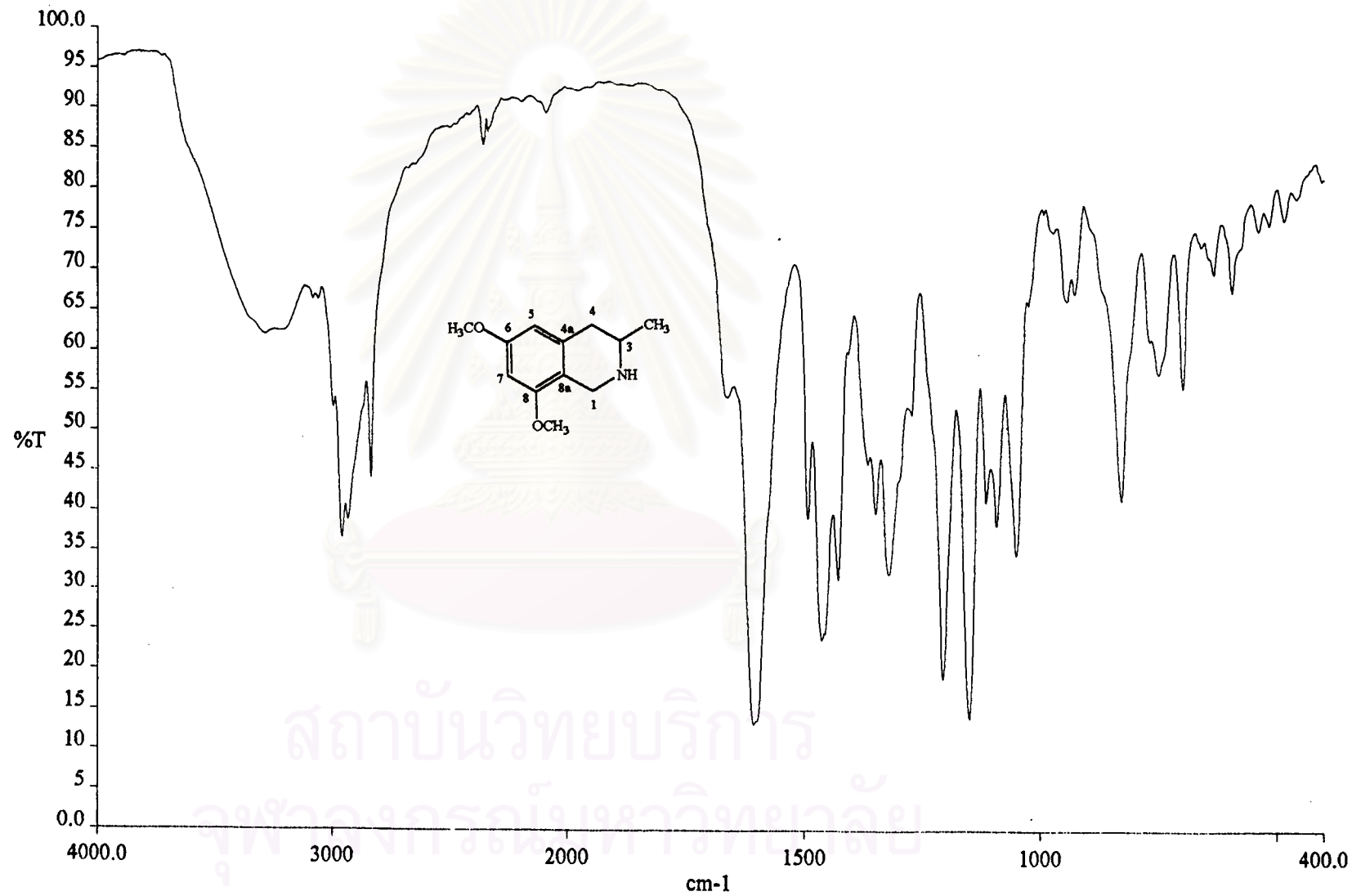
Figure 42 The IR spectrum (Neat) of 6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-06)
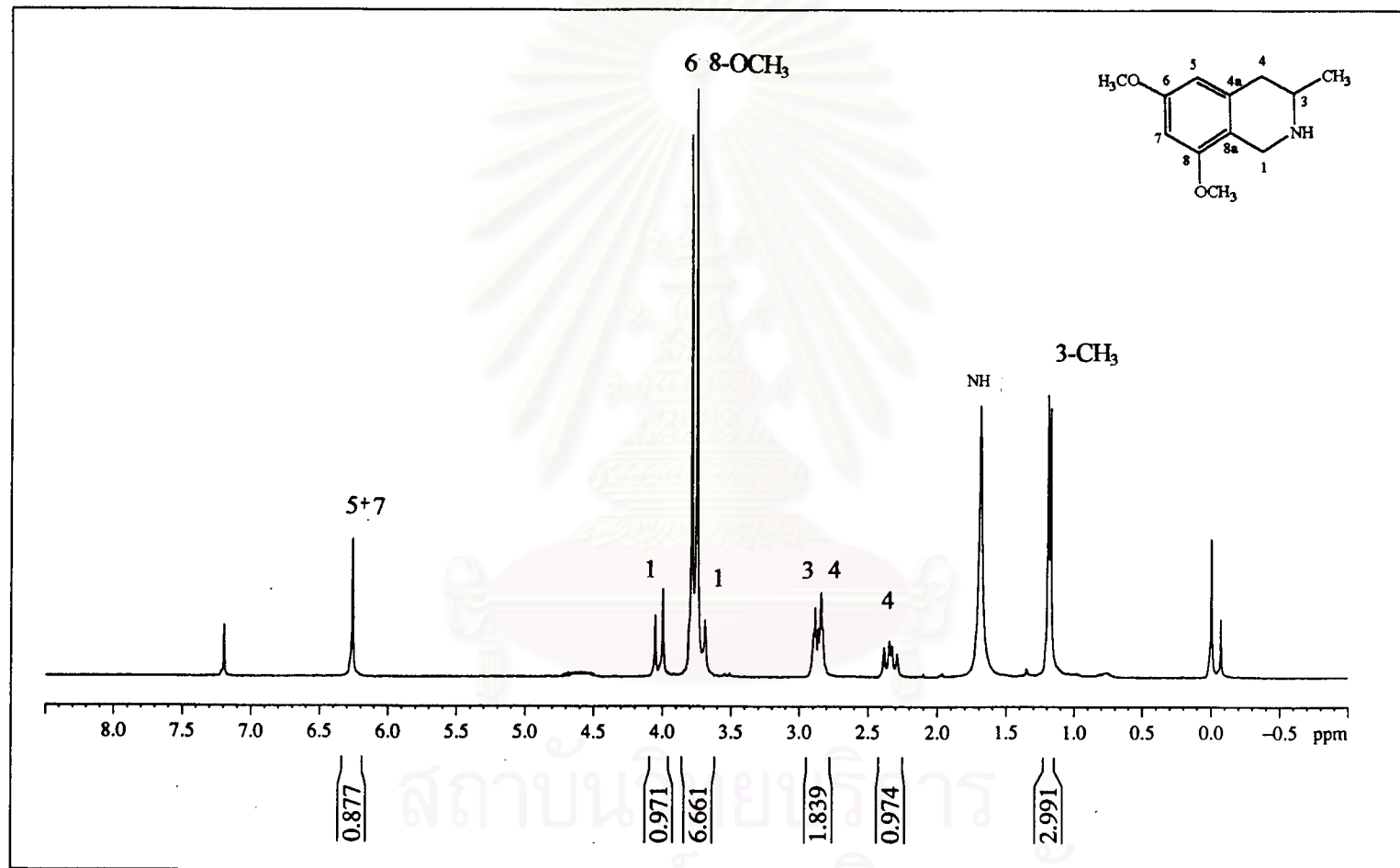
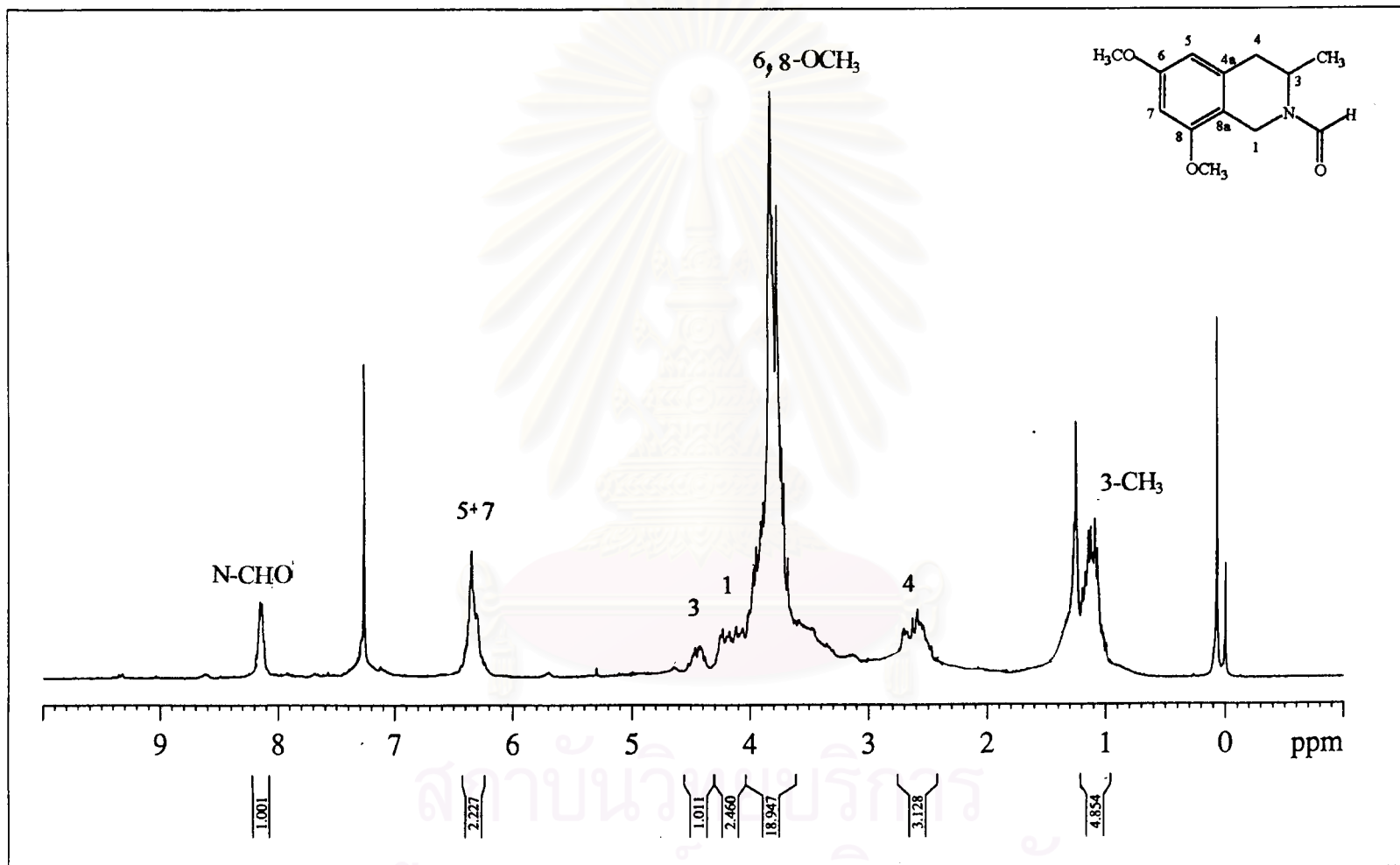Figure 43 The 300 MHz ^{1}H-NMR spectrum of 6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-06)
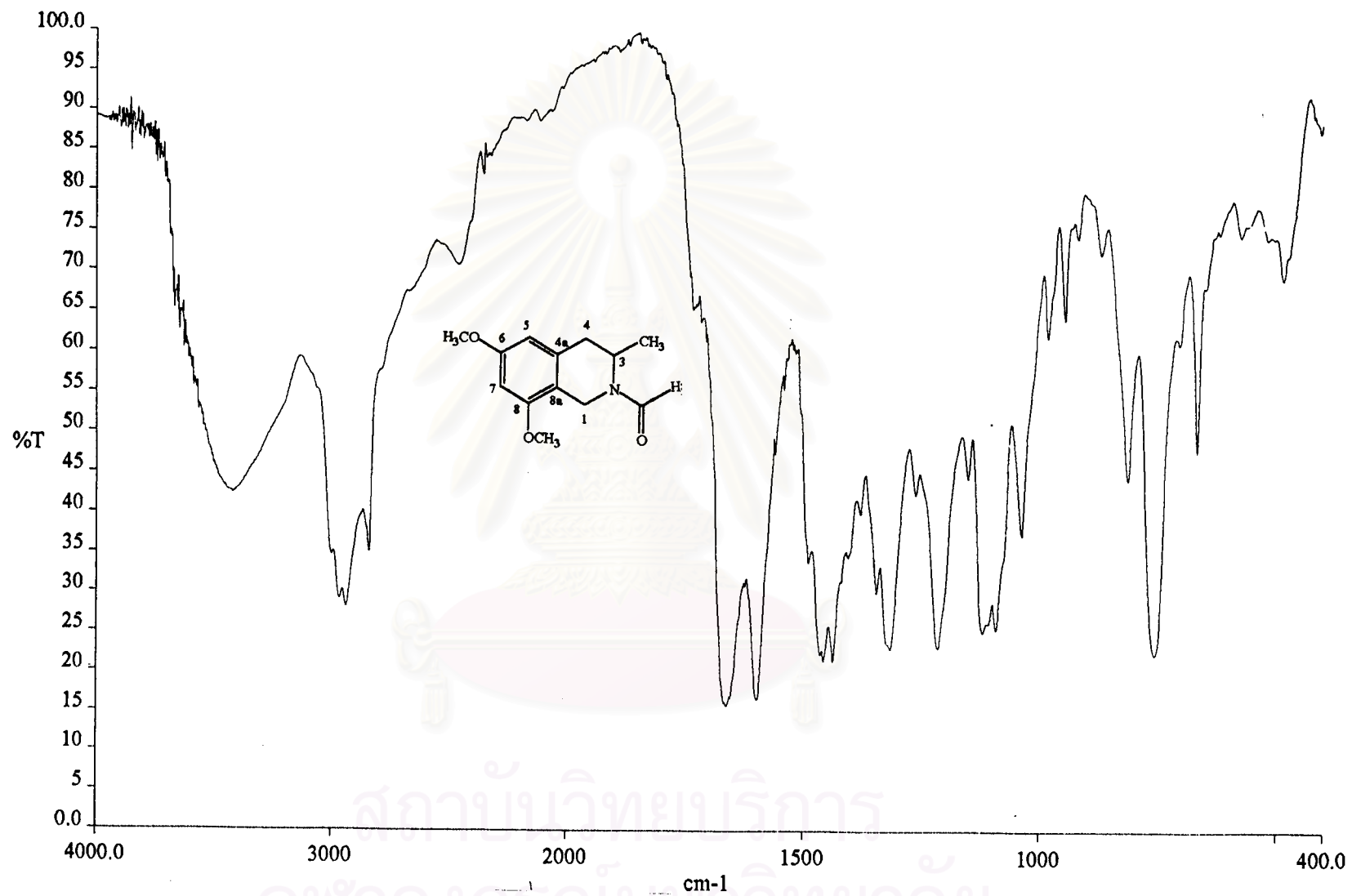
Figure 44 The IR spectrum (Neat) of 2-formyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-07)

Figure 45 The 300 MHz ^{1}H-NMR spectrum of 2-formyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-07)
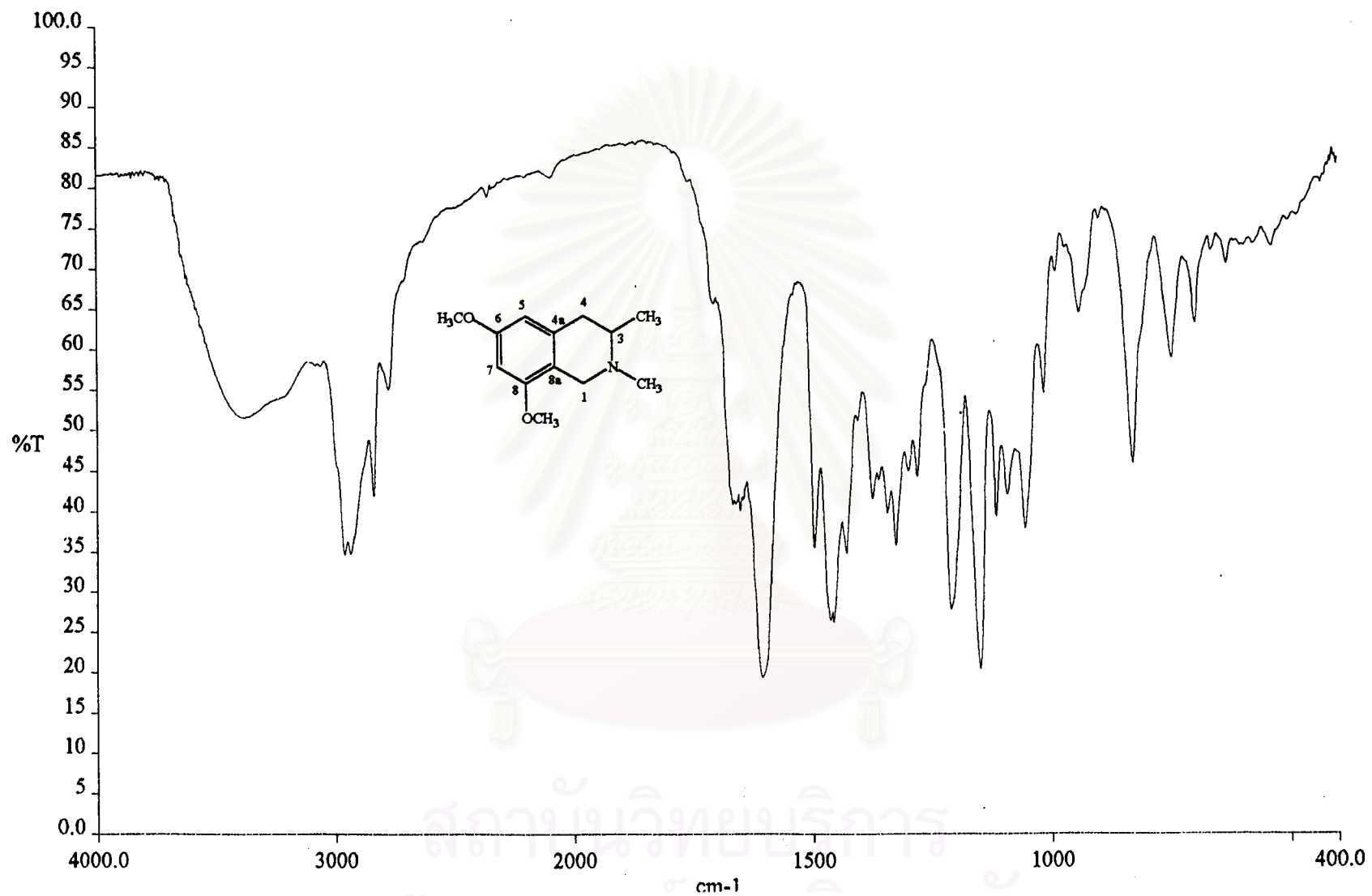
Figure 46 The IR spectrum (Neat) of 6,8-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydro-isoquinoline (CU-19-08)
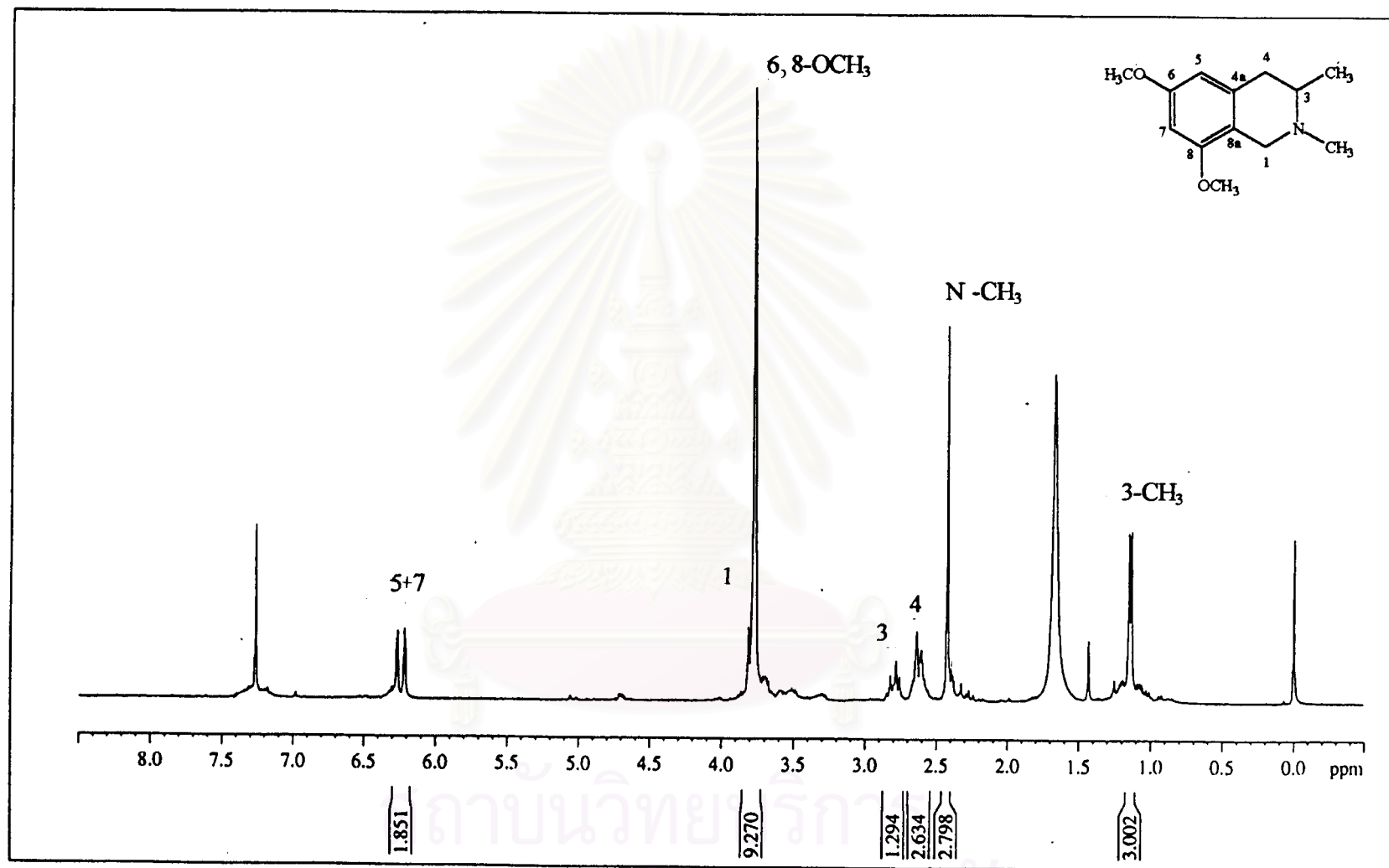
Figure 47 The 300 MHz ^{1}H-NMR spectrum of 6,8-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydro-isoquinoline (CU-19-08)
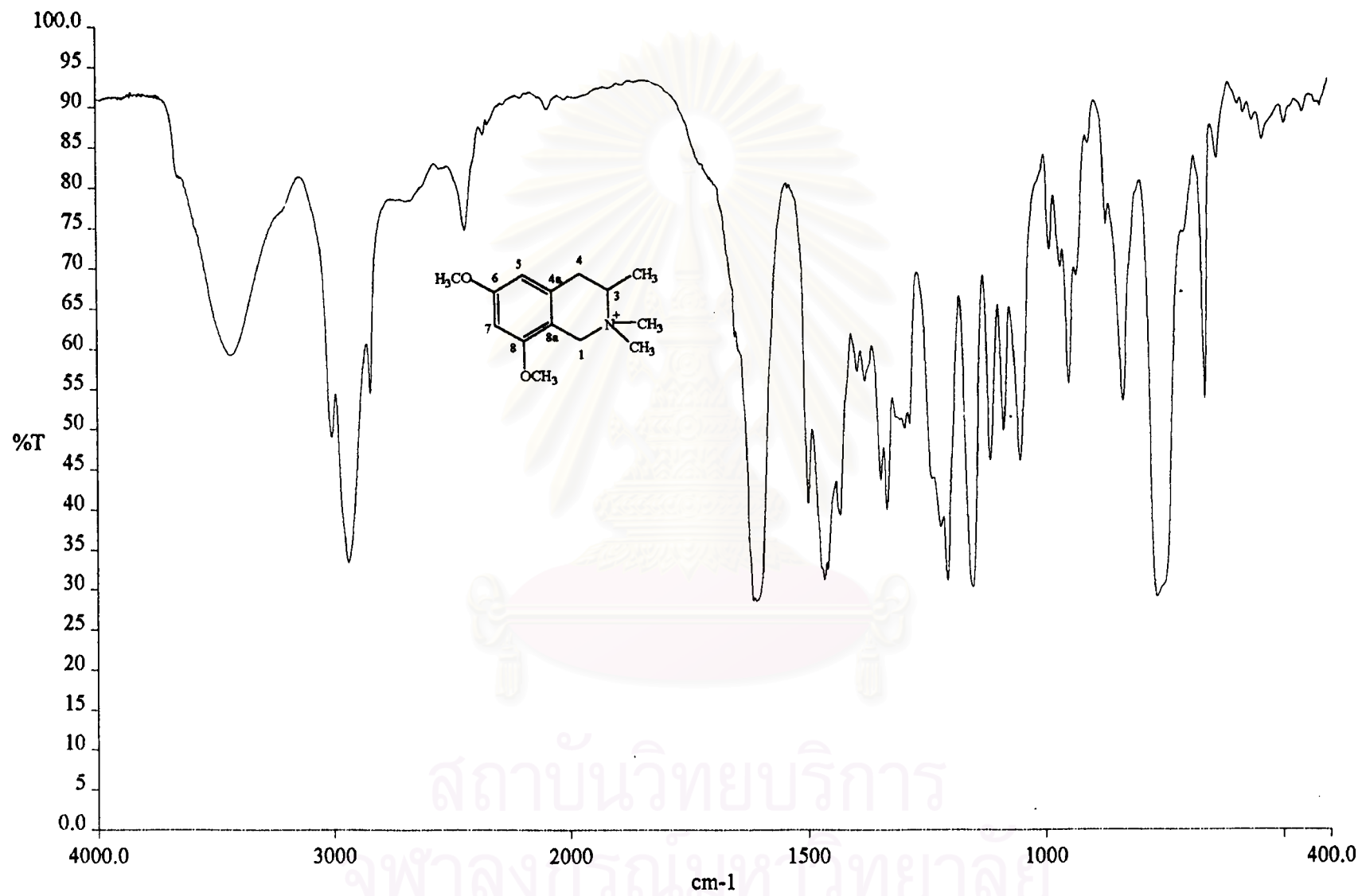
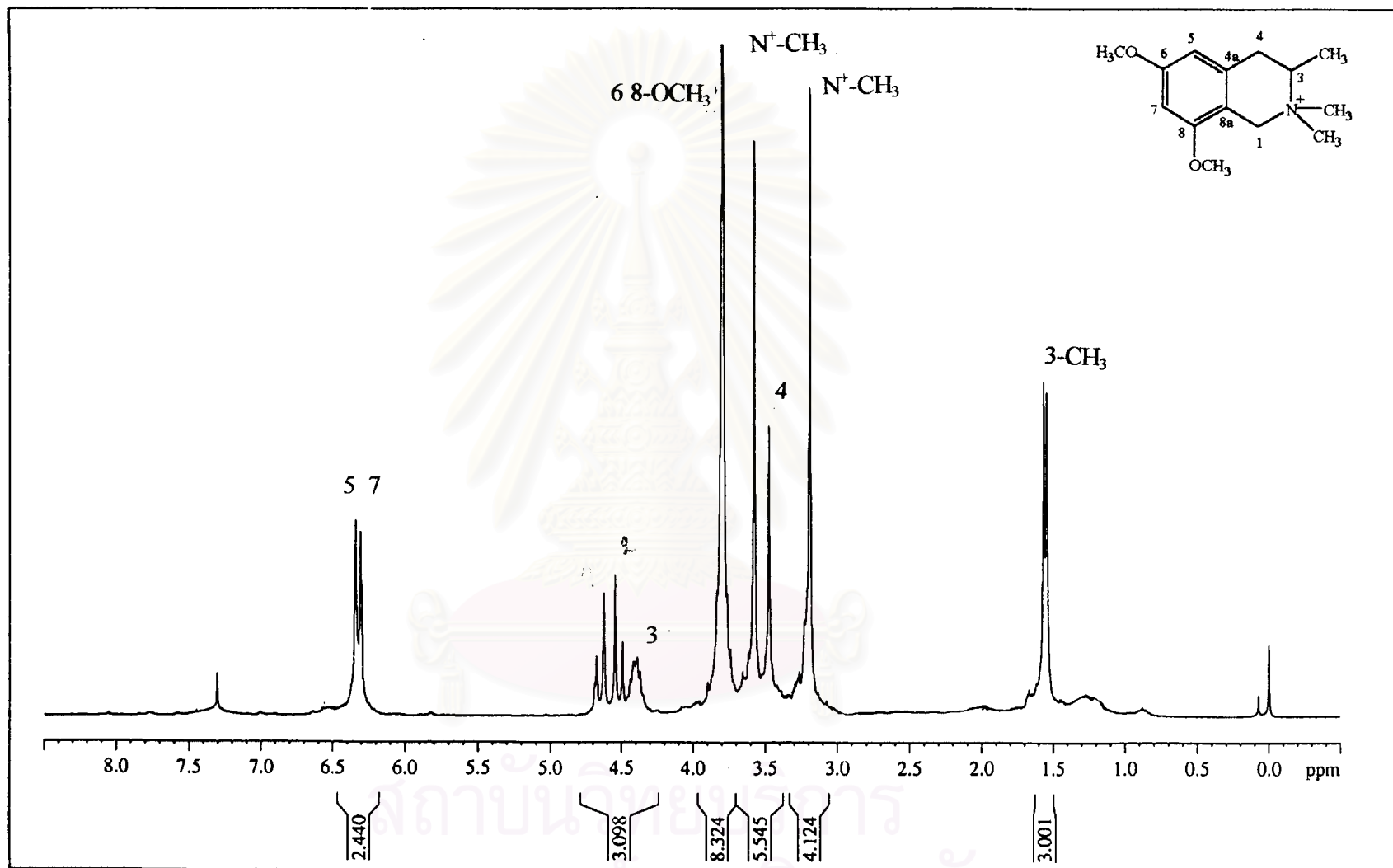Figure 48 The IR spectrum (Neat) of 6,8-dimethoxy-2,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-09)

Figure 49 The 300 MHz ^{1}H-NMR spectrum 6,8-dimethoxy-2,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-09)
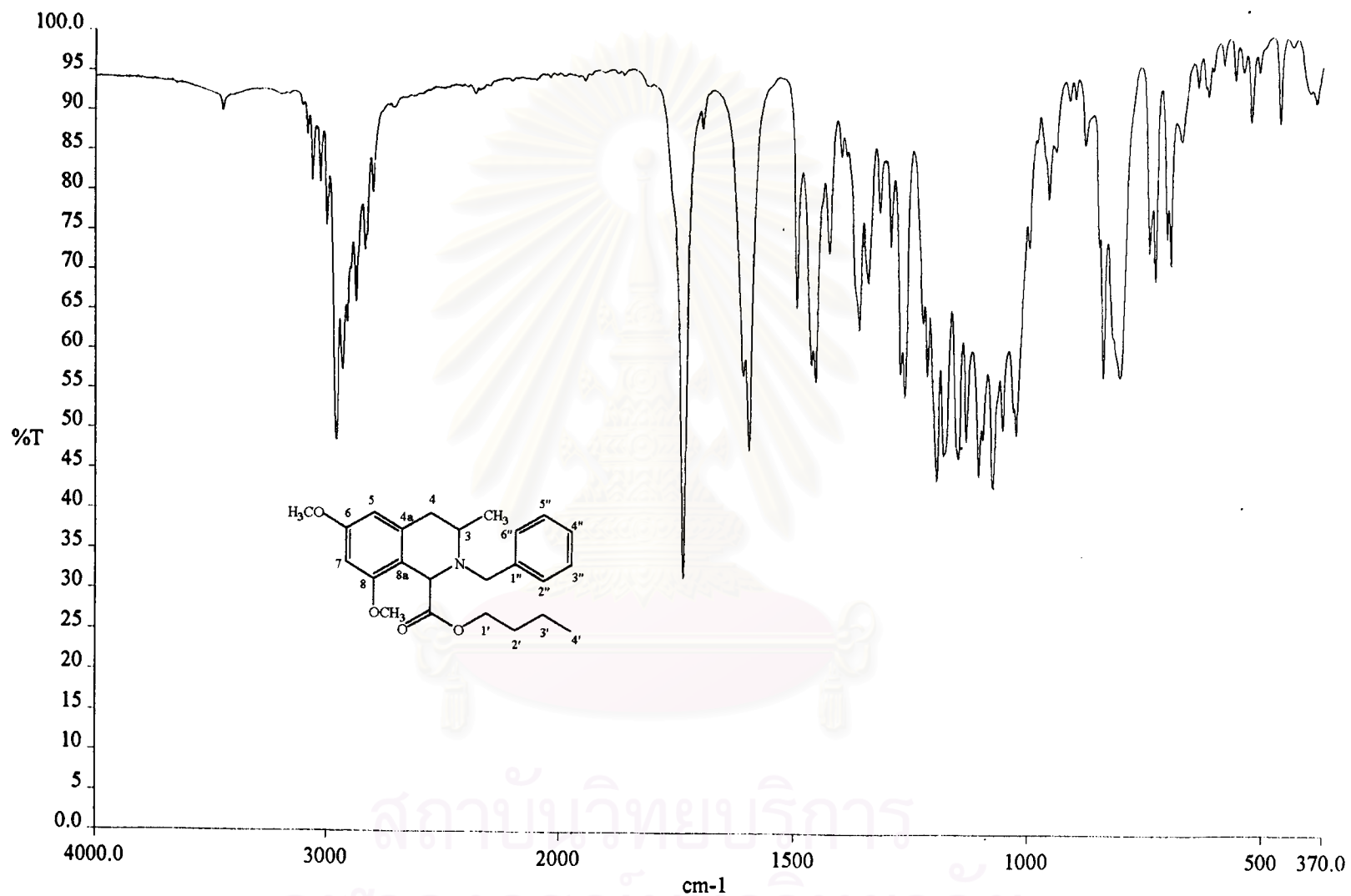
Figure 50 The IR spectrum (Neat) of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-10)
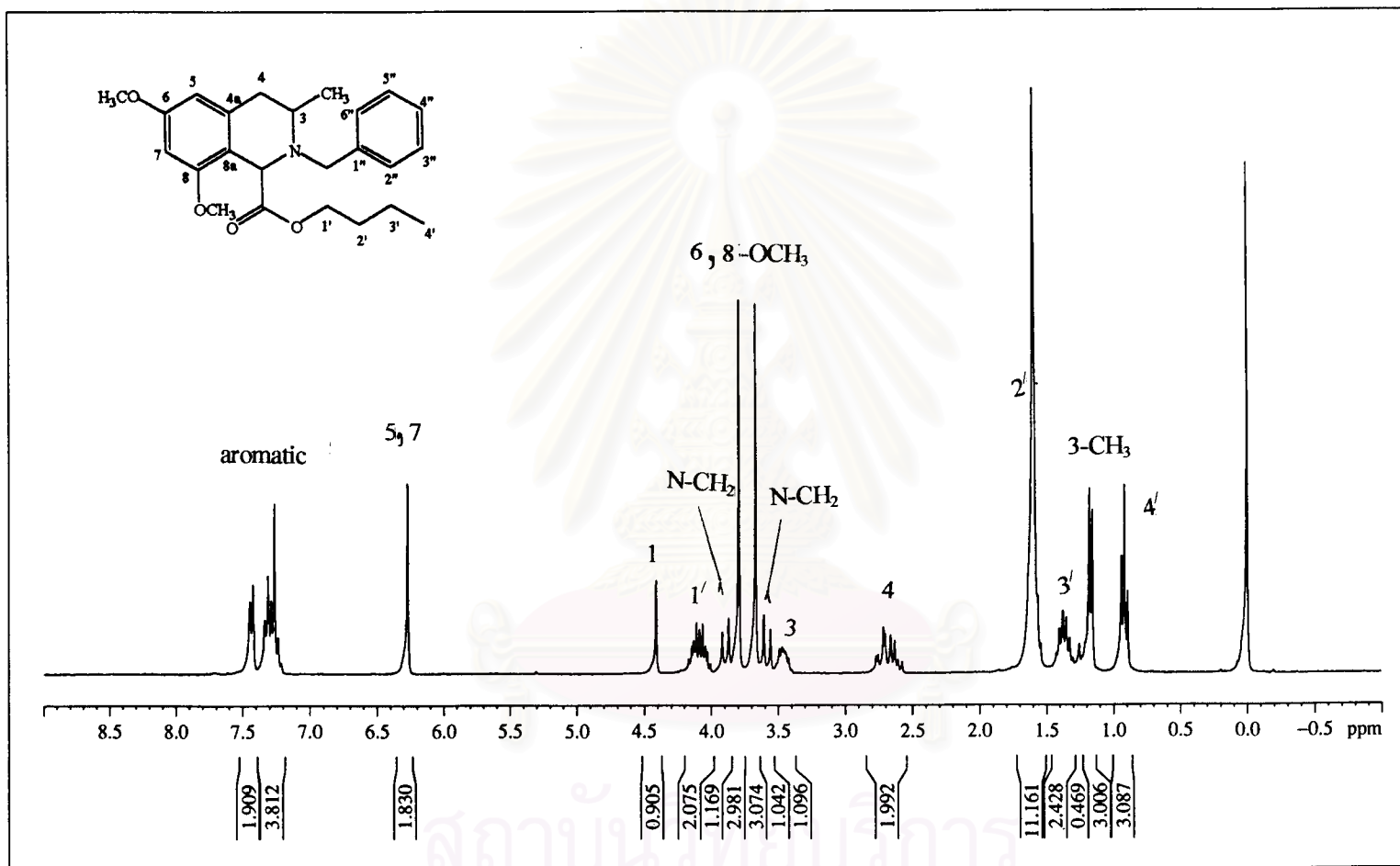
Figure 51 The 300 MHz ^{1}H-NMR spectrum of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-10)
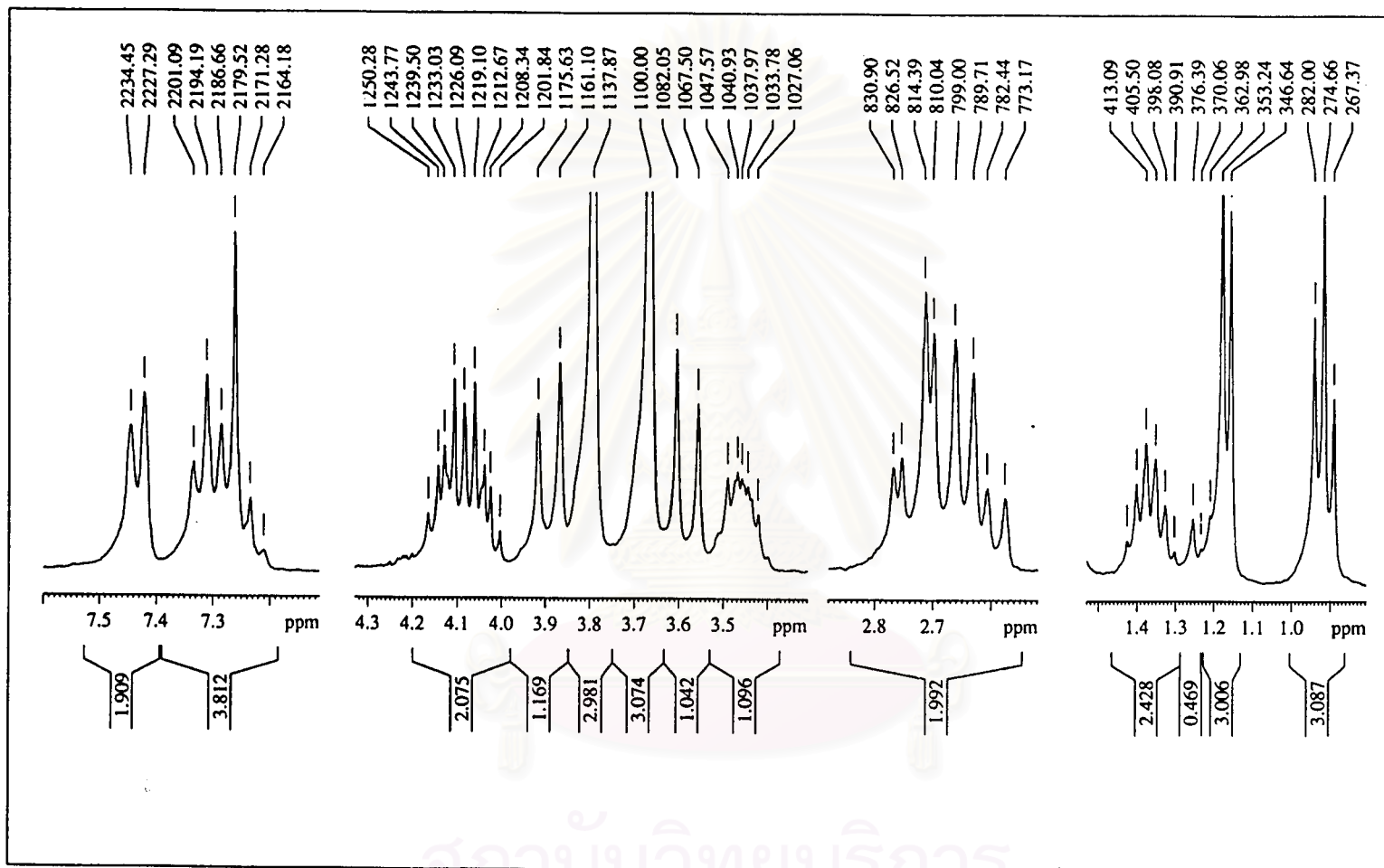
Figure 52 The 300 MHz ¹H-NMR spectrum of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate
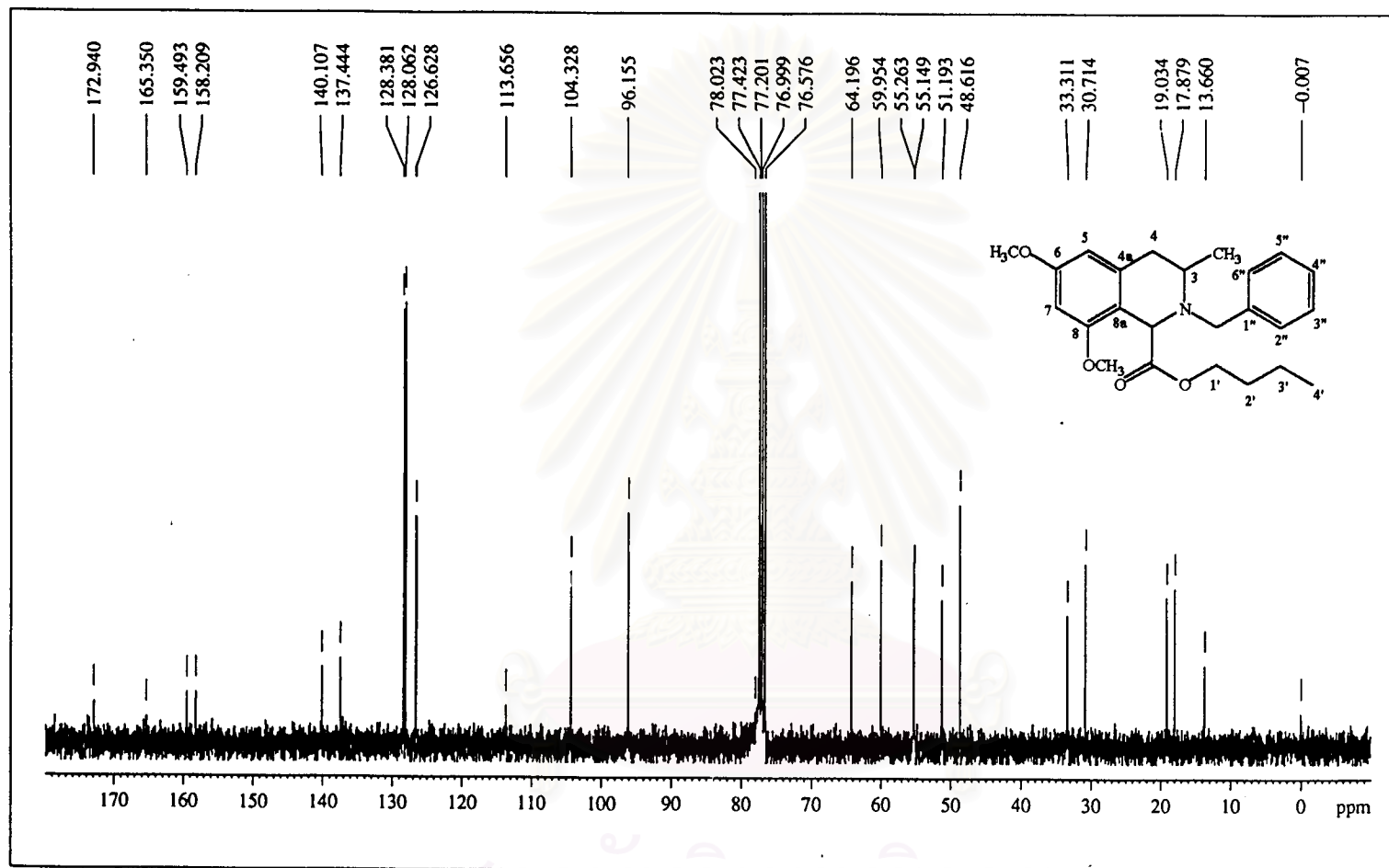(CU-19-10) (Enlarged scale)

Figure 53 The 75 MHz ^{13}C-NMR spectrum of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-10)

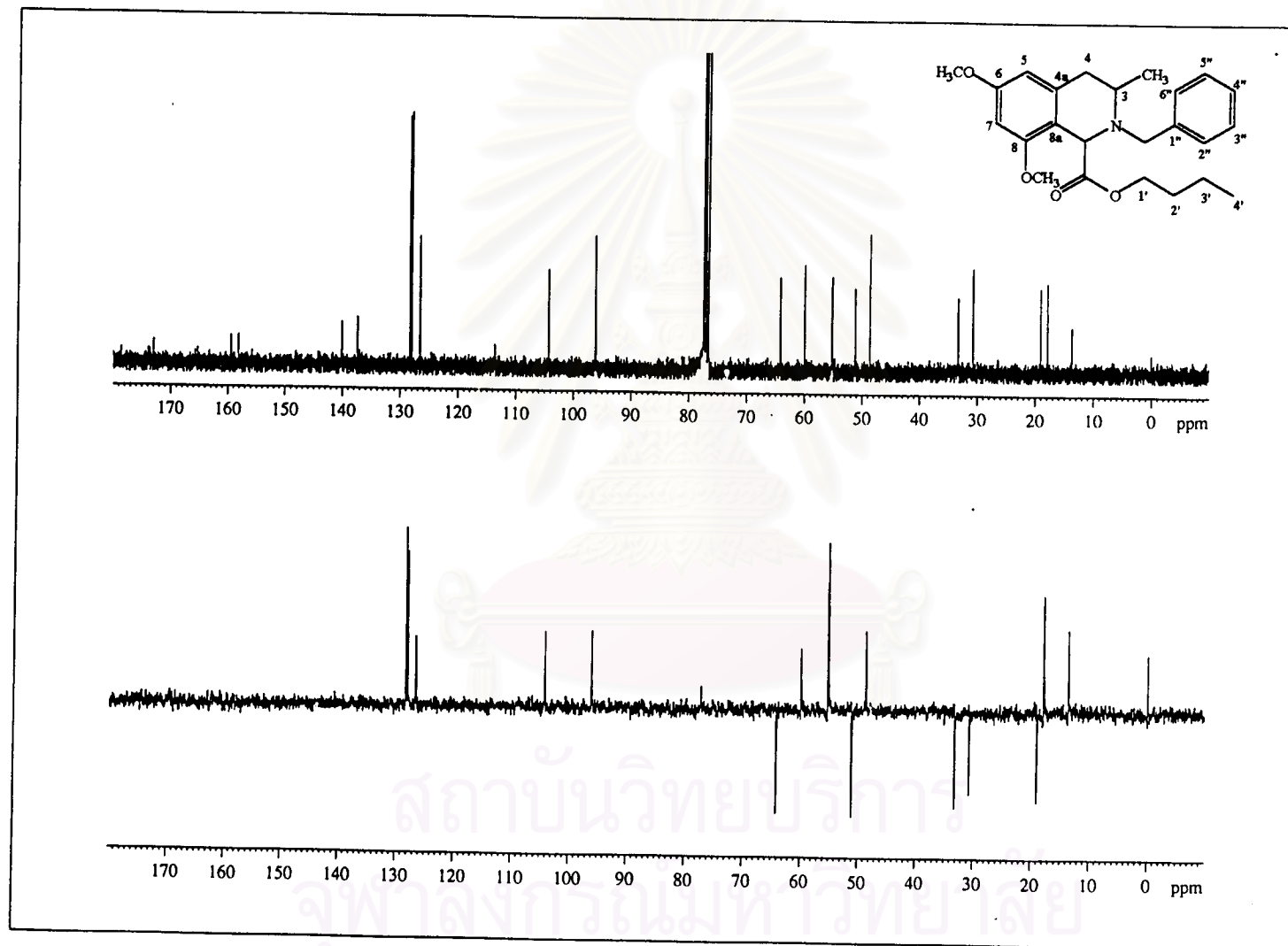Figure 54 The 75 MHz ^{13}C-NMR and DEPT 135 spectra of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-
1-carboxylate (CU-19-10)

Figure 55 The 300 MHz COSY spectrum of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate
(CU-19-10)
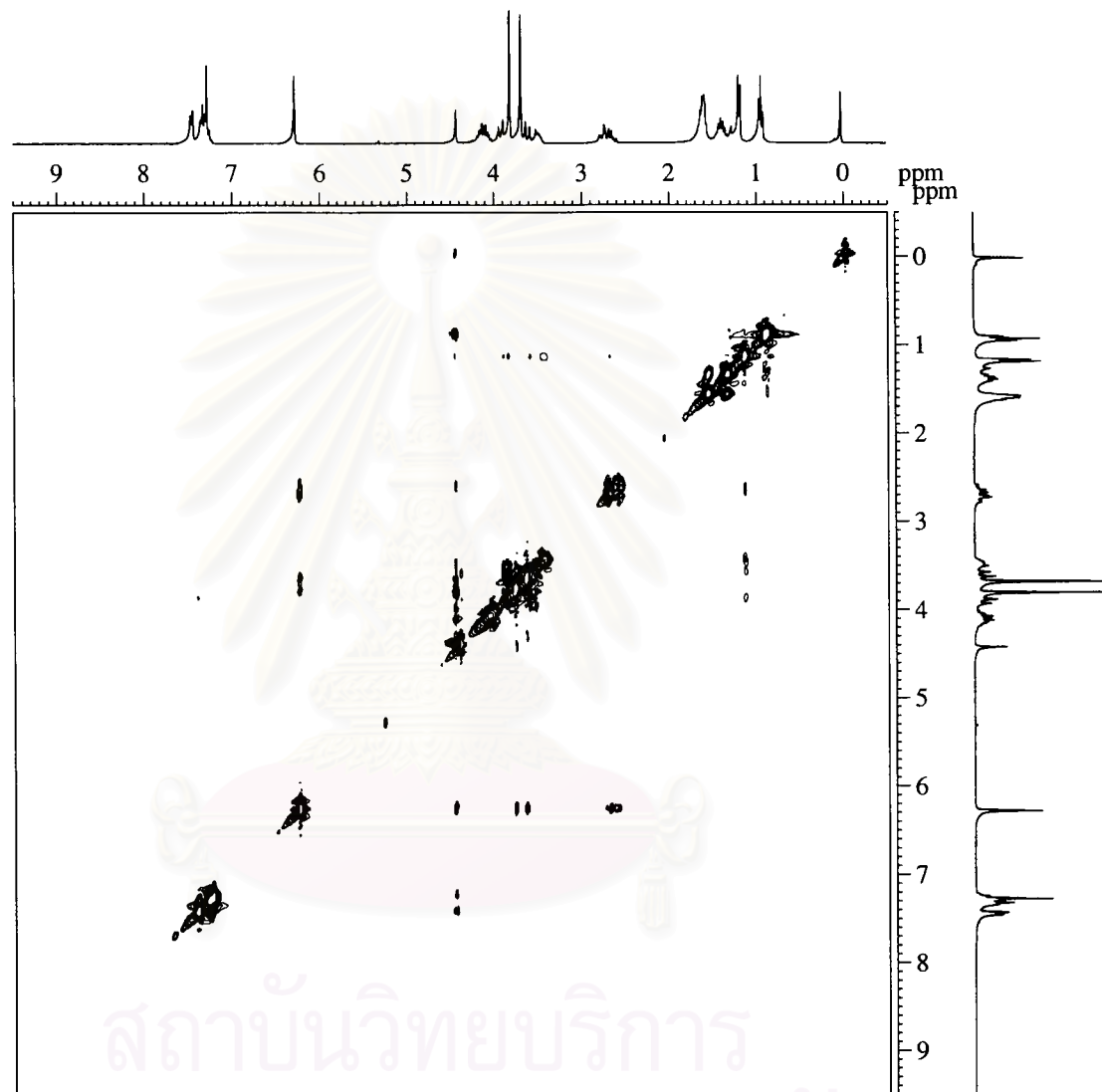
Figure 56 The ROESY spectrum of butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate
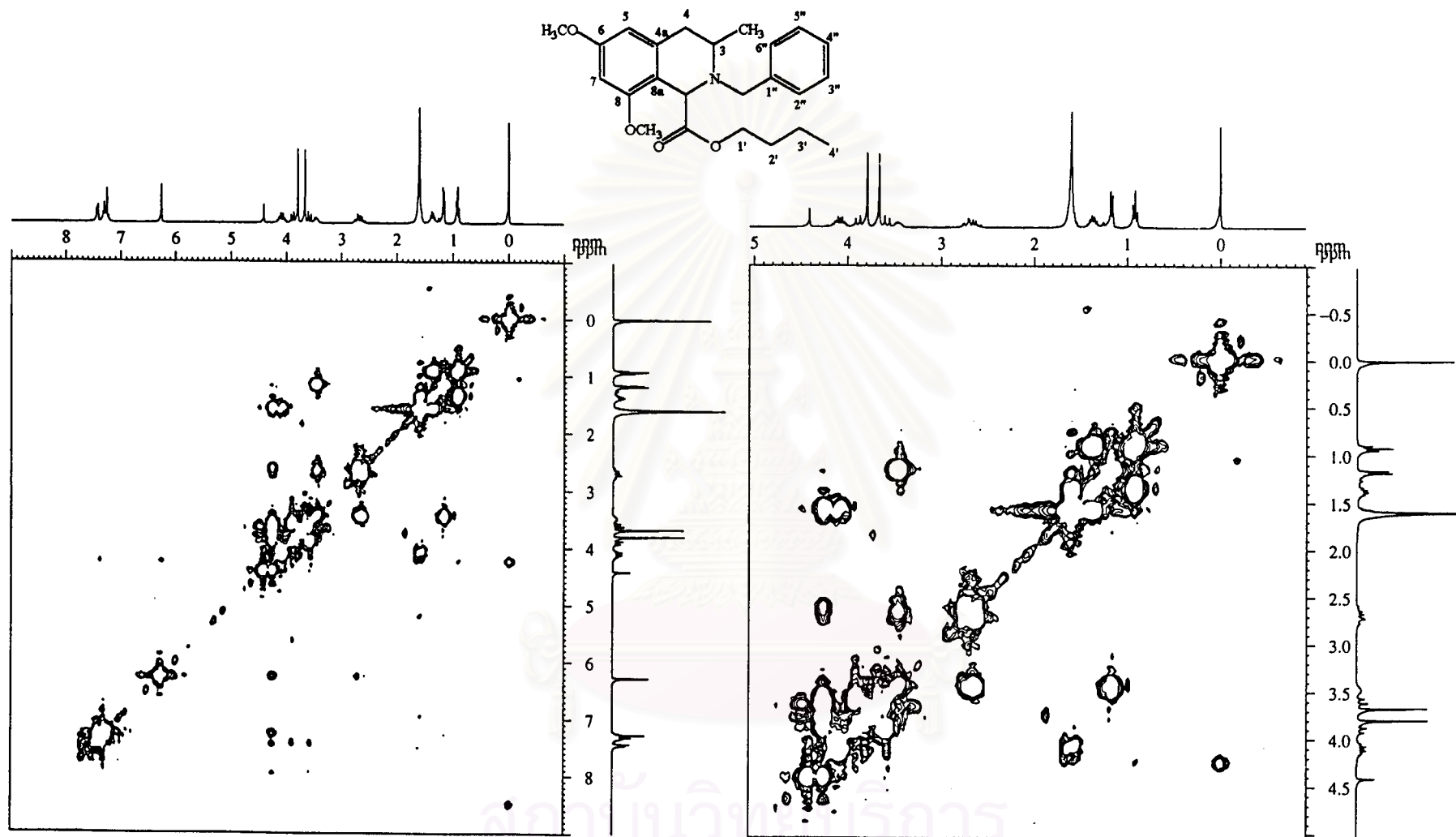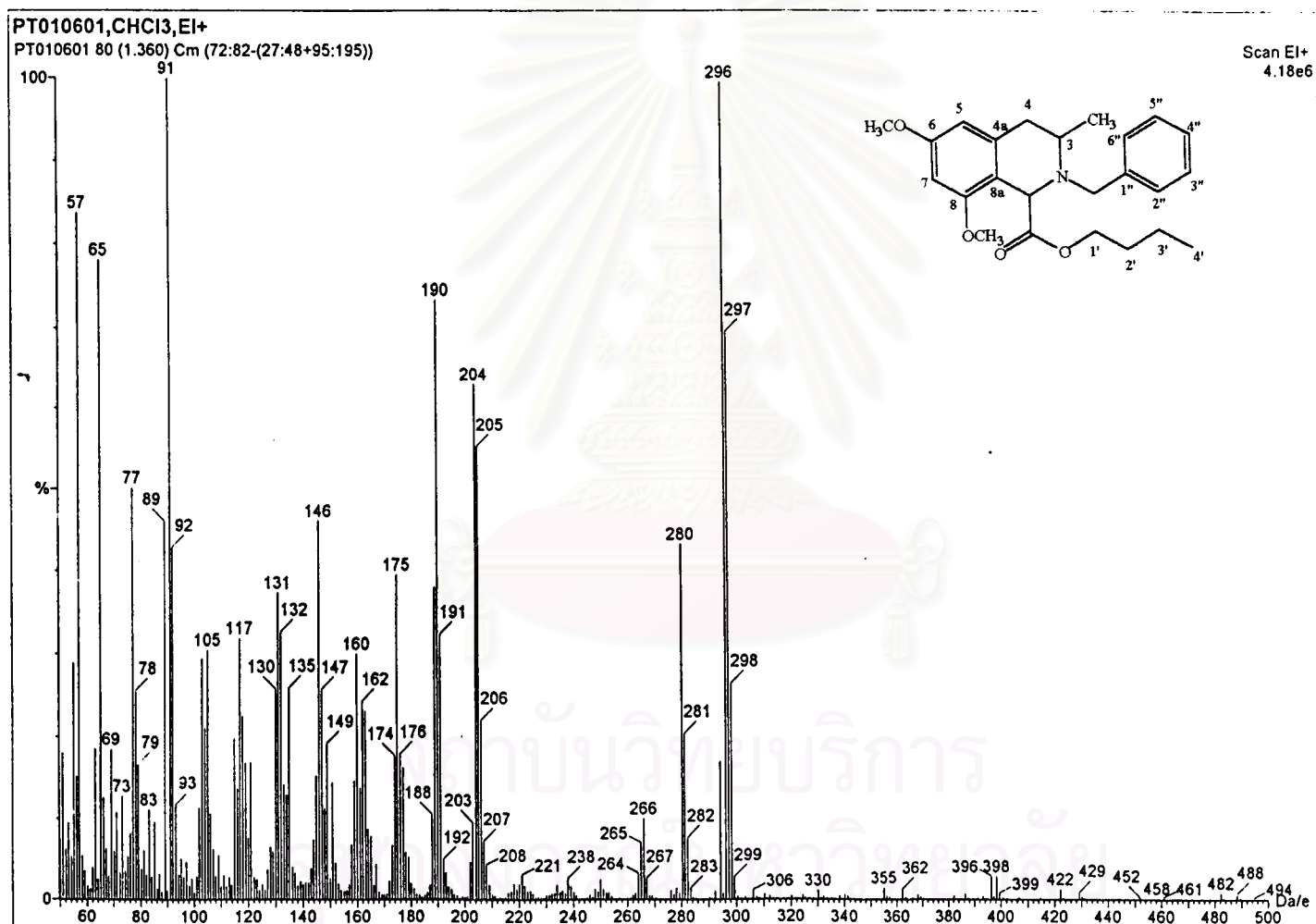
(CU-19-10)

Figure 57 The electron impact mass spectrum butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-10)

Figure 58 The 300 MHz ^{1}H-NMR spectrum of A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-
tetrahydroisoquinoline-1-carboxylate

Figure 59 The 75 MHz ^{13}C-NMR spectrum of A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate

Figure 60 The 75 MHz DEPT 135 spectrum of A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate

Figure 61 The 300 MHz COSY spectrum of A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate
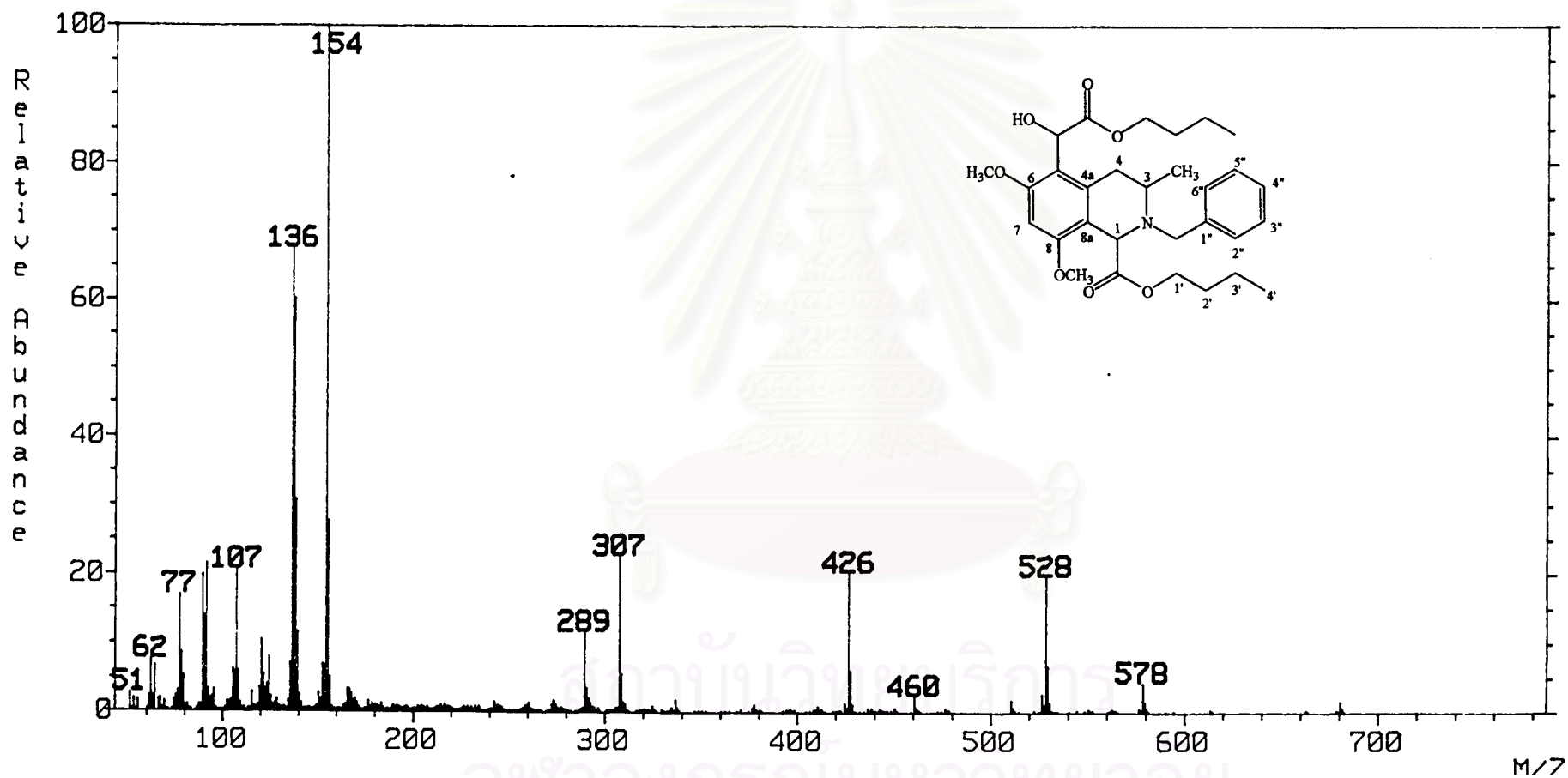
Figure 62 The Mass spectrum of A : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-

tetrahydroisoquinoline-1-carboxylate
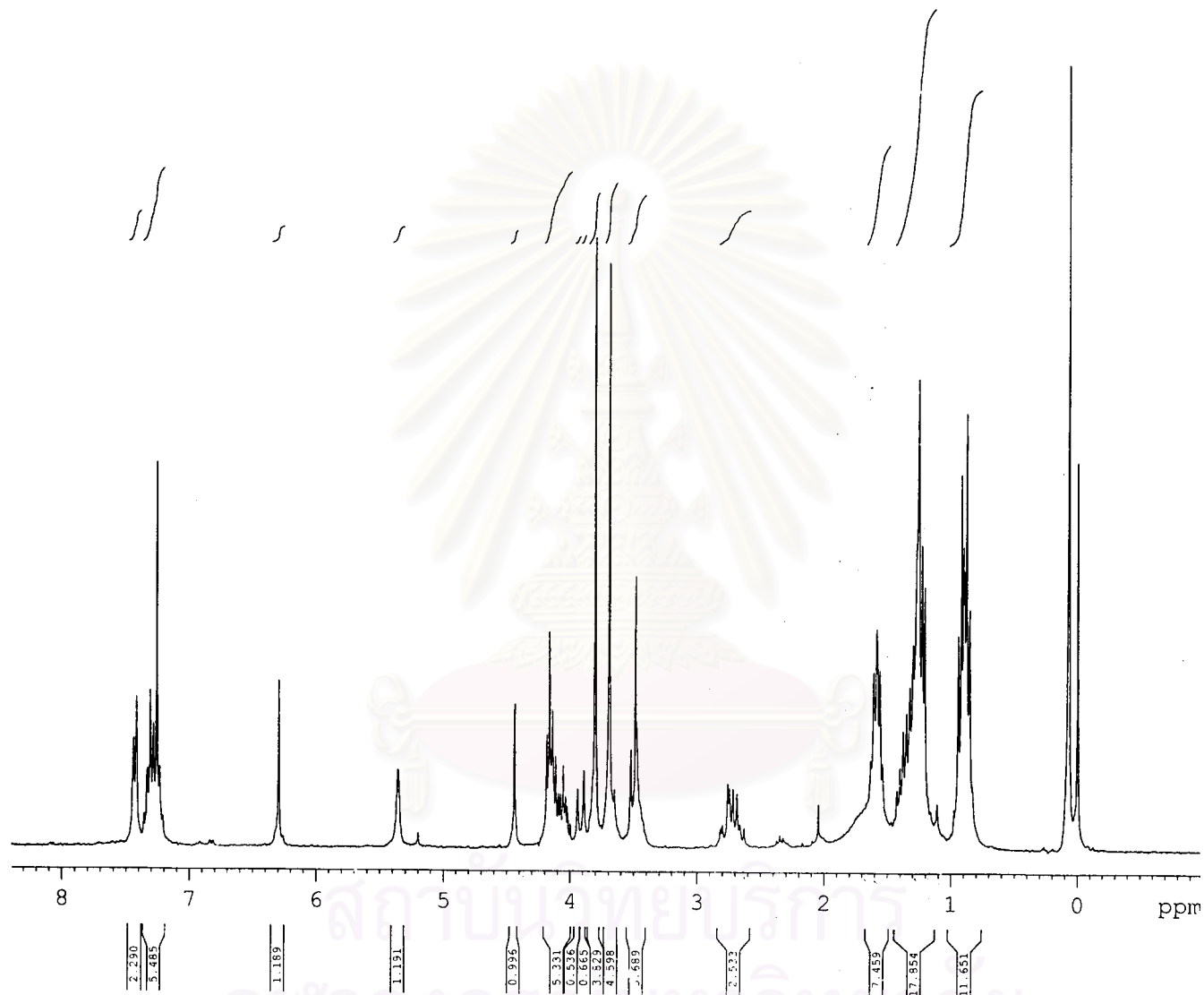
Figure 63 The 300 MHz ^{1}H-NMR spectrum of B : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-
tetrahydroisoquinoline-1-carboxylate
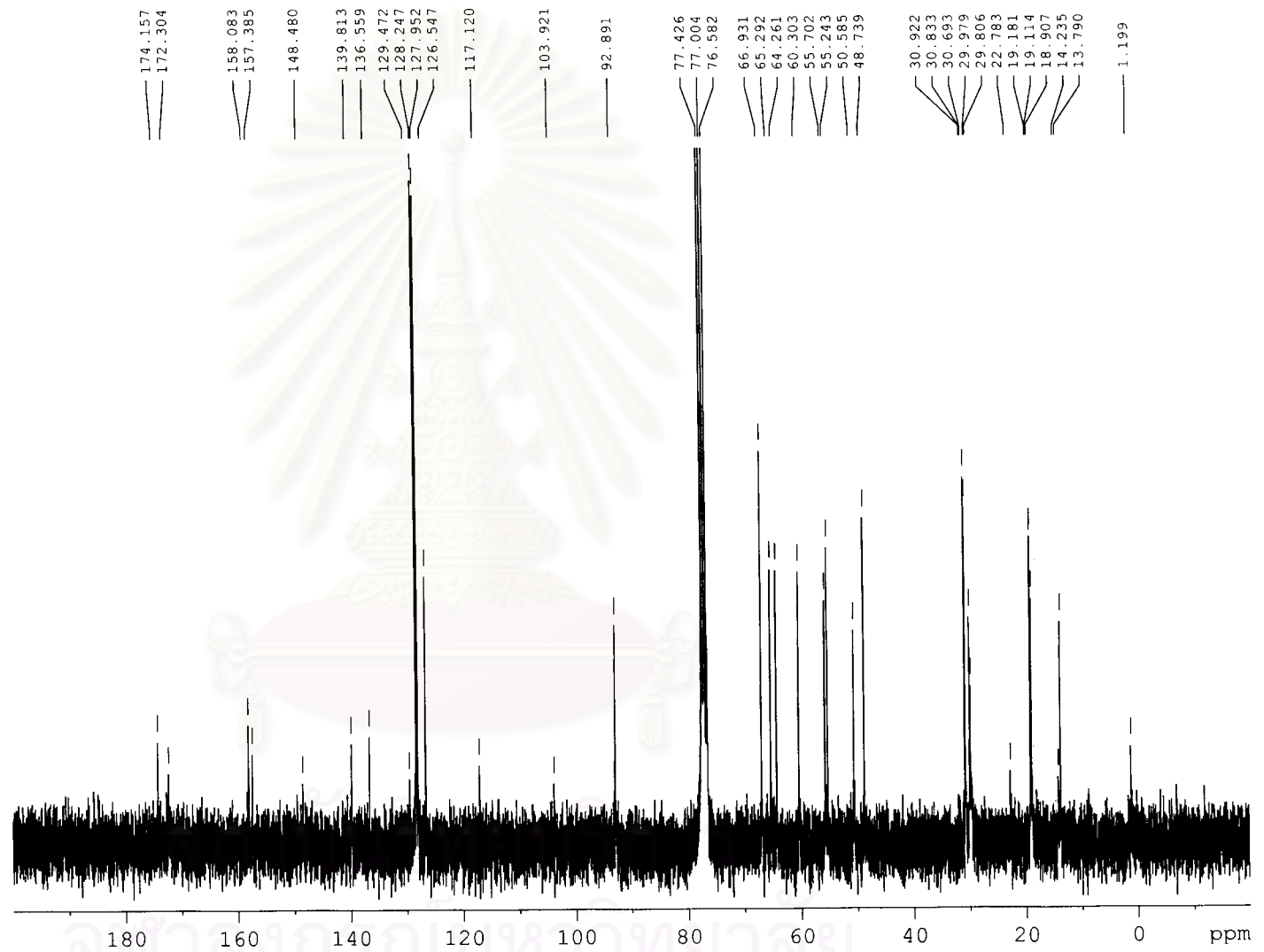
Figure 64 The 75 MHz ^{13}C-NMR spectrum of B : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-
tetrahydroisoquinoline-1-carboxylate
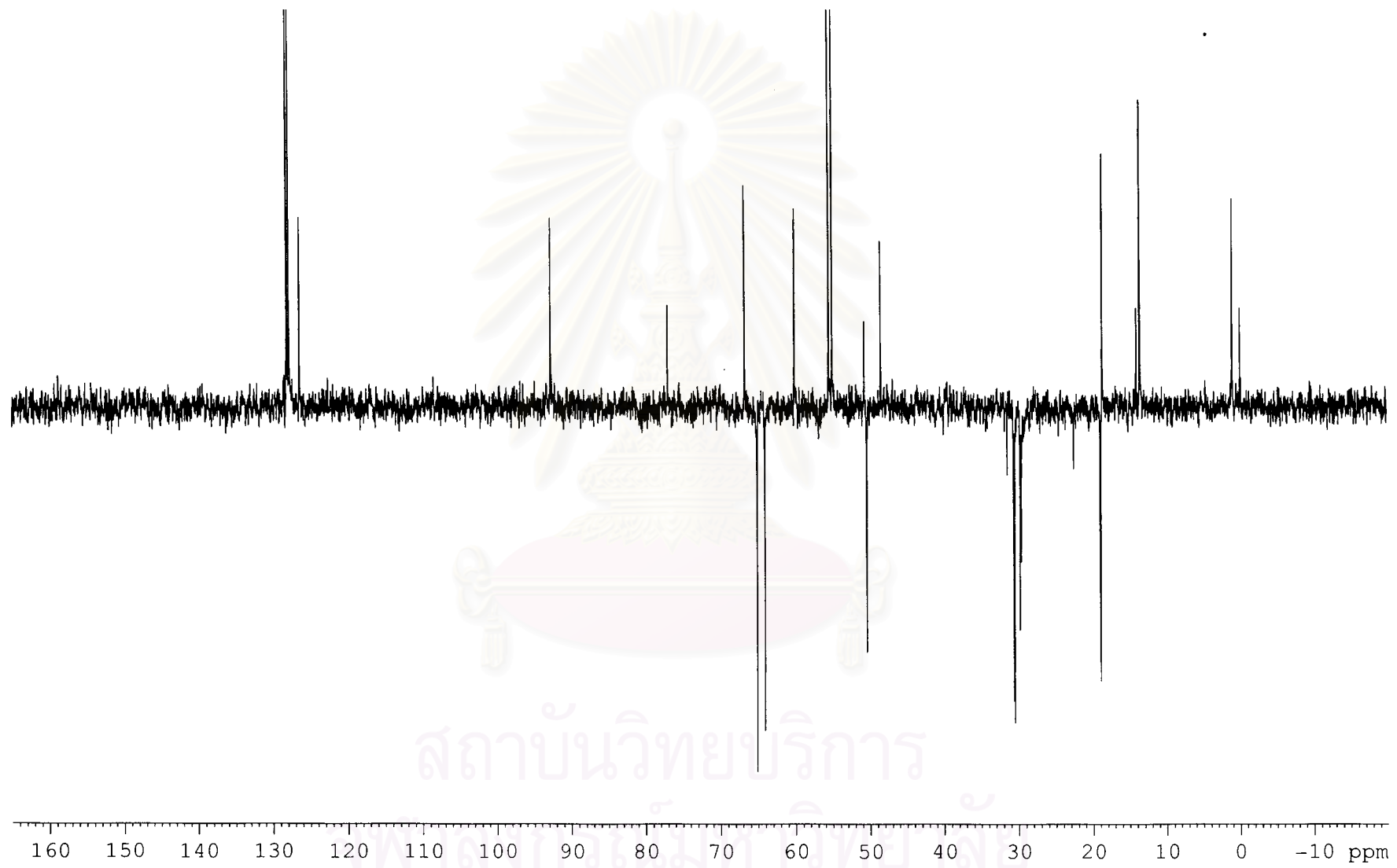
Figure 65 The 75 MHz DEPT 135 spectrum of B : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-
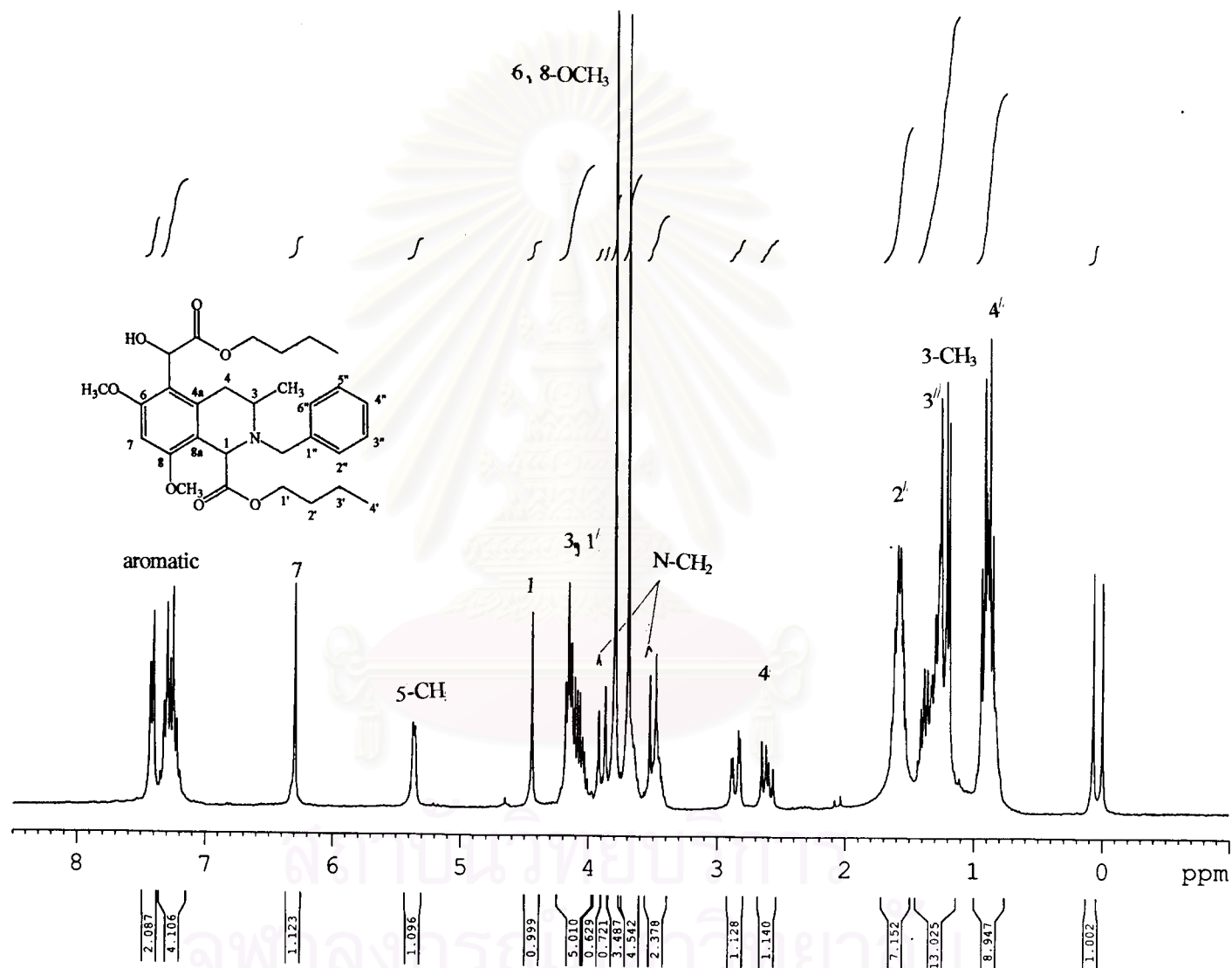
tetrahydroisoquinoline-1-carboxylate
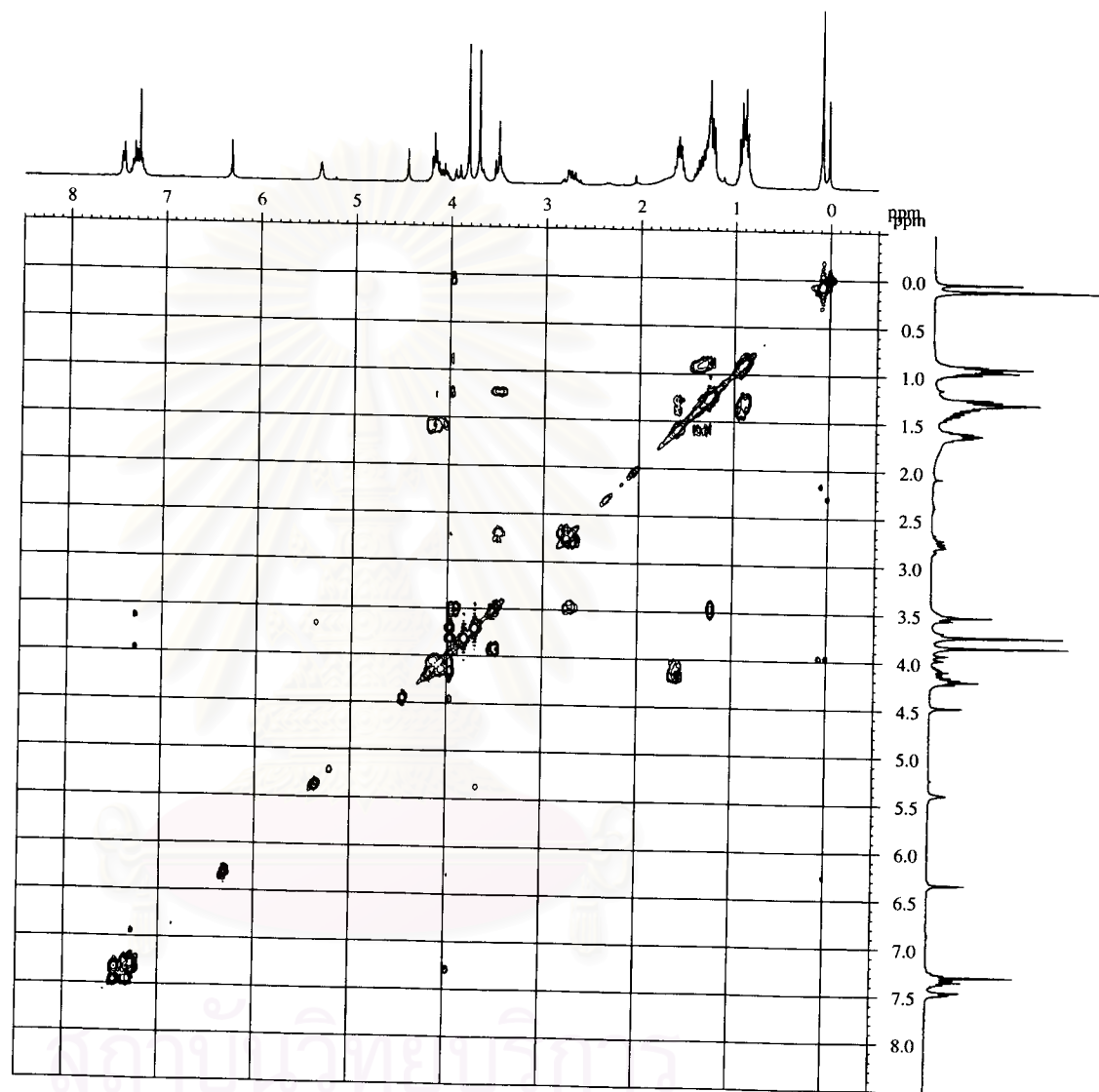
Figure 66 The 300 MHz COSY spectrum of B : butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate
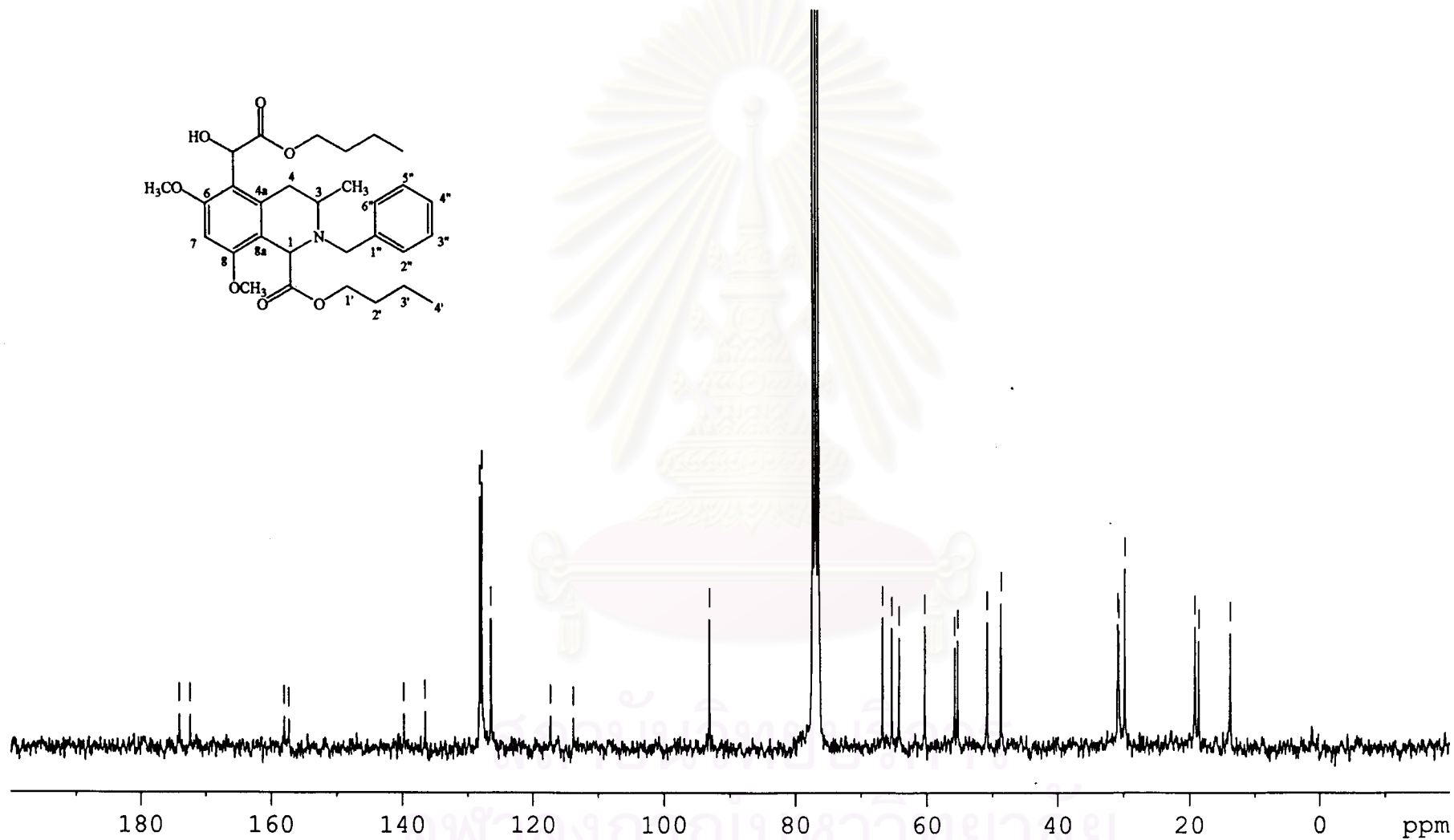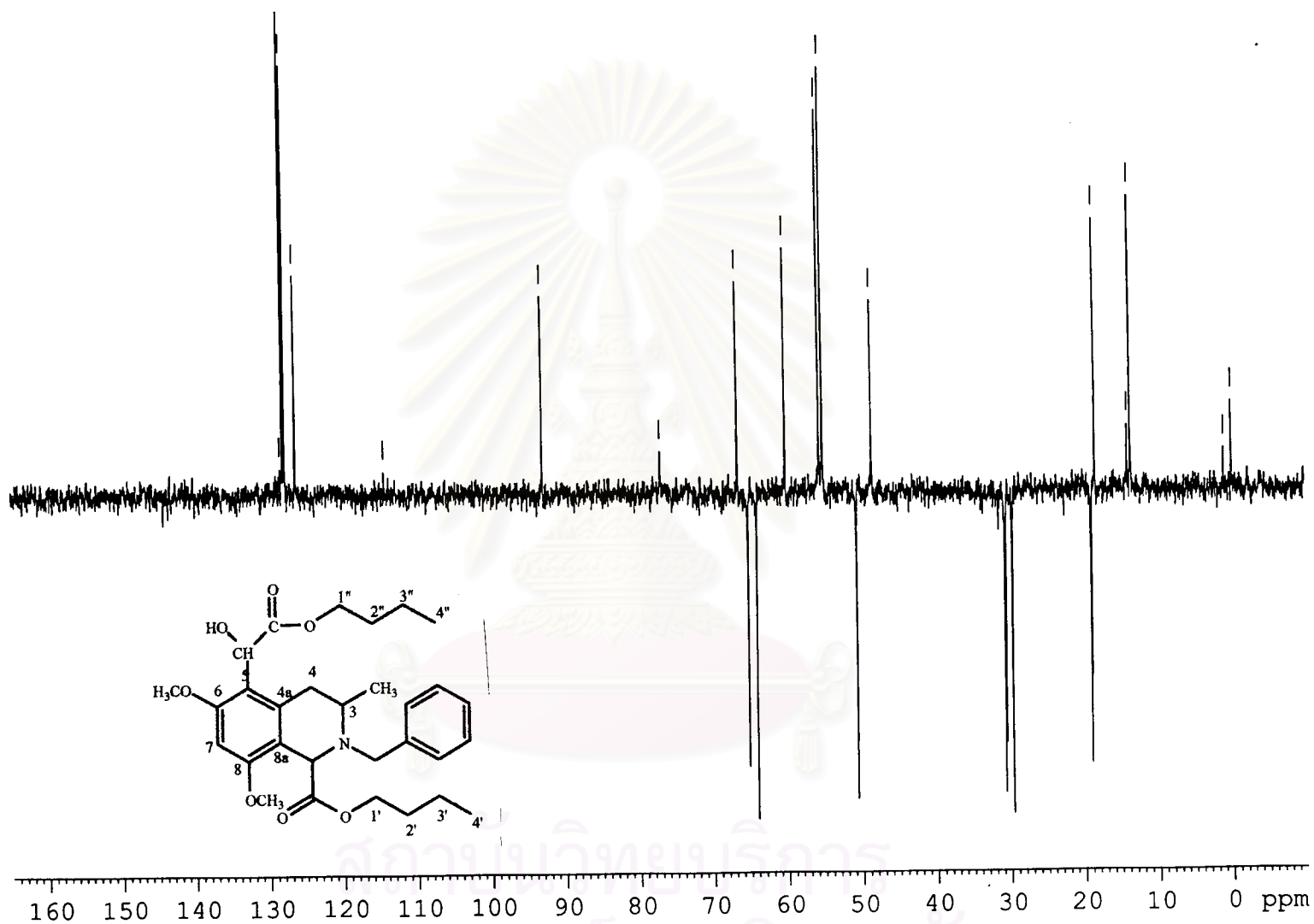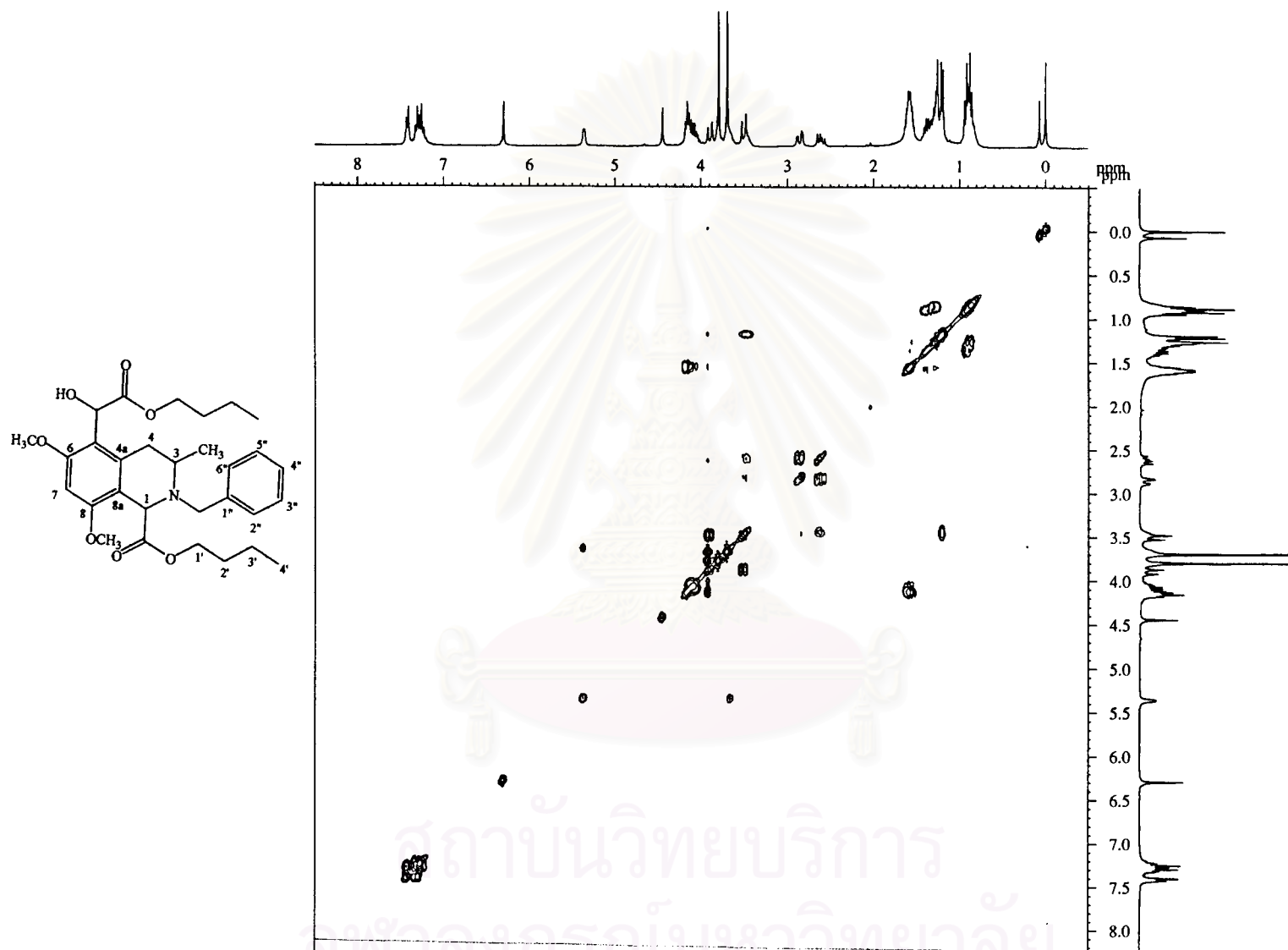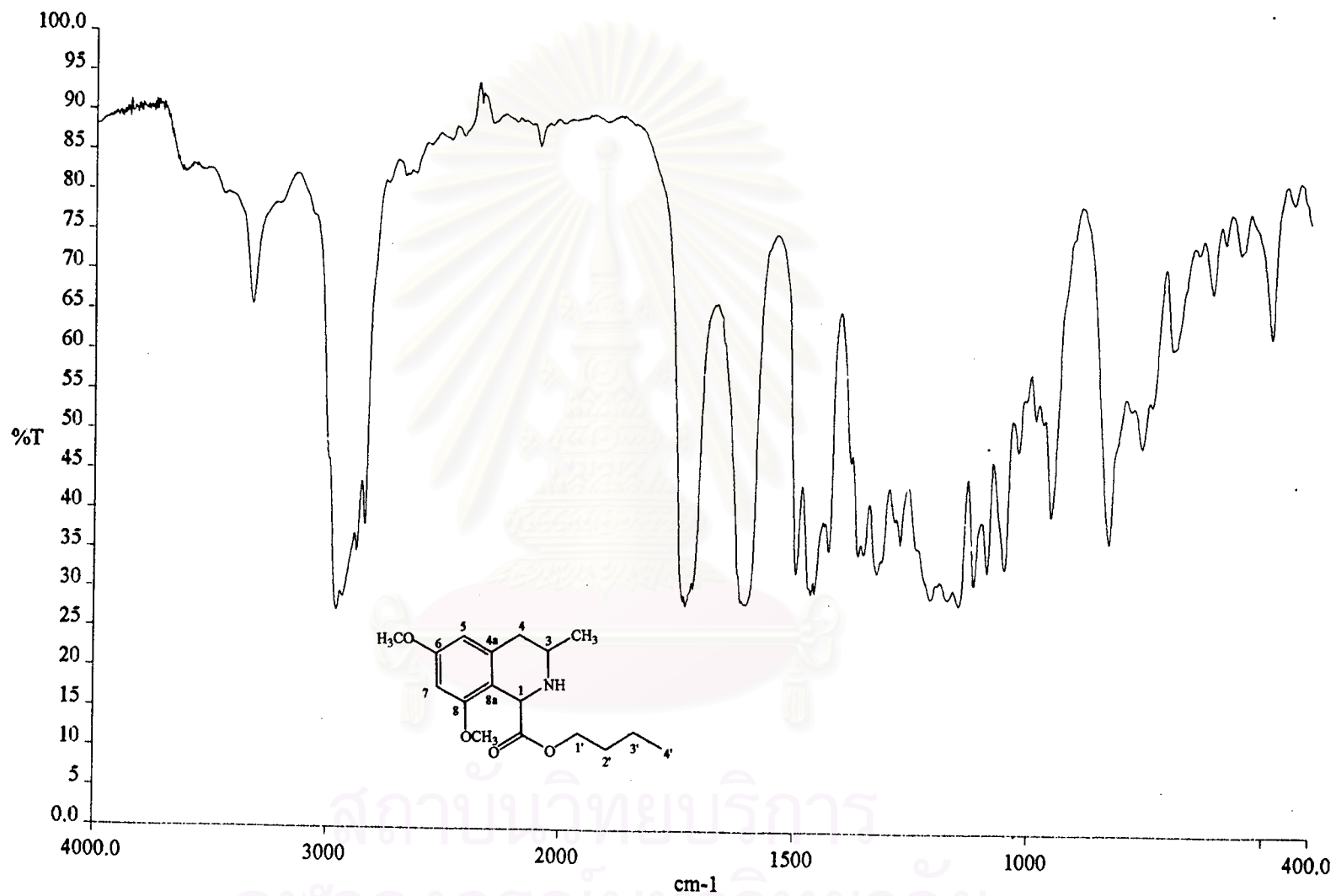
Figure 67 The IR spectrum (Neat) of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-11)
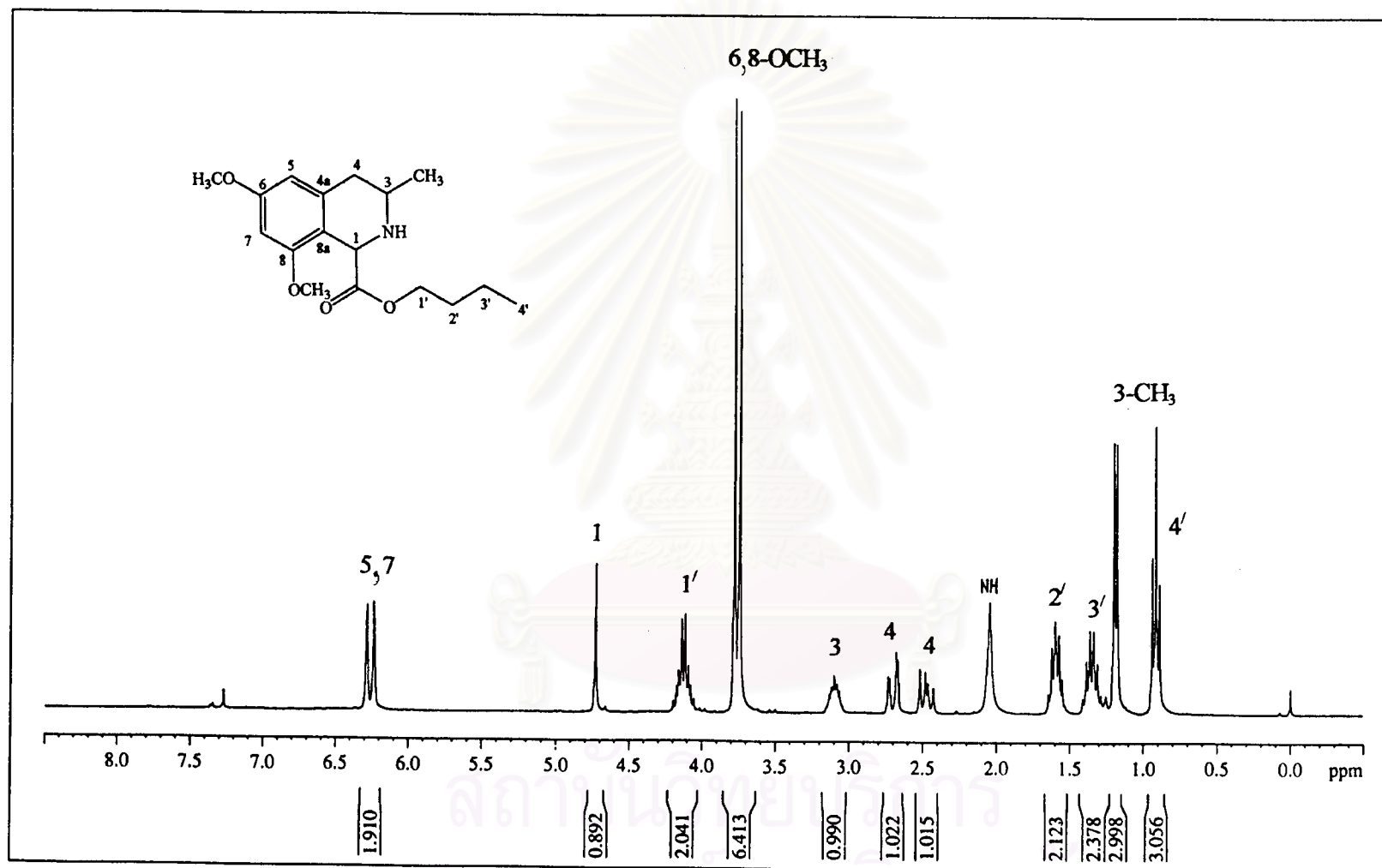
Figure 68 The 300 MHz ^{1}H-NMR spectrum of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-11)
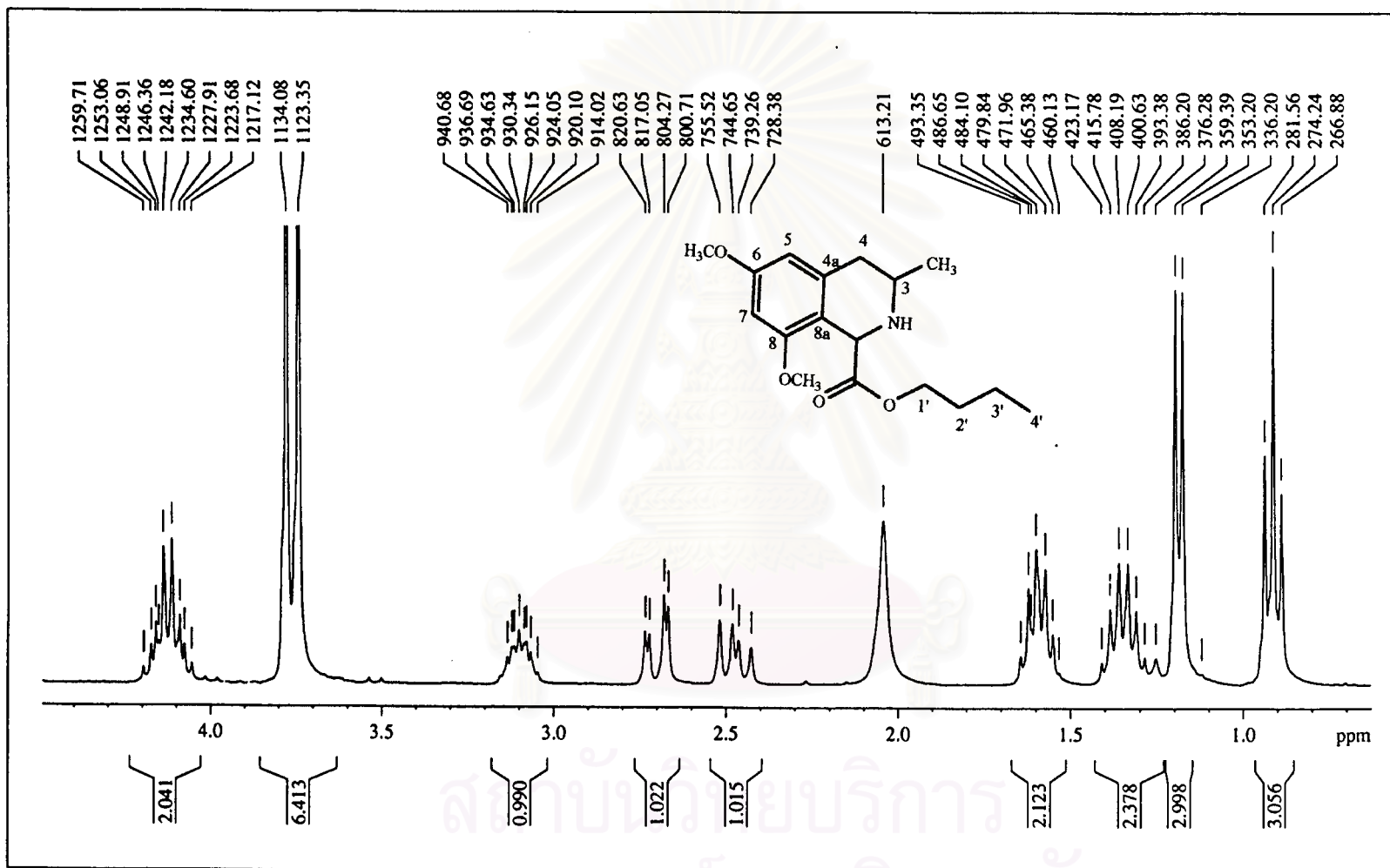
Figure 69 The 300 MHz ^{1}H-NMR spectrum of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-11) (Enlarged scale)
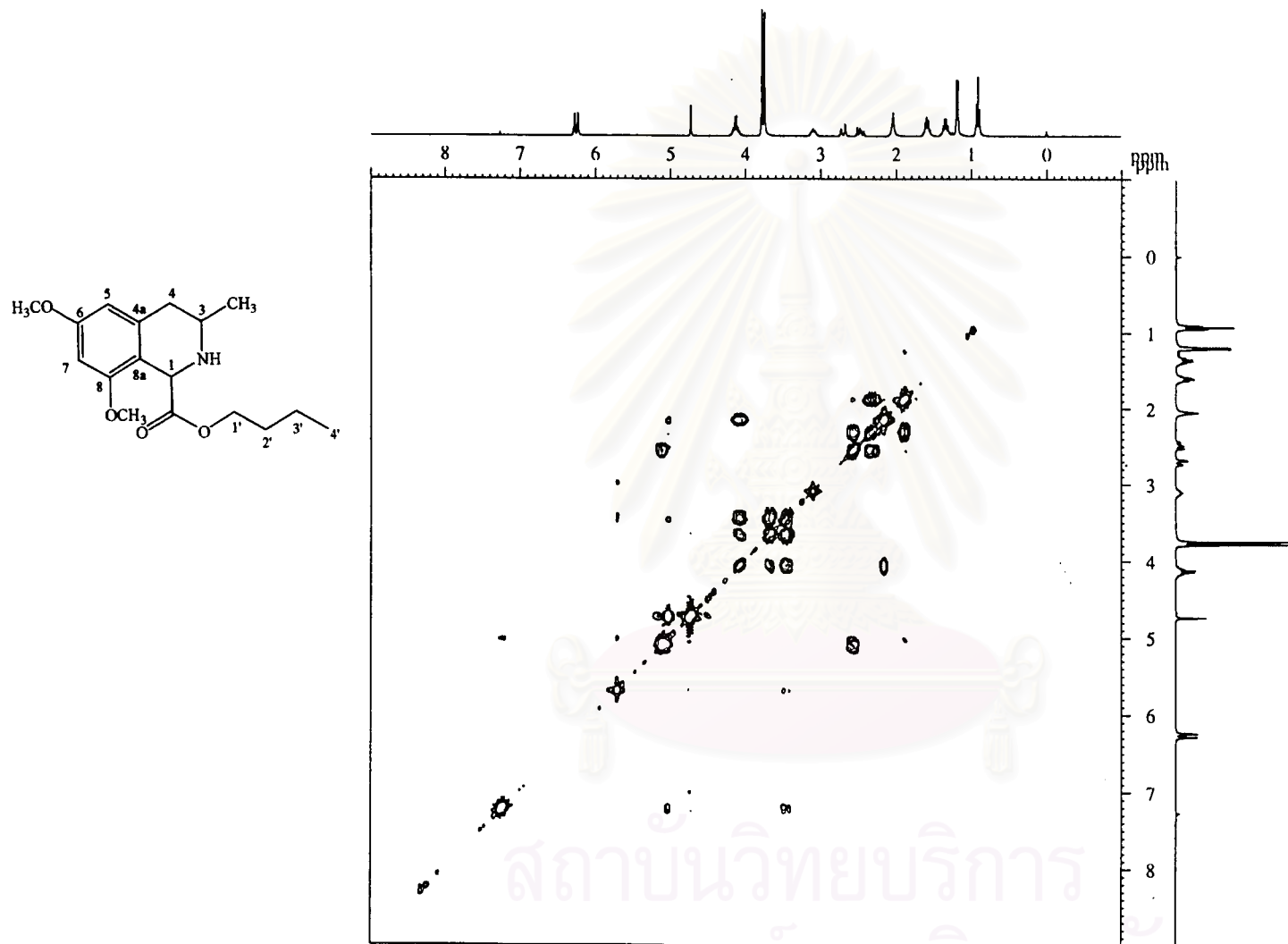
Figure 70 The 300 MHz COSY spectrum of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-11)
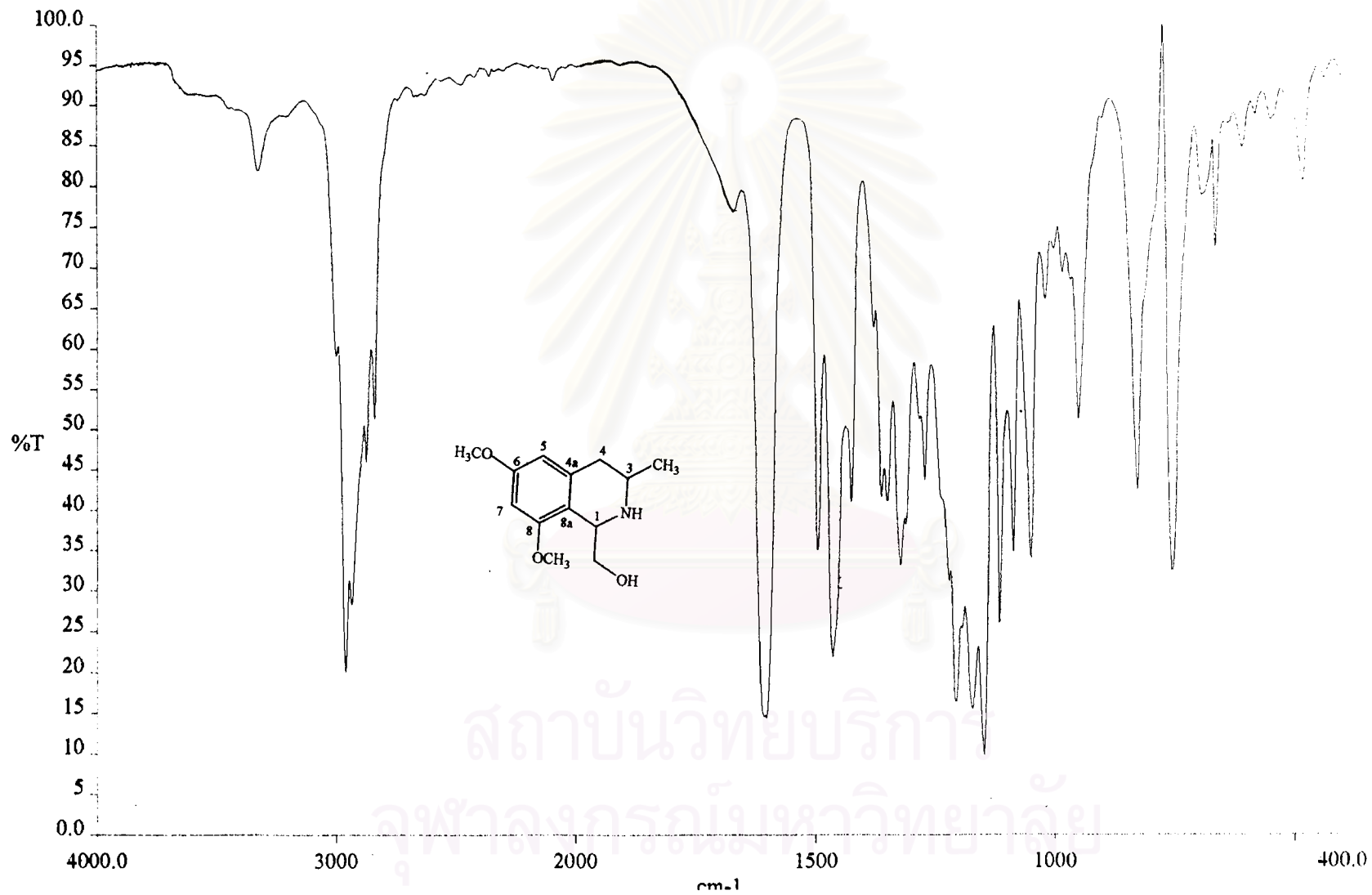
Figure 71 The IR spectrum (Neat) of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-12)
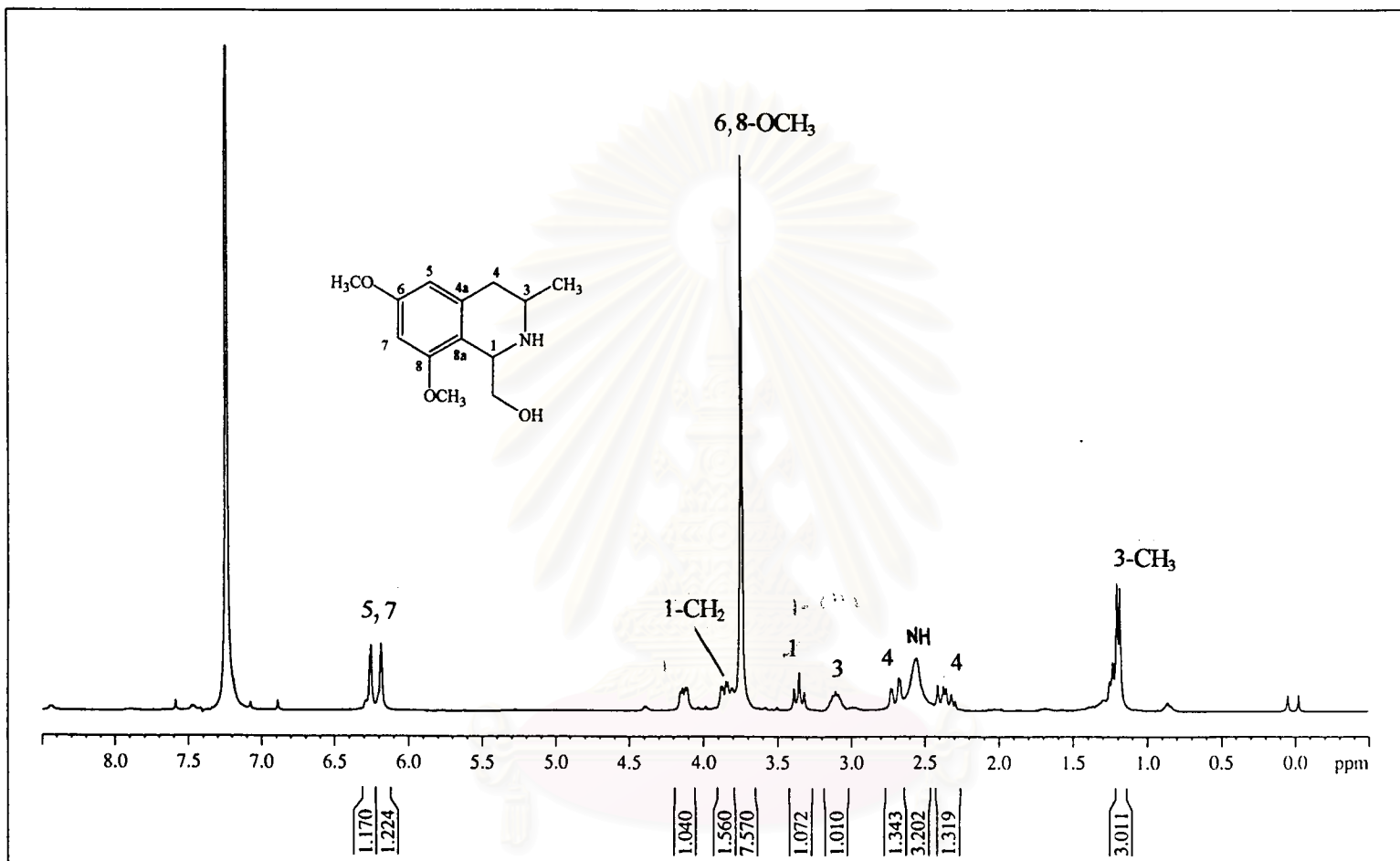
Figure 72 The 300 MHz ^{1}H-NMR spectrum of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-12)
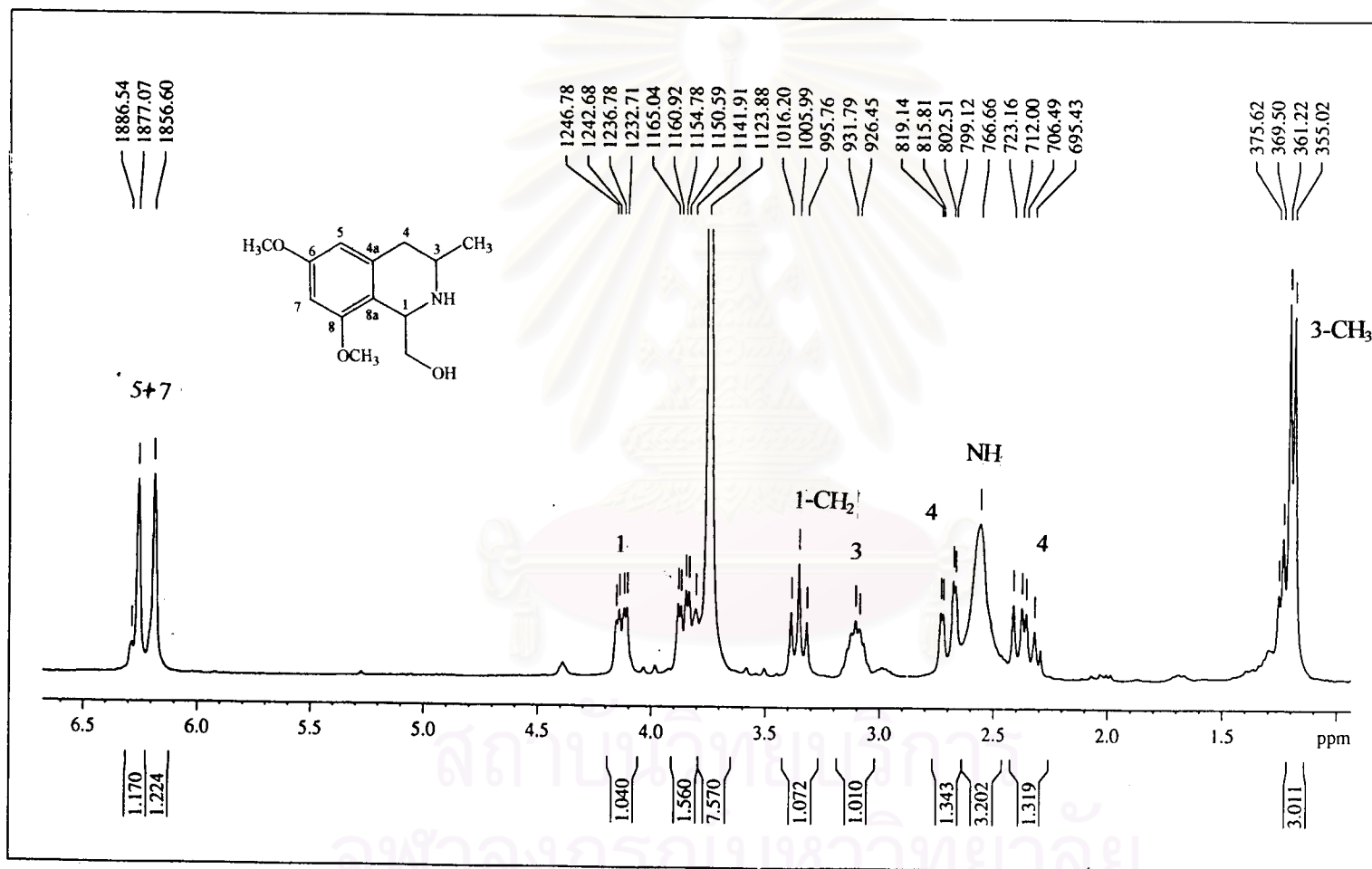
Figure 73 The 300 MHz ^{1}H-NMR spectrum of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-12) (Enlarged scale)
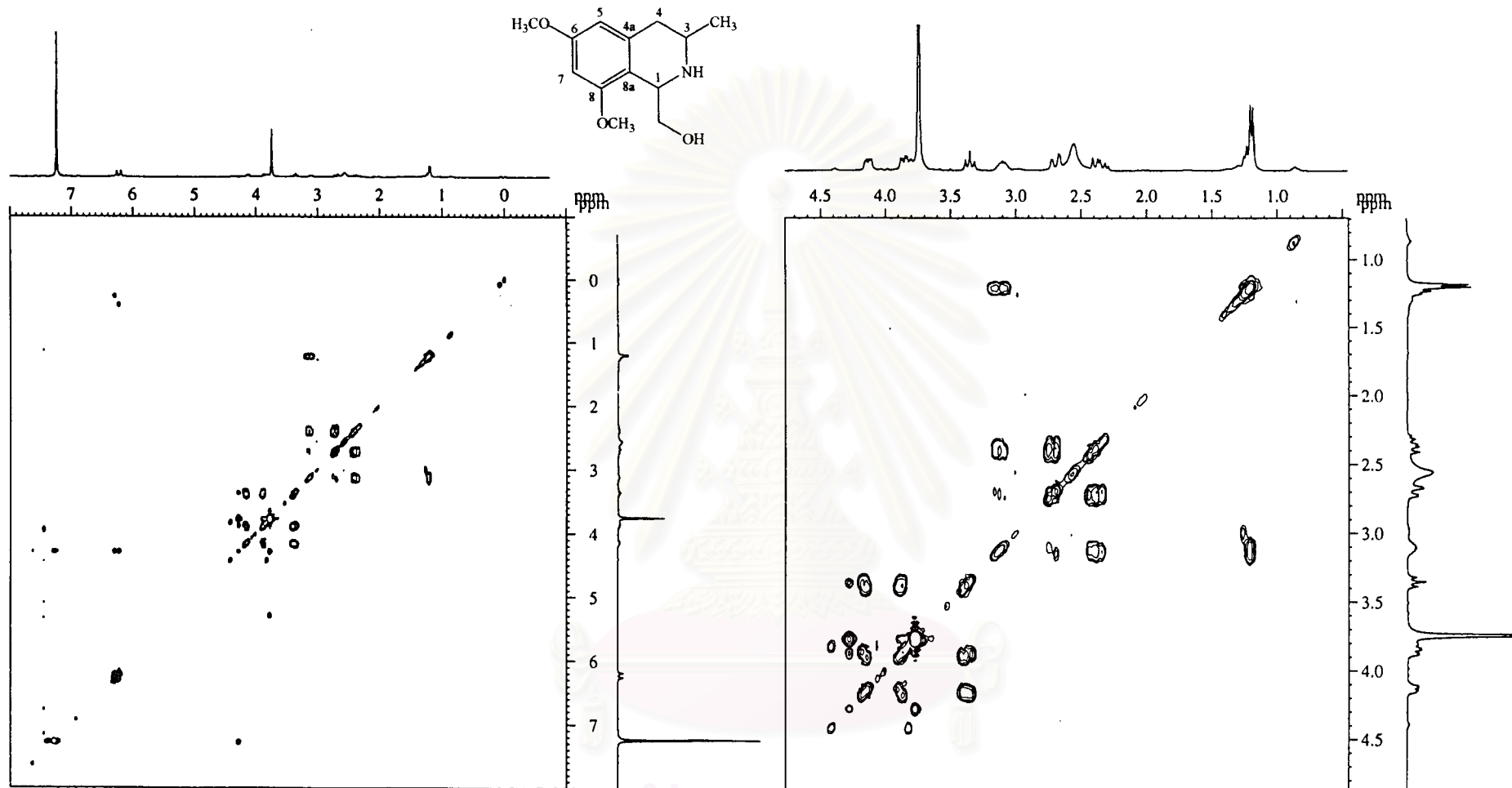
Figure 74 The 300 MHz COSY spectrum of 6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-12)
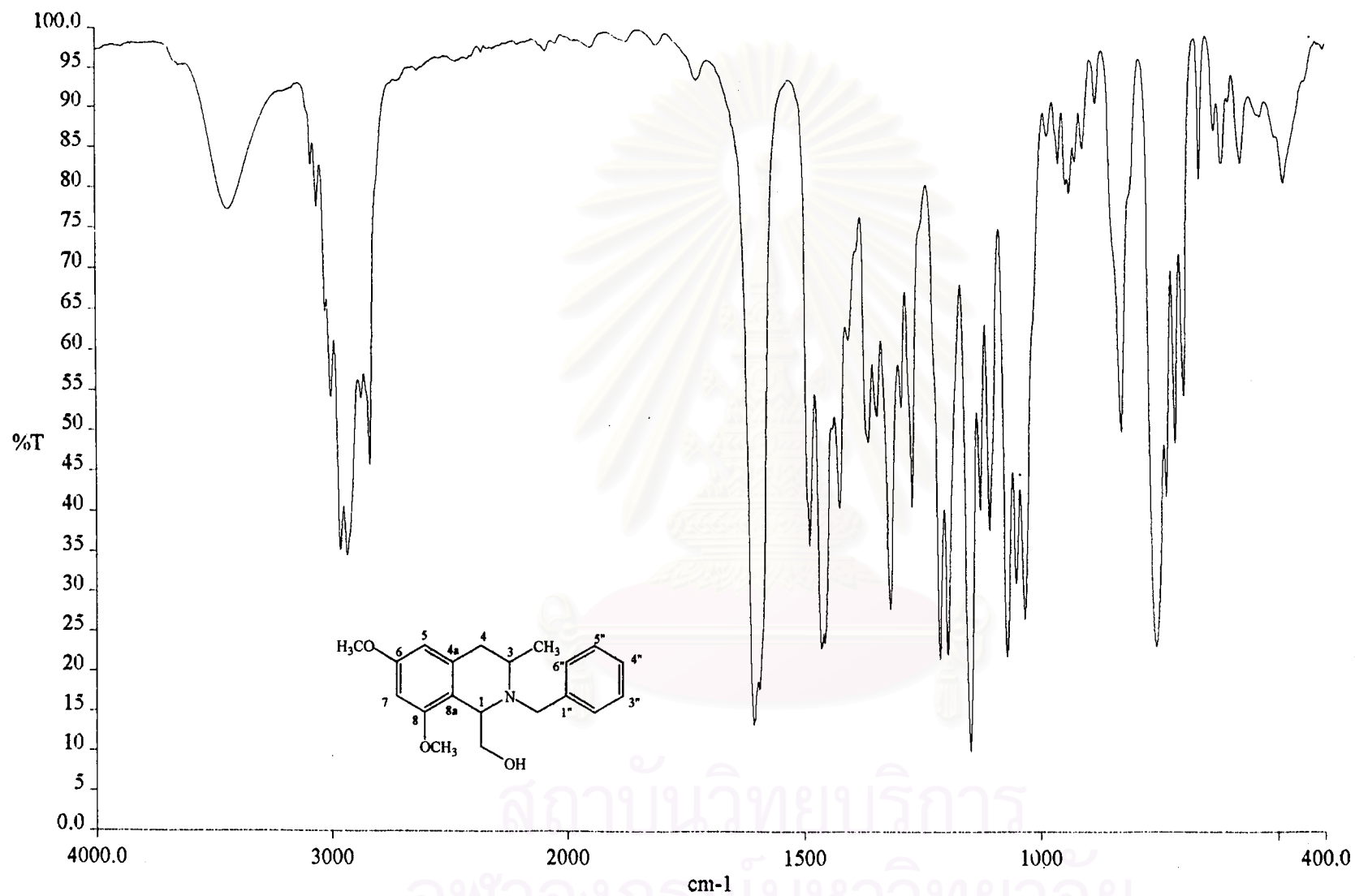
Figure 75 The IR spectrum (Neat) of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-13)
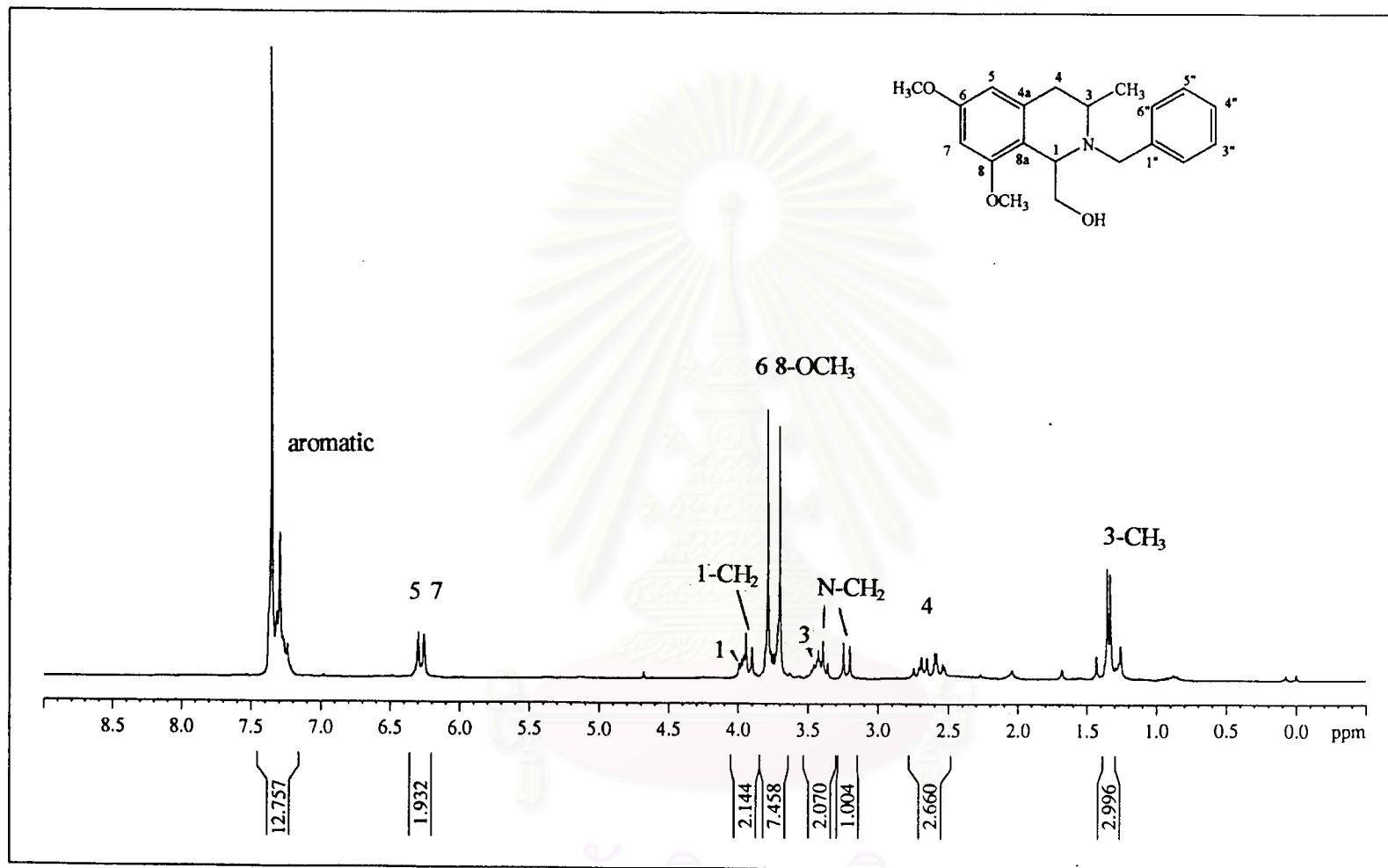
Figure 76 The 300 MHz ^{1}H-NMR spectrum 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-13)
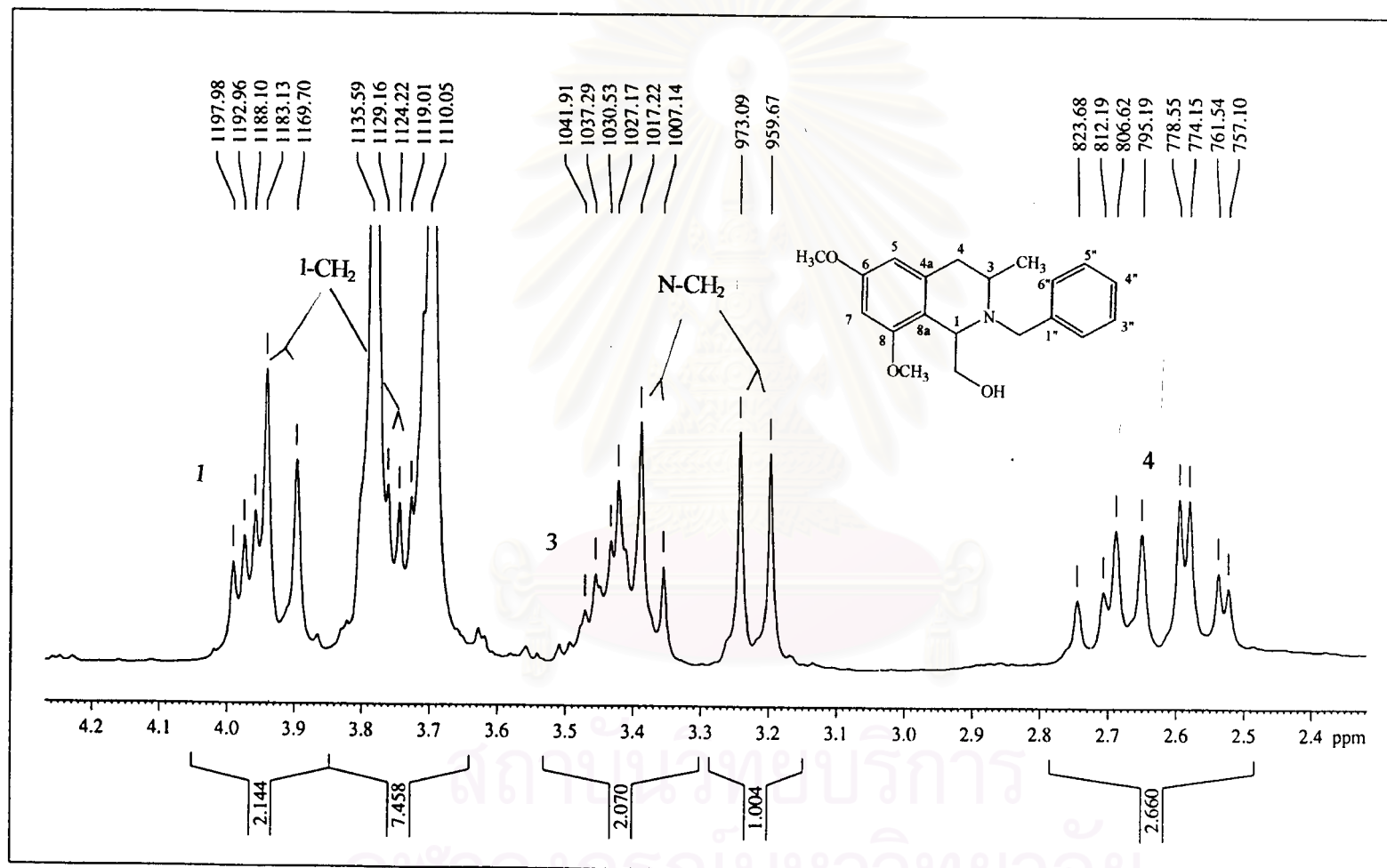
Figure 77 The 300 MHz ^{1}H-NMR spectrum of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-13) (Enlarged scale)

122
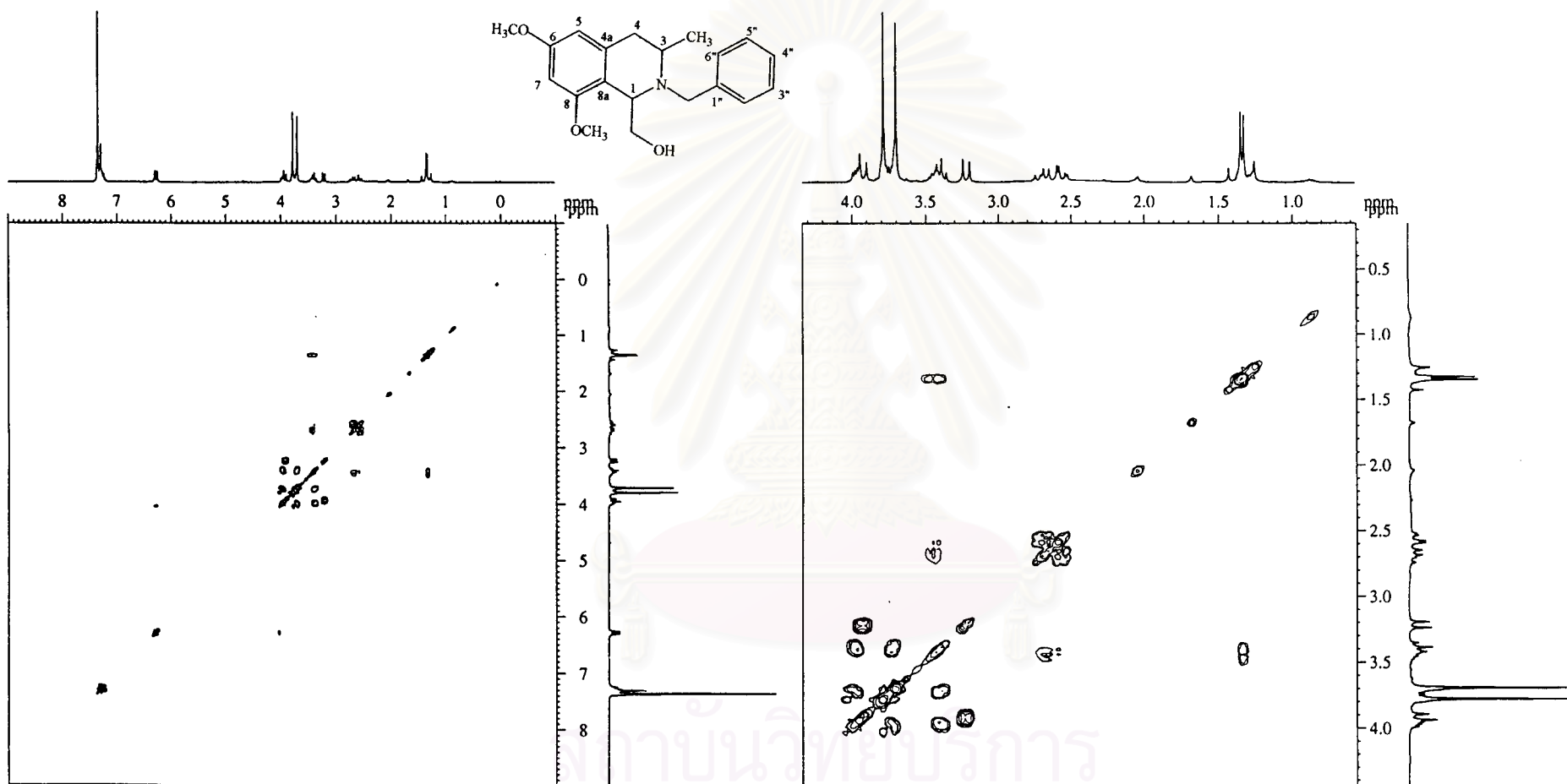
Figure 78 The 300 MHz COSY spectrum 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline
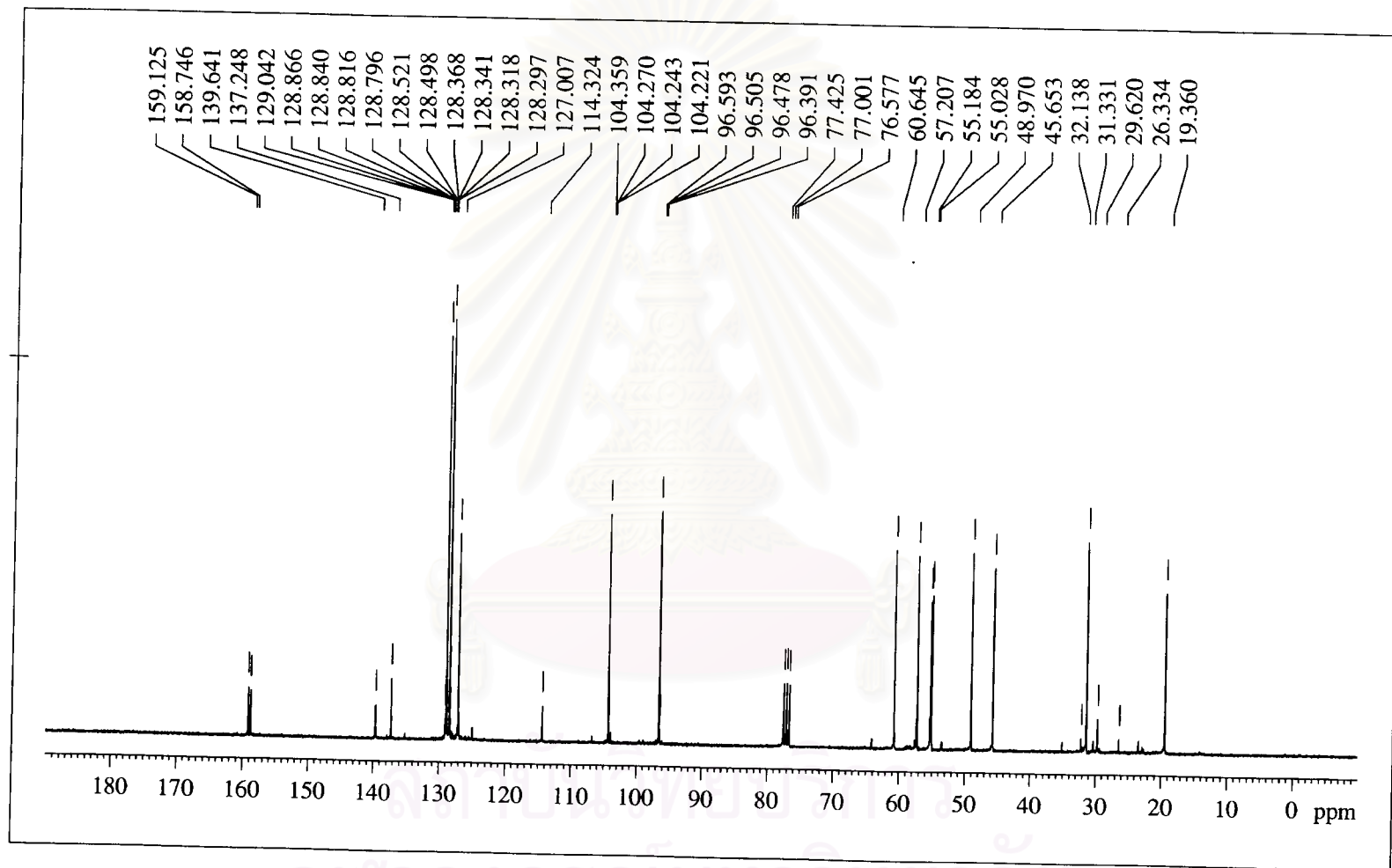
(CU-19-13)

Figure 79 The 75 MHz ^{13}C-NMR spectrum of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline
(CU-19-13)
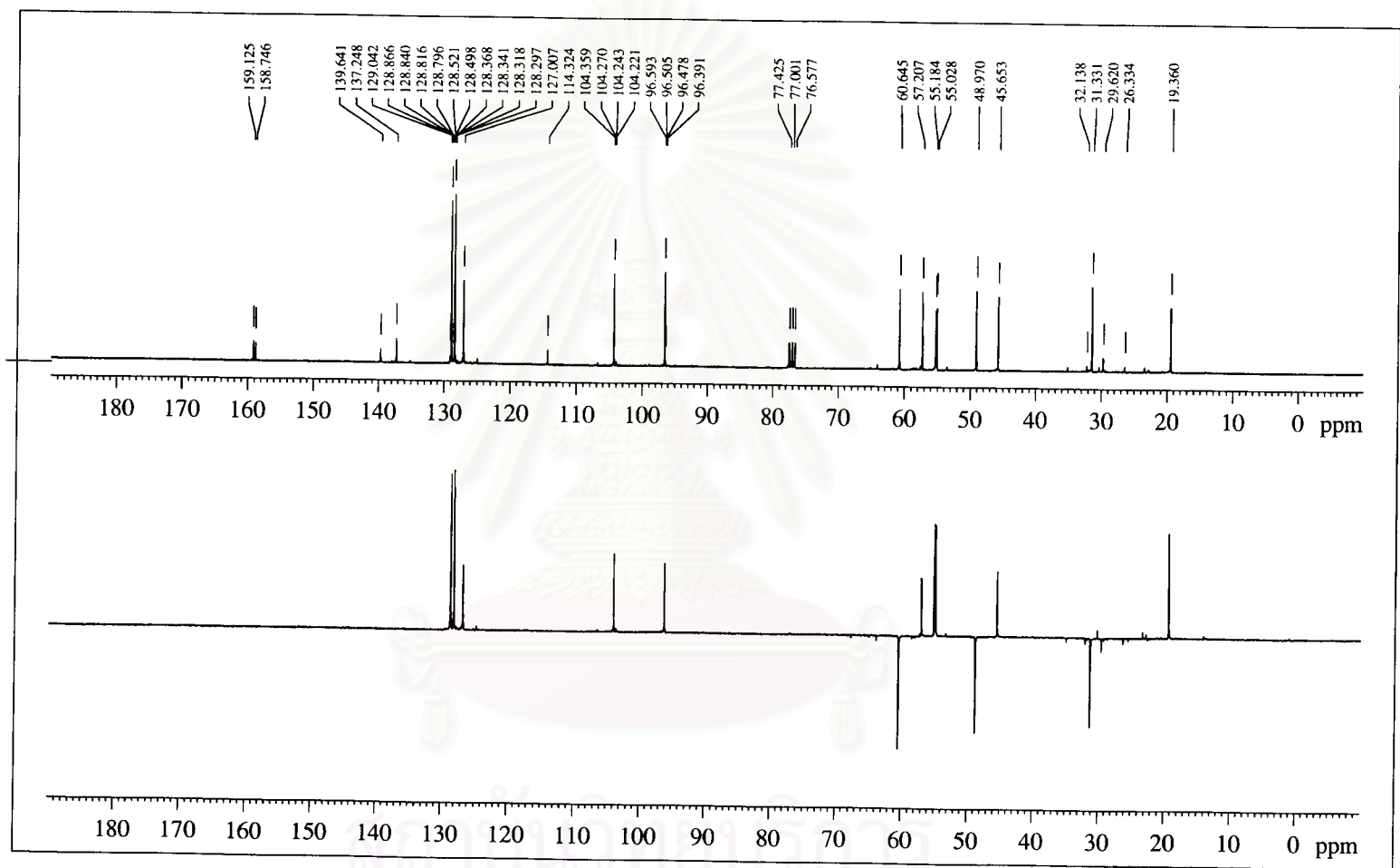
Figure 80 The 75 MHz DEPT 135 spectrum of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline
(CU-19-13)
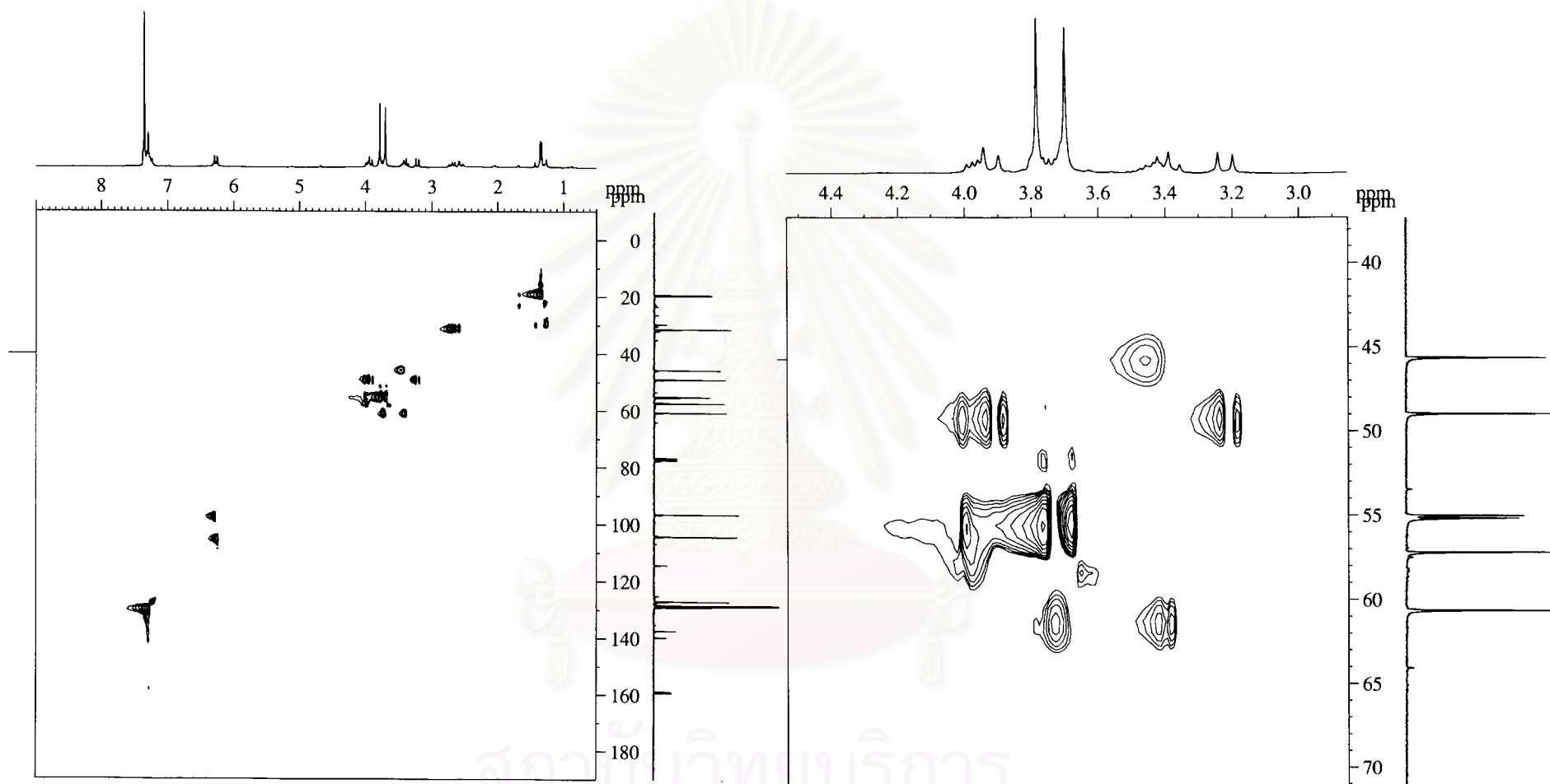
Figure 81 The 300 MHz COLOC spectrum of 2-benzyl-6,8-dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydroisoquinoline
(CU-19-13)

CHAPTER IV

RESULTS AND DISCUSSION

The synthetic procedures in this study can be divided into three major steps as follows.

I. The synthetic of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methyl ethylamine

CU-19-01   CU-19-02
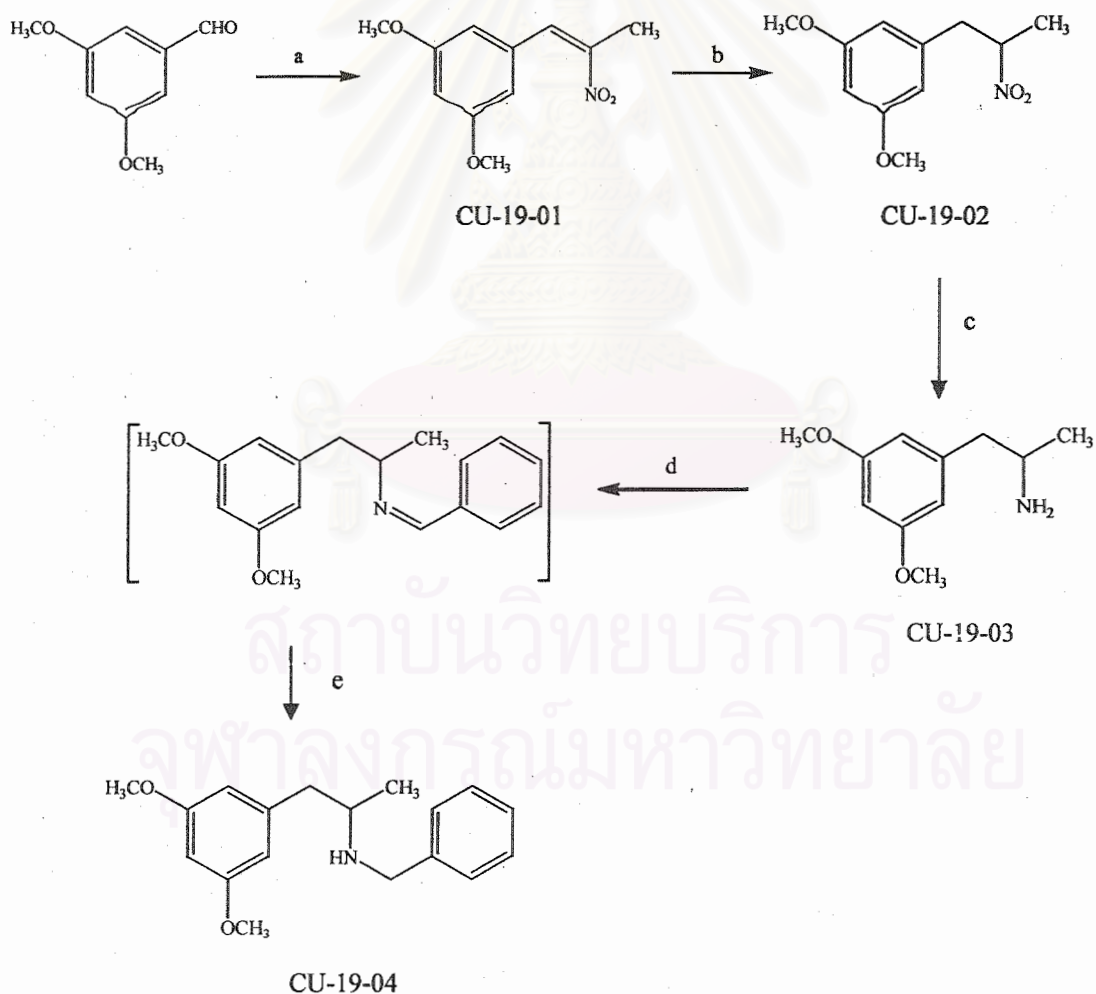
CU-19-03

CU-19-04

Scheme 4   The synthetic of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methyl-ethylamine; **a)** CH₃CH₂NO₂, NH₄OAc, reflux; **b)** NaBH₄, IPA/CHCl₃, SiO₂, rt; **c)** 10% Pd/C, H₂, EtOH; **d)** benzaldehyde, benzene, reflux ; **e)** NaBH₄, EtOH, rt.

3,5-Dimethoxy-β-nitrostyrene (CU-19-01)

The condensation of 3,5-dimethoxy benzaldehyde with nitroethane was carried out under refluxing condition in the presence of ammonium acetate. Acetate anion, as a base, generate the carbanion of nitroethane of which the nitro group provide the stabilization through the delocalization of negatively charge. The carbanion nucleophilic attack to the carbonyl carbon of the aldehyde to form a C=C bond. The addition produces a hydroxy compound which usually followed by dehydration (Figure 82). Finally, the yellow crude products can be recrystallized from methanol to give an excellent yield (95%) of 3,5-dimethoxy-β-nitrostyrene.
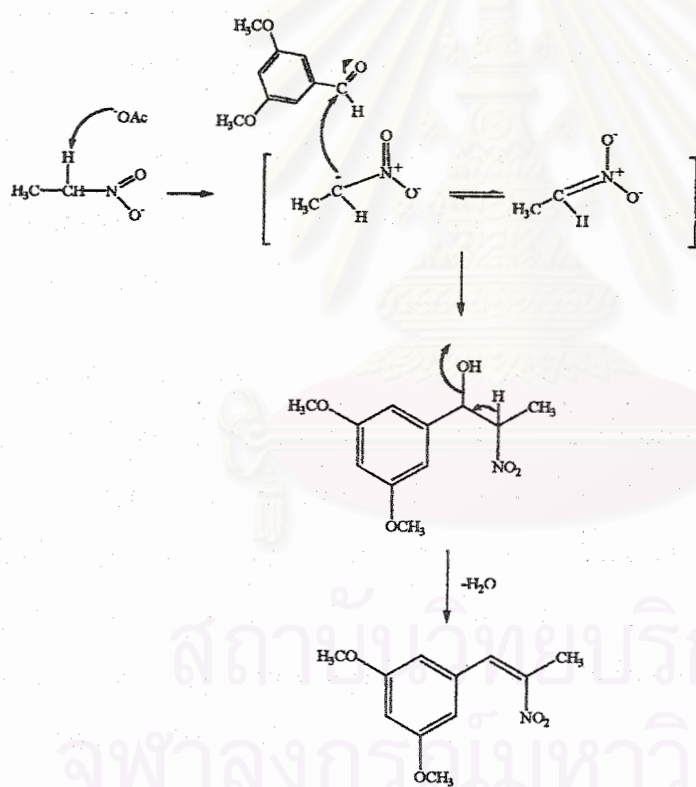
Figure 82   The reaction mechanism of the condensation between 3,5-dimethoxy benzaldehyde and nitroethane

The IR spectrum of product was showed in Figure 13, the nitro styrene displays symmetric C=C (aliphatic) stretching vibration at 1649 cm^{-1}, asymmetric NO$_2$ stretching vibration absorbs at 1519 cm^{-1}. The bands at the region of 1210-1157 cm^{-1} are the results of the asymmetric C-O-C stretching vibration.

The 300 MHz ^{1}H-NMR spectrum of product in CDCl$_3$/TMS was showed in Figure 14. The olifenic proton signal at δ 8.02 and the methyl proton signal at δ 2.54 confirm the propylene side chain. The data were tabulated (Table 3).

2-(3,5-Dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)

To reduce carbon-carbon double bond of 3,5-dimethoxy-β-nitrostyrene, sodium borohydride was used. Furthermore, silica gel was added to increase surface of reaction

Since the final solution is a basic solution, glacial acetic acid was added in order to neutralize the alkaline and destroy the excess NaBH$_4$. Then silica gel was eliminated by filtration and excess solvent was be used to wash the silica gel in order to minimize the absorption of the product by the silica gel. The filtrates were extracted with 5% sodium bicarbonate to wash the excesses acid in previous step and washed with water before concentration by rotary evaporator to give the products.

The IR spectrum of product was showed in Figure 16 and showed no absorption of C=C stretching vibration at 1649 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 17, 18 and the data were tabulated in Table 3.

2-(3,5-Dimethoxyphenyl)-1-methylethylamine (CU-19-03)

To convert the nitro compound to the amine compound, catalytic hydrogenation is the choice. Here in this investigation, 10% Pd/C in ethanol solution was used. The reaction mixture was shaken under pressure of hydrogen gas in a Parr hydrogenator.

Mechanisticly, the nitro compound first adsorbed on the catalyst (10% Pd/C) surface and simultaneous transfer of two hydrogen atom from the catalyst to the adsorbed molecular and finally desorption of the reduced molecule. To work up the reaction, insoluble catalyst was eliminated by filtration, carefully washing of the Pd/C with excess solvent must be carried out in order to maximize with the yield, concentrated the organic solvent to give a crude products. The amine compound separated from the neutral nitro compound which may be presented by partitioning in aqueous acidic solution. The acidic aqueous solution was basified to convert to the free amine. The amine compound was separated from the aqueous and was extracted with organic solvent. After concentrated the organic solvent to give the product.

IR spectrum of product was showed in Figure 20 and showed the N-H stretching vibration at 3200 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 21, 22 and the data were tabulated in Table 3.

N-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine (CU-19-04)

The purpose of introducing a benzyl group on the nitrogen of the phenylethylamine is to control the stereoselectivity of the next ring closure step so that the main stereoisomer can be prepared. Formation of N-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine required two consequent steps. The first step is the formation of the imine intermediate by reacting benzaldehyde and phenylethylamine in benzene, which will obtain the schiff base after dehydratation. The next step, is to reduce the carbon-nitrogen double bond of the schiff base by using sodium borohydride. The reaction mechanism was showed in Figure 83.

IR spectrum of product was showed in Figure 24.

The 300 M ^{1}H-NMR of product was showed in Figure 25, 26 and the data were tabulated in Table 3.
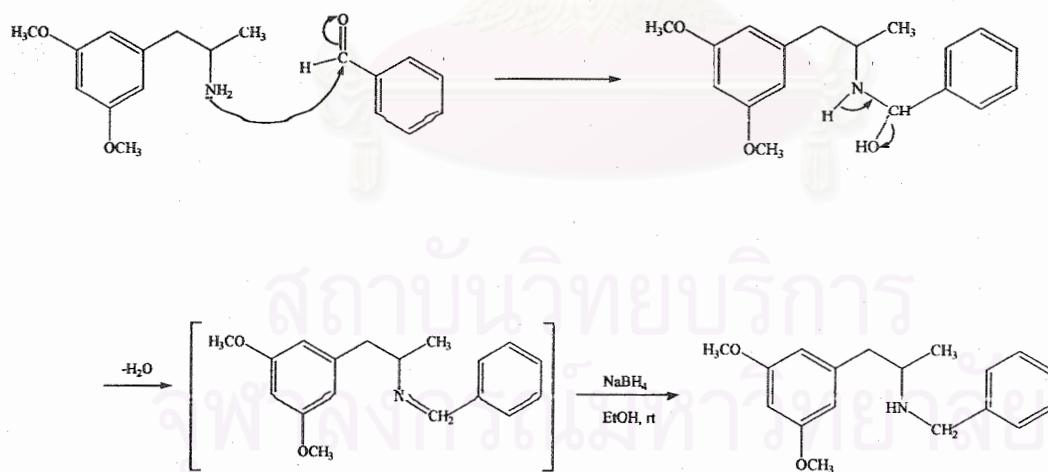
Figure 83 The reaction mechanism to synthesis of N-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine

Table 3 The ^{1}H-NMR spectral data of CU-19-01, CU-19-02, CU-19-03, and CU-19-04

positions	δ_H (ppm), mult, (J in Hz)			
	CU-19-01	CU-19-02	CU-19-03	CU-19-04
1-CH$_3$	2.54, s	1.52, d, (6.5)	1.12,d,(6.3)	1.09,d,(6.2)
1	-	4.77,m	3.16,m	2.93,m
2	8.02, s	2.91,dd,(13.7,6.7) 3.25,dd,(13.7,7.3)	2.44,dd,(13.1,8.3) 2.66,dd,(13.1,5.1)	2.57,dd,(13.2,6.2) 2.67.dd,(13.3,7.4)
2$'$	6.56, s	6.30,s	6.34,m	6.30,s
3$'$-OCH$_3$	3.84, s	3.75,s	3.77,s	3.74,s
4$'$	6.54, s	6.34,s	6.34,m	6.30,s
5$'$-OCH$_3$	3.84, s	3.75,s	3.77,s	3.74,s
6$'$	6.56, s	6.30,s	6.34,m	6.30,s
NH	-	-	1.67,s	1.75,s
N-CH$_2$Ph	-	-	-	3.69,d,(13.2) 3.80,d,(13.3)
aromatic-H	-	-	-	7.18-7.34

II. The Procedures for Cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine to the Tetrahydroisoquinoline with Paraformaldehyde
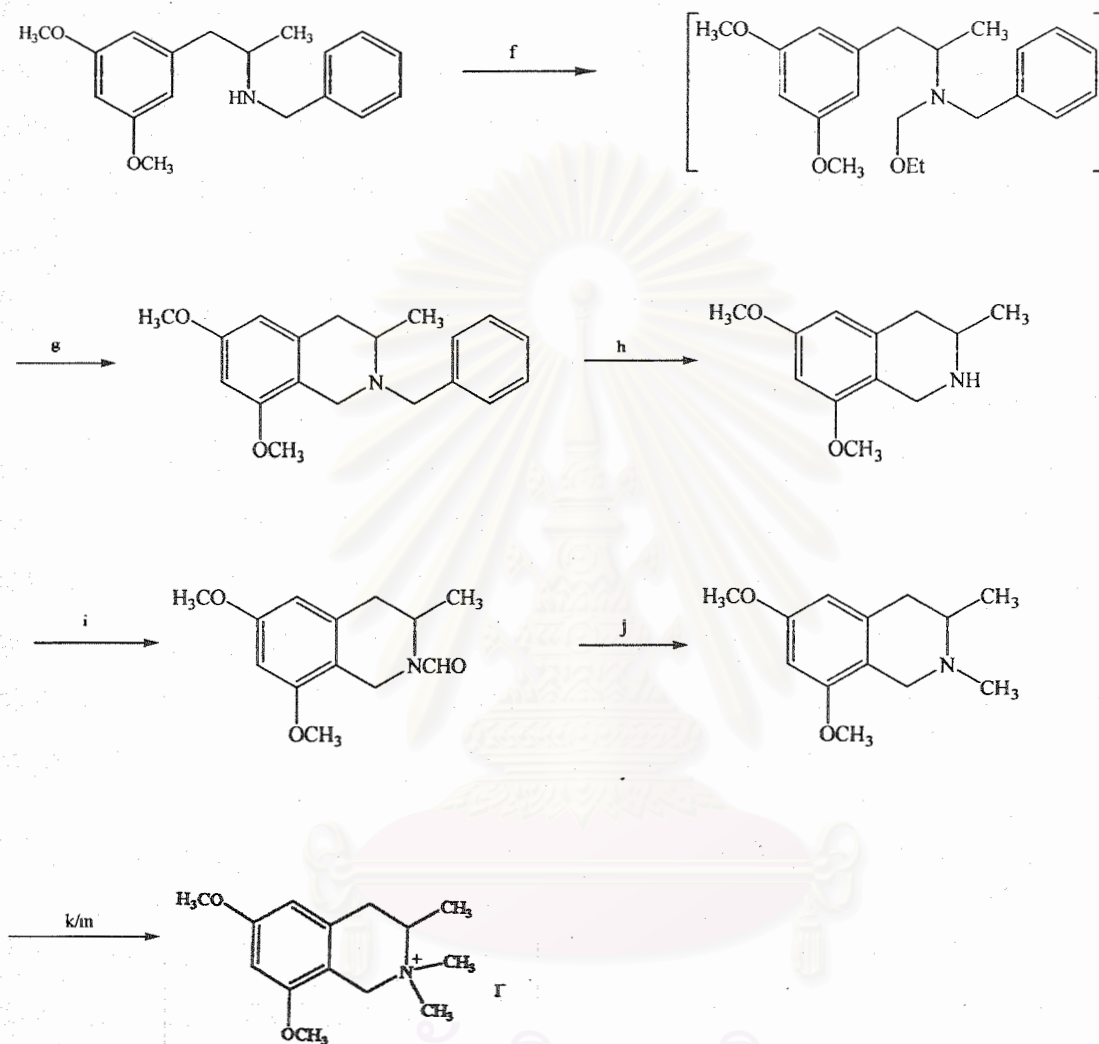
Scheme 5 The synthetic routes of 1,2,3,4-tetrahydroisoquinoline; f) HCHO, K$_2$CO$_3$, EtOH , rt; g) 0.5 M TFA in CH$_2$Cl$_2$, 0 °C; h) 10% Pd/C, H$_2$, EtOH; i) formic acid, acetic anhydride,heat; j) LiAlH$_4$, dry THF, heat; k) MeI, CH$_2$Cl$_2$, rt; m) MeI, dry THF, 80 °C.

2-Benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-05)

Ring closure cyclization of the phenylethylamine to tetrahydroiso-quinoline can be carried out by several methods, as previous mentioned. Here, cyclization through the N,O-acetal intermediate which is a facial, mild and applicable condition, was chosen. In addition, variable substitutes at position 1 of the tetrahydroisoquinoline can be easily prepared by using the correspond aldehyde. In this report, paraformaldehyde was used to cyclize the prepared N-benzyl-2-(3,5-dimethoxyphenyl)-1-methylehtylamine

The N,O-acetal intermediate can be easily prepared by stirring the phenylethylamine and an aldehyde in the presence of potassium carbonate in ethanol at room temperature. The crude N,O-acetal was obtained be filtering off the insoluble substance and evaporate the solvent. Then the N,O-acetal intermediate was stirred in CH_2Cl_2 at 0 °C and equivalent amount of 0.5 M TFA in CH_2Cl_2 was slowly added to catalyze the ring cyclization. The mechanism of this ring cyclization was showed in Figure 84.

IR spectrum of product was showed in Figure 28.

The 300 M ^{1}H-NMR of product was showed in Figure 29, 30 and the data were tabulated in Table 4.
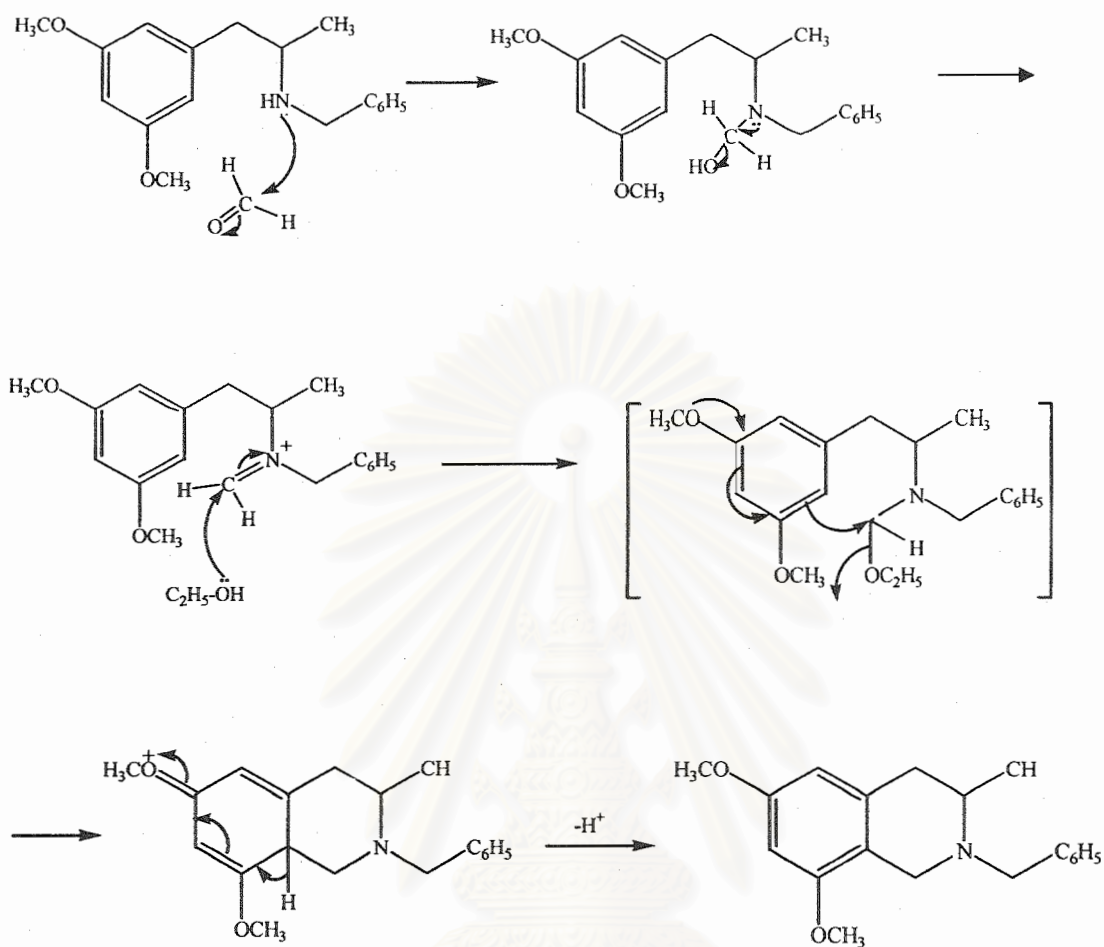
Figure 84   The reaction mechanism of ring cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylehtylamine to form the 1,2,3,4-tetrahydroiso-quinoline

However, in the presence of excess TFA, cyclization process did not stop at the tetrahydroisoquinoline step but trend to dimerize to yield the bis tetrahydroisoquinoline. The reaction mechanism of the dimer formation can be illustrated at Figure 85.
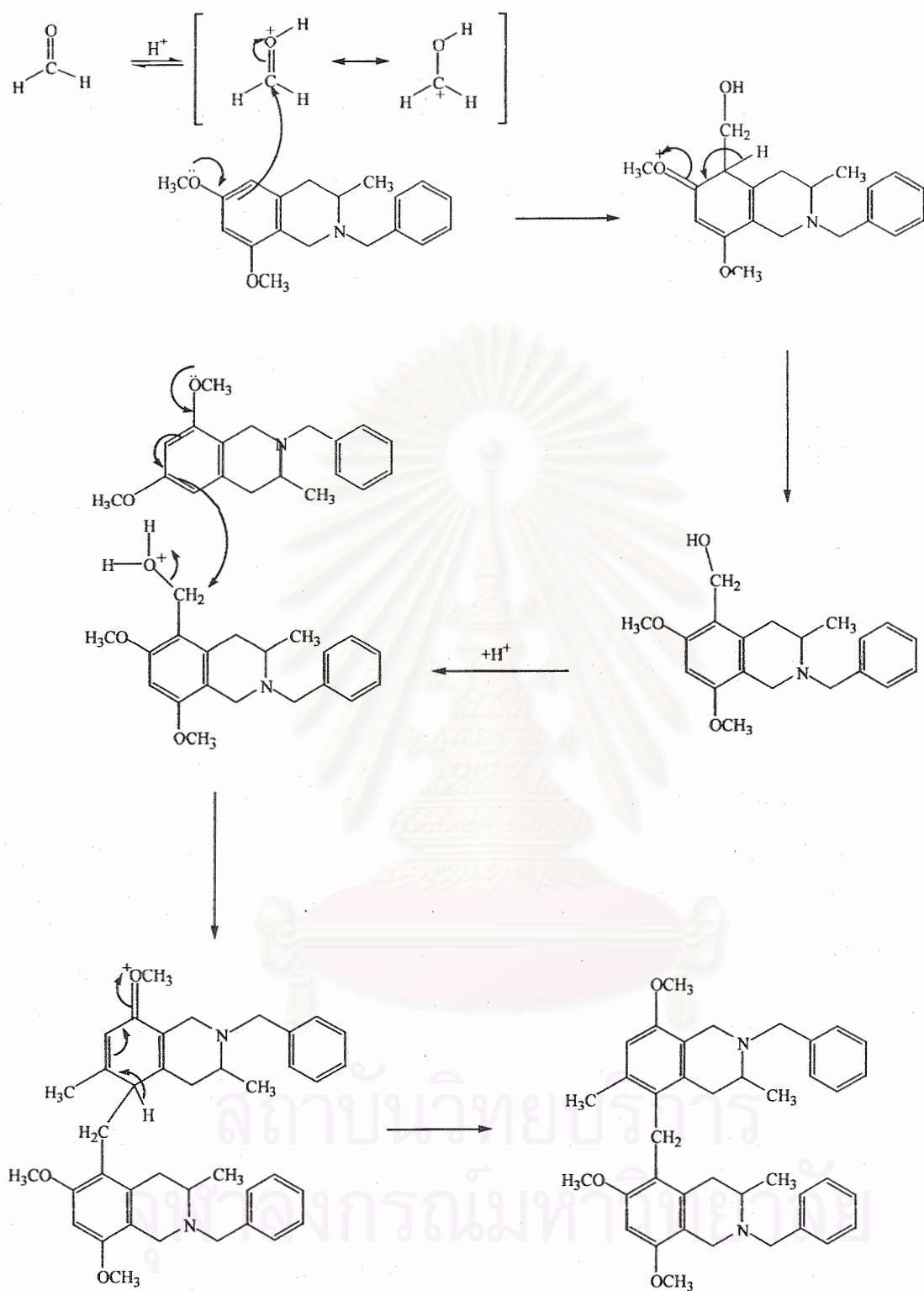
Figure 85 The reaction mechanism of the dimerization in excess TFA to obtain the bistetahydroisoquinoline

6,8-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-19-06)

Debenzylation of *N*-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydro-isoquinoline can be easily prepared by the catalytic hydrogenation using 10% Pd/C in ethanol.

IR spectrum of product was showed in Figure 42.

The 300 M ^{1}H-NMR of product was showed in Figure 43 and the data were tabulated in Table 4.

6,8-Dimethoxy-2-formyl-3-methyl-,2,3,4-tetrahydroisoquinoline (CU-19-07)

The 6,8-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline was formylated with formic acid in the presence of acetic anhydride , which probably reacted as the mixed anhydride, upon heating gave the amide compound. The reaction mechanism was showed in Figure 86.

The IR spectrum of product was showed in Figure 44 and exhibited the C=O stretching vibration of the formyl group at 1661 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 45. In addition, the ^{1}H-NMR of N-CHO proton showed signal broad singlet at δ 8.12 ppm also supported the N-CHO functionality. The ^{1}H-NMR data tabulated in Table 4.
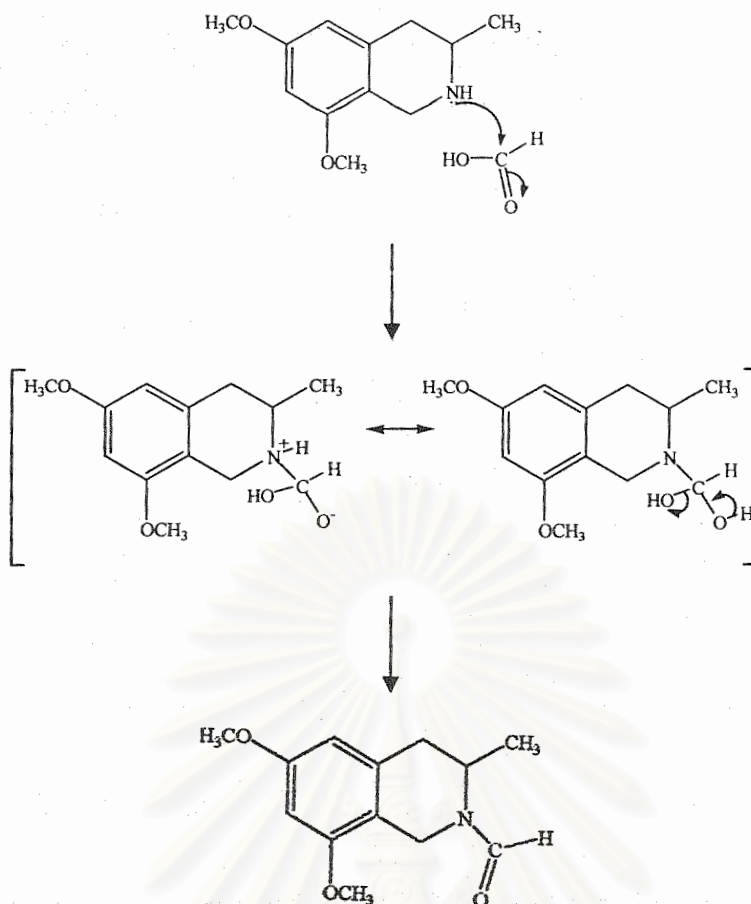
Figure 86 The reaction mechanism of the formylation reaction

6,8-Dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-08)

The reaction of the formamide with LiAlH$_4$ produced an methylamine. The mechanism of amide reduction involves addition of hydride to the carbonyl carbon atom of an initially formed amide salt, followed by loss of the oxygen atom as an aluminium oxide. The resulting imine is rapidly reduced to give the amine, that was illustrated in Figure 87.
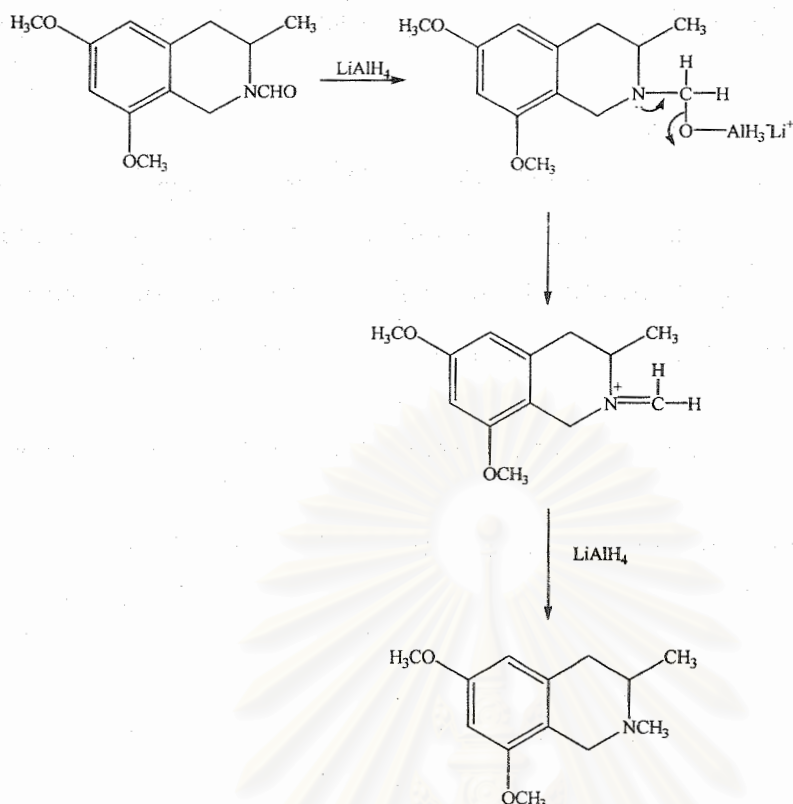
Figure 87 The reduction mechanism of 2-Formyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline to 6,8-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline

The IR spectrum of product was showed in Figure 46. The IR results supported this structure by disappearance of the absorption of N-CHO stretching vibration.

The 300 M ^{1}H-NMR of product was showed in Figure 47. In addition, the ^{1}H-NMR no showed signal of N-CHO proton also supported the existing N-CHO functionality. The ^{1}H-NMR data tabulated in Table 4.

6,8-Dimethoxy-2,2,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (CU-19-09)

Quaternarization of tertiary amine can be easily prepared by using methyl iodide. With the mild condition, methyl iodide was stirred with the amine at room temperature for 96 h to yield 78% of the product. while the vigorous condition, heating at 80 °C for 10 min to yield 80% of the product.

The IR spectrum of product was showed in Figure 48.

The 300 M ^{1}H-NMR of product was showed in Figure 49 and the data tabulated in Table 4.

Table 4 The ^{1}H-NMR spectral data of CU-19-05, CU-19-06, CU-19-07, CU-19-08, and CU-19-09

positions	δ_H (ppm), mult, (J in Hz)				
	CU-19-05	CU-19-06	CU-19-07	CU-19-08	CU-19-09
1	3.58,d,(13.3) 3.80,d,(13.3)	3.70,d,(16.4) 4.04,d,(16.3)	4.10 4.20	3.82	4.52,d,(5.6) 4.65,d,(15.7)
NH	-	1.68,s	-	-	-
3	3.05,m	2.90,m	4.45	2.78,m	4.41,m
3-CH$_3$	1.07,d,(6.4)	1.18,d,(6.1)	1.18	1.14,d,(5.7)	1.55,d,(6.4)
4	2.51,dd,(16.2,4.7) 2.95,dd,(16.4,4.8)	2.33,dd,(16.9,11.4) 2.85,m	2.58,m	2.62,m	3.47,s
5	6.21 or 6.23	6.30	6.34	6.22 or6.26	6.31 or6.34
6-OCH$_3$	3.68 or3.74	3.77 or 3.79	3.80	3.78,s	3.80,s
7	6.21 or 6.23	6.30	6.34	6.22 or6.26	6.31 or6.34
8-OCH$_3$	3.68 or 3.74	3.77 or 3.79	3.80	3.78,s	3.80,s
N-CH$_2$Ph	3.57, s	-	-	-	-
aromatic -H	7.28,m	-	-	-	-
NCHO	-	-	8.12,s	-	-
N-CH$_3$	-	-	-	2.47,s	-
N$^+$-CH$_3$	-	-	-	-	3.20,s 3.58,s

III. The Procedures for Cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine to the Tetrahydroisoquinoline with Butyl glyoxalate
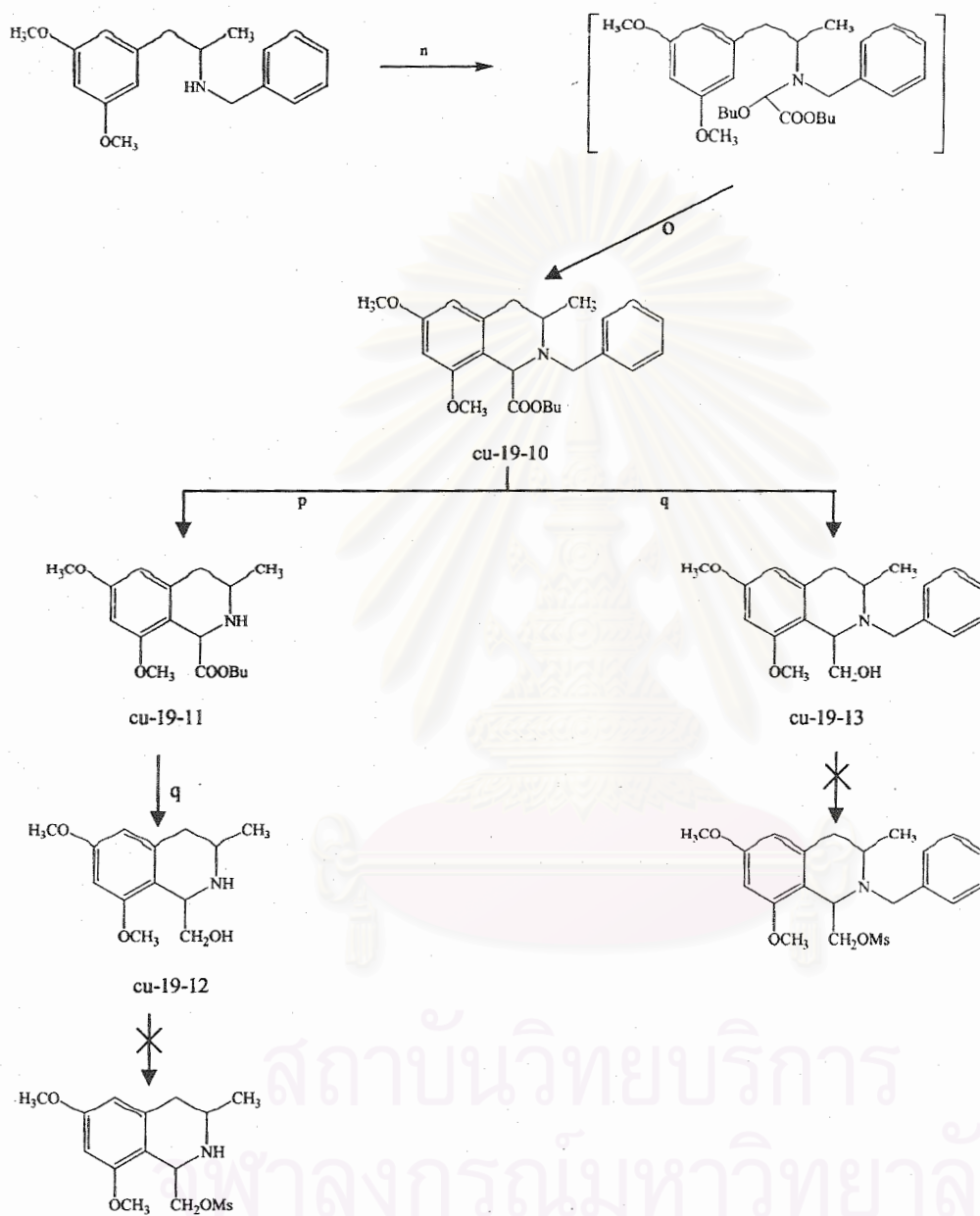
Scheme 6   The synthetic routes of 1,2,3,4-tetrahydroisoquinoline; **n)** butyl glyoxalate, K_2CO_3, n-BuOH, rt; **o)** 0.5 M TFA in CH_2Cl_2, 0 °C; **p)** 10% Pd/C, H_2, EtOH; **q)** $LiAlH_4$, dry THF, heat

Butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroiso-

quinoline-1-carboxylate (CU-19-10)

N-Benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine and butyl glyoxalate was cyclized through the *N,O*-acetal intermediate. Therefore, butyl glyoxalate was prepared as the material for this cyclization.

Dibutyl L-(+)-tartrate was oxidized with periodic acid to the butyl glyoxalate. The reaction was carried out in dry ether at room temperature. The vigorous strring is necessary to activate the oxidative cleavage of dibutyl L-(+)-tartrate.

Butyl glyoxalate can be prepared in n-butanol in the presence of potassium carbonate. Then *N,O*-acetal intermediate will be cyclized to tetrahydroisoquinoline with 1 equivalent of 0.5 M TFA in CH_2Cl_2 at 0 ^{o}C (Figure 88).

The IR spectrum of product was showed in Figure 50 and showed C=O (ester) stretching vibration at 1735 cm^{-1} and overtone absorption at 3330 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 51, 52 and the data tabulated in Table 5.
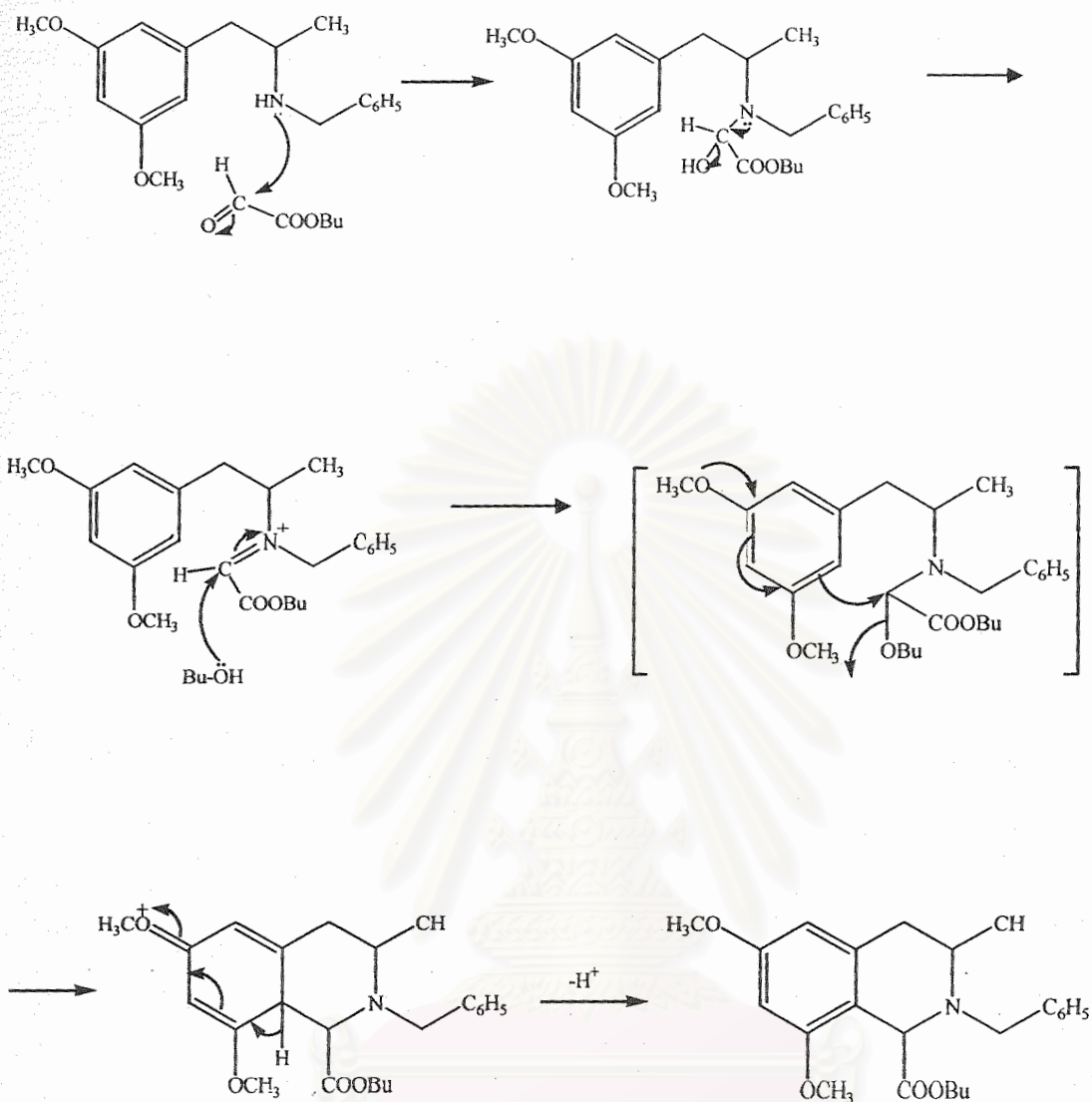
Figure 88 The reaction mechanism of ring cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylehtylamine to form the 1,2,3,4-tetrahydroiso-quinoline

Again, when excess of TFA was used in the cyclization the mixture of diastereoisomer of butyl-2-benzyl-6,8-dimethoxy-5-(2-hydroxybutylacetate)-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate was obtained as shown structure below.

When the *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylehtylamine and butyl glyoxalate were stirred in ethanol instead of butanol in the step of *N,O*-acetal formation after cyclization to tetrahydroisoquinoline with 1 equivalent TFA, the mixture of ethyl ester and butyl ester were obtained.
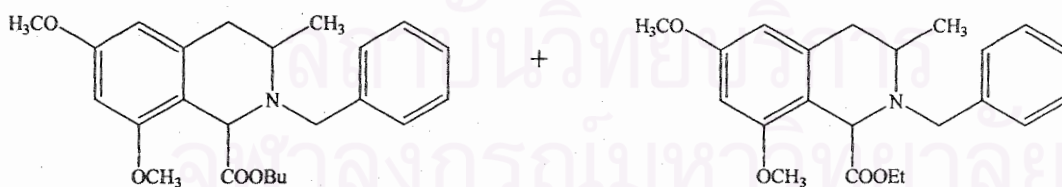
Butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-19-11)

Debenzylation of Butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate can be prepared by the catalytic hydrogenation using 10% Pd/C in ethanol.

IR spectrum of product was showed in Figure 67.

The 300 M ^{1}H-NMR of product was showed in Figure 68, 69 and the data were tabulated in Table 5.

6,8-Dimethoxy-1-hydroxymethyl-3-methyl-1,2,3,4-tetrahydro-isoquinoline (CU-19-12)

The ester group at the position 1 of butyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate was reduced to alcohol group with LiAlH$_4$ in dry THF.

IR spectrum of product was showed in Figure 71. The –OH stretching vibration showed absorption at 3324 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 72, 73 and the data were tabulated in Table 5.

2-Benzyl-1-hydroxymethyl-3-methyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (CU-19-13)

The ester group at the position 1 of Butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate was reduced to alcohol group with LiAlH$_4$ in dry THF.

IR spectrum of product was showed in Figure 75. The –OH stretching vibration showed absorption at 3436 cm^{-1}.

The 300 M ^{1}H-NMR of product was showed in Figure 76, 77 and the data were tabulated in Table 5.

Table 5 The ^{1}H-NMR spectral data of CU-19-10, CU-19-11, CU-19-12, and CU-19-13

position	δ_H (ppm), mult, (J in Hz)			
	CU-19-10	CU-19-11	CU-19-12	CU-19-13
1	4.41	4.72,s	4.15,dd,(10.9,4.1)	3.98,dd,(9.8,5.0)
1-CH$_2$	-	-	3.35,t,(10.2)	3.38,t,(10.1)
			3.85,dd,(10.3,4.1)	3.75,
3	3.46,m	3.09,m	3.09,m	3.43,m
3-CH$_3$	1.17,d,(6.6)	1.18,d,(6.18)	1.19,d,(6.2)	1.34,d,(6.6)
4	2.62,dd,(16.6,9.3)	2.47,dd,(16.2,10.8)	2.37,dd,(16.6,5.5)	2.55,dd,(17.0,4.4)
	2.74,dd,(16.5,4.4)	2.73,dd,(16.3,3.6)	2.72,dd,(16.7,3.4)	2.73,dd,(17.0,11.5)
5	6.27	6.24 or 6.28	6.25 or 6.29	6.24 or 6.29
6-OCH$_3$	3.67 or 3.79	3.74 or3.78	3.74,s	3.69 or 3.78
7	6.27	6.24 or 6.28	6.25 or 6.29	6.24 or 6.29
8-OCH$_3$	3.67 or 3.79	3.74 or3.78	3.74,s	3.69 or 3.78
NH		2.05,s	2.58,s,br	
N-CH$_2$	3.58,d,(14.5)			3.21,d,(13.4)
	3.89,d,(14.5)			3.95,d,(13.4)
aromatic	7.2-7.5	-	-	7.28-7.40
1$^/$	4.08,m	4.12,m	-	-
2$^/$	1.56,m	1.61,m	-	-
3$^/$	1.34,m	1.32,m	-	-
4$^/$	0.92,t,(7.3)	0.91,t,(7.35)	-	-

CHAPTER V

CONCLUSION

By using ancistrotectorine as a lead molecule, the analogs of tetrahydroisoquinoline, mimic to the tetrahydroisoquinoline moiety of ancistrotectorine were synthesized in order to explore the muscular relaxation activity of ancistrotectorine. The target compounds were synthesized through the *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine, which was cyclized through *N*,O-acetal intermediate. The synthetic procedures for this research were divided into three major series as follows.

1. The *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine was initially prepared by condensing 3,5-dimethoxy benzaldehyde and nitroethane to give the nitrostyrene derivatives. Reduction of aliphatic double bond of the nitrostyrene with NaBH$_4$, yielded the nitroethane, which upon the catalytic hydrogenation with 10% Pd/C under hydrogen gas gave the 2-(3,5-dimethoxyphenyl)-1-methylethylamine. The adducts of benzaldehyde and 2-(3,5-dimethoxyphenyl)-1-methylethylamine gave the schiff base intermediate which was reduced with NaBH$_4$ to give *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine, the key starting material for cyclization of 1,2,3,4-tetrahydroisoquinoline compounds.

2. Cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methyl ethyl-amine to the 1,2,3,4-tetrahydroisoquinoline can be prepared via two consequent steps. Firstly, the amine reacted with the aldehyde in presence of K$_2$CO$_3$ to give the *N*,O-acetal intermediate. Secondly, the intermediated was treated with 1 equimolar of 0.5 M TFA in CH$_2$Cl$_2$ at 0°C to give the tetrahydroisoquinoline. When paraformaldehyde was used, the 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline was obtained which can be debenzylated with

catalytic hydrogenation by 10% Pd/C. Debenzylation product was converted to the *N*-formyl derivative which was reduced with LiAlH$_4$ to give the *N*-methyl analog, which was further reacted with methyl iodide to yield the dimethyl quaternary compound. Cyclization of the *N,O*-acetal intermediate in excess TFA resulted a side reaction which yield the bis tetrahydroisoquinoline occured at C-5 position of the tetrahydroisoquinoline nucleus.

3.   Cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methyl ethyl-amine and butyl glyoxalate gave *N,O*-acetal intermediate and treated with 0.5 M TFA in CH$_2$Cl$_2$ at 0 ^{o}C to afford butyl 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate. The compound was debenzylated and reduced with LiAlH$_4$ gave the hydroxy methyl on the position 1 of tetrahydroisoquinoline. Mesylation with MsCl to the hydroxy group at position 1 in various conditions were not successful.

Cyclization with butyl glyoxalate also tetrahydroisoquinoline yield the compound with 2 asymmetric carbon, position 1, and 3. However the resulting product proved to be the trans enantiomeric pair.

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VITA

Miss Ploenthip Puthongking was born on November 22, 1974 in Kalasin, Thailand. She received her Bachelor of Science in Pharmacy in 1998 from the Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, Thailand. She received the University Development Commission (UDC) scholarship in 1999. Now she is a staff of the Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Science, Khon Kaen, Thailand.