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SYNTHESIS AND PROPERTIES OF META-TERPHENYL DERIVATIVES

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การศึกษาปฏิกิริยาฮาร์ทเพื่อสังเคราะห์อนุพันธ์สารประกอบเมตา-เทอร์เฟนิล โดยใช้สารตั้งต้น 2 แบบ คือ 3,5-ไดโบรโม-4-ไอโอโดโทลูอีนและ 1,3-ไดคลอโรเบนซีน ทำปฏิกิริยากับกรินยาร์ดรีเอเจนต์ที่มากเกินพอ และหยุดปฏิกิริยาด้วยอิเล็กโทรไฟล์หลายชนิด ทำให้ได้ผลิตภัณฑ์ที่เป็นอนุพันธ์ของสารประกอบเมตา-เทอร์เฟนิลต่างๆ โดยพิสูจน์โครงสร้างของผลิตภัณฑ์ที่สังเคราะห์ได้ด้วย เทคนิคโปรตอนและคาร์บอนนิวเคลียร์แมกนีติคเรโซแนนซ์ แก๊สโครมาโทกราฟีและแมสสเปกโทรเมตรี ซึ่งผลิตภัณฑ์ที่สามารถสังเคราะห์ ได้แก่ 3,5-ไดฟีนิลโทลูอีน (59%) และ 3,5-ไดฟีนิลไอโอโดโทลูอีน (73 %)ซึ่งสังเคราะห์จาก 3,5-ไดโบรโม-4-ไอโอโดโทลูอีน ส่วน เมตา-เทอร์เฟนิล (30%) และ 2,6-ไดฟีนิลไอโอโดเบนซีน (23%) สังเคราะห์ได้จาก 1,3-ไดคลอโรเบนซีน

นอกจากนั้นยังได้ศึกษาถึงปัจจัยอื่นๆอีก 3 ประการที่ส่งผลต่อปริมาณของผลิตภัณฑ์ที่ได้จากการสังเคราะห์จาก 1,3-ไดคลอโรเบนซีน ซึ่งสามารถวิเคราะห์ติดตามผลของปฏิกิริยาได้ด้วยเทคนิคแก๊สโครมาโทกราฟีและพบว่า ได้สภาวะที่ดีที่สุดในการทำปฏิกิริยาโดย การเติม 1,3-ไดคลอโรเบนซีนลงในกรินยาร์ดรีเอเจนต์ที่อุณหภูมิต่ำ (-10 องศาเซลเซียส)ใช้ความเข้มข้นของสารตั้งต้นที่สูง (0.29 โมลาร์) และระยะเวลาที่เหมาะสมในการดำเนินปฏิกิริยาที่รีฟลักซ์คือ 3 ชั่วโมง

ภาควิชา.....เคมี.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เคมี.....ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2547.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

45724736323: MAJOR CHEMISTRY
KEY WORD: HART REACTION, GRIGNARD REAGENT

MISS WARARAT RADCHADAWONG; SYNTHESIS AND PROPERTIES OF META-TERPHENYL DERIVATIVES
THESIS ADVISOR: ASST. PROF. YONGSAK SRITANA-ANANT, Ph.D., THESIS CO-ADVISOR: ASST. PROF. WORAWAN BHANTHUMNAVIN, Ph.D., 60 pp., ISBN 974-53-1607-5

The study of Hart reaction for the syntheses of *m*-terphenyl derivatives were performed in a one-pot fashion using excess phenyl Grignard reagent reacting either with 3,5-dibromo-4-iodotoluene or 1,3-dichlorobenzene. Working up the reaction mixtures by various electrophiles gave the corresponding *m*-terphenyl derivatives. The products were analyzed by proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance spectroscopy, Gas Chromatography and Mass Spectrometry. The *m*-terphenyl derivatives obtained were 59% of 3,5-diphenyltoluene, 73% of 3,5-diphenyl-4-iodotoluene starting from 3,5-dibromo-4-iodotoluene. When 1,3-dichlorobenzene was used as the substrate, 30% yield of *m*-terphenyl and 23% yield of 2,6-diphenyliodobenzene were obtained.

Three factors affecting the yield of *m*-terphenyl prepared from 1,3-dichlorobenzene, monitored by Gas Chromatography (GC), were investigated. The most efficient condition was found with the addition of the 1,3-dichlorobenzene substrate into Grignard reagent at low temperature (-10 °C), using high concentration of the substrate (0.29 M) and runing the reaction at reflux for 3 h.

Department……Chemistry……..Student's Signature…….....
Field of Study……Chemistry…….Advisor's Signature…….....
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LIST OF ABBREVIATIONS

^{o}C	=	degree celsius
$CDCl_3$	=	deuterated chloroform
eq	=	equivalent
exp	=	experiment
FID	=	flame ionization detector
g	=	gram
GC	=	gas chromatography
GC-MS	=	gas chromatography-mass spectrometry
h	=	hour
Hz	=	hertz
lit	=	literature
m	=	multiplet (NMR)
min	=	minute
mL	=	milliliter
mol	=	mole
mp	=	melting point
M	=	molar
NMR	=	nuclear magnetic resonance
Ph	=	phenyl
ppm	=	parts per million
RT	=	room temperature (approximately 30 °C)
s	=	singlet (NMR)
THF	=	tetrahydrofuran
δ	=	chemical shift

CHAPTER I

INTRODUCTION

1.1 Steric Effects

Steric effect is the effect on a chemical or physical property[1] (structure, rate or equilibrium constant) upon introduction of substituents having different steric requirements. The steric effect in a reaction is ascribed to the difference in steric energy between, on the one hand, reactants and, on the other hand, a transition state (or products). A steric effect on a rate process may result in a rate increase ("steric acceleration") or decrease ("steric retardation"). It usually arises from contributions ascribed to strain as the sum of

(1) non-bonded repulsions.

(2) bond angle strain.

(3) bond stretches or compressions.

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electronic effects alone. In this case, it can often be shown that steric effects are influencing the rate. For example, Table 1.1 lists the relative rates for the S_N2 ethanolysis of certain alkyl halides. All these compounds are primary bromides;

Table 1.1 Relative rate of reaction of RBr with ethanol[2]

R	Relative Rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

The branching is on the second carbon, so field-effect differences should be small. As Table 1.1 shows, the rate decreases with increasing β branching and reaches

a very low value for neopentyl bromide. The great decrease in rate can be attributed to steric hindrance, a sheer physical blockage to the attack of the nucleophile.

Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position could induce.[2]

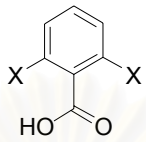


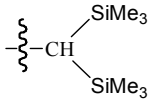
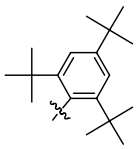
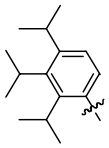
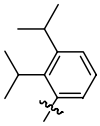
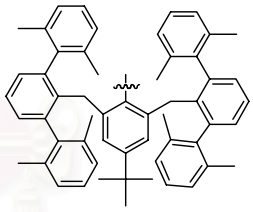
Figure 1.1 Structure of 2,6-disubstituted benzoic acids

1.2 Ligand designs

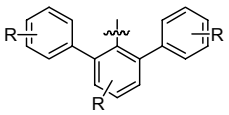
The quest for molecules possessing main group elements in low coordinate environments,[3] a molecule with a main group element engaging in multiple bonds or an element with a low coordination number, has been an important area of research for the past 30 years.[4] In many cases, molecules with elements carrying unusual bonding modes can be isolated when the center of interest possesses at least one sterically demanding substituent. Stability with respect to cyclic or oligomeric alternatives can be imposed by sterically demanding groups.[5]

Numerous ligand designs[3] have been used to prepare molecules with elements in unusual bonding modes, and sometimes the chemistry observed for these systems is ligand dependent. Alkyl and aryl substituents that have been extensively employed are shown in Table 1.2

Table 1.2 Steric ligands and their structures

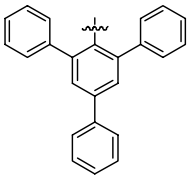
ligand	structure
$(SiMe_3)_2CH$[6]	
Mes* (2,4,6-tri-*tert*-butylphenyl)[7]	
Trip (tri-*iso*-propylphenyl)[7]	
Dipp (di-*iso*-propylphenyl)[6]	
Bmt[8]	

For the most part, these ligands are readily prepared,[3] and some are commercially available. A relatively new ligand design is the generalized *m*-terphenyl ligand. A series of these ligands is presented in Figure 1.2. These substituents are easily prepared, very bulky and offer the most synthetic utility. Substituents in the position between the two *ortho* aryl groups are effectively in a "pocket". They can often experience strong associations to the *ortho* aryl groups via a π-arene interaction.



1

R = H, Me, Et, etc.



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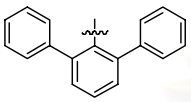

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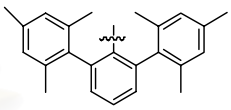

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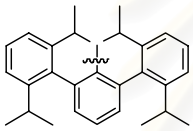

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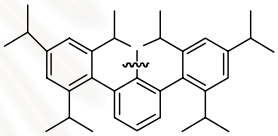


6

Figure 1.2 *m*-Terphenyl ligands

1.3 The *m*-terphenyl[9]

In the study of organic synthesis, production of carbon-carbon bond is the most important task, but not always easy to come by, especially the production of various carbon-carbon bonds in one pot fashion. The reaction in one pot does not only help to reduce processes and steps in the synthesis but also reduce the associate expense and duration. One of the production of the carbon-carbon bond of aromatic compounds that caught interests of organic synthesis is the *m*-terphenyl system. (Figure 1.3)

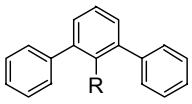


Figure 1.3 *m*-terphenyl derivatives

The *m*-terphenyl compounds are the aromatic compounds which are of importance to organic chemistry in terms of theory and synthetic utility. In the fields of the organic synthesis and organometallics, the property of *m*-terphenyl derivatives which has a specific concave structure, allows them to make central functionality surrounded by two aromatic ring units, hence create a special situation of the interaction between π electrons of the aromatic groups and the functional group at the center (such as "R" group in Figure 1.3). Moreover, they bring about steric hindrances and obstruct a way to access this central functionality which may lead to a selectivity of chemical reaction.[9,10]

1.4 The synthesis of the *m*-Terphenyl derivative

m-Terphenyl compounds is a class of polyaromatic compounds which has an exceptional rigid structure for controlling a specific three-dimensional conformation owing to limitation of single bond's rotation between aromatic groups. It causes the flanking aromatic groups not to orderly arrange on a same plane surface and turns their π-aromatic rings electrons to the central functionality. This puts the central functional groups in an environment surrounded by negative charges of π-electrons. Therefore, they show their special properties that are different from normal conditions, which come from the interactions with those electrons.[10,11] Moreover, both sides of aromatic groups which are in the perpendicular conformation to the central functionality cause a steric hindrance which obstruct the access to the central functionality. A total of electronic and of steric-hindrance effects may make these central functionality have additional special properties, such as the selectivity to certain chemical reactions.

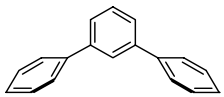
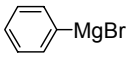
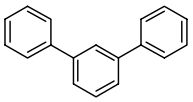
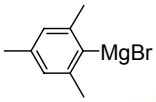
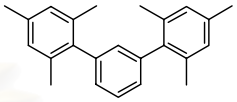
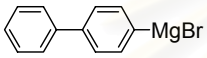
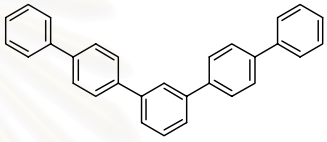
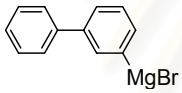
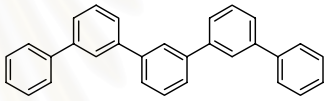
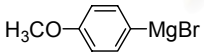
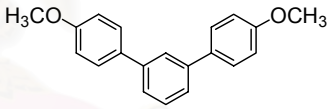
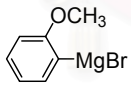
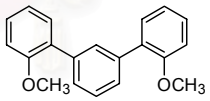
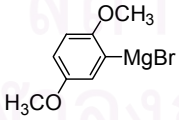
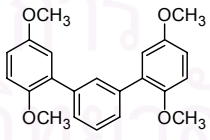
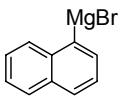
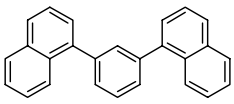
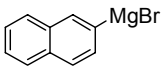
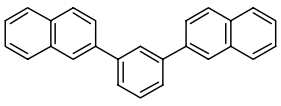


Figure 1.4 Conformation of *m*-terphenyl

1.4.1 A One-pot Synthesis of *m*-Terphenyls via a Two-Aryne Sequence

2,6-Dibromoiodobenzene (**1**)[11] can be readily prepared from 2,6-dibromoaniline[12] via diazotization and treatment with potassium iodide. A solution of **1** in THF was added dropwise to somewhat over the theoretical 3 equiv of aryl-Grignard in the same solvent, usually at room temperature but in some instances at reflux. After additional stirring for a few hours, the mixture was quenched with dilute aqueous acid. To give *m*-terphenyl derivatives in one step. This procedure was named as “Hart reaction”. The results with many Grignard reagents are summarized in Table 1.3

Table 1.3 *m*-Terphenyls from 2,6-Dibromoiodobenzene and Aryl-Grignard reagents

entry	ArMgBr	Conditions	product	yield(%)
1		rt, 3 h		77
2		rt, 3 h		70
3		rt, 5 h		73
4		rt, 5 h		62
5		rt, 5 h		80
6		reflux, 10 h		85
7		reflux, 10 h		25
8		rt, 5 h		57
9		rt, 5 h		64

1.4.2 Two Routes to *m*-Terphenyls from 1,3-Dichlorobenzenes[13]

Method A

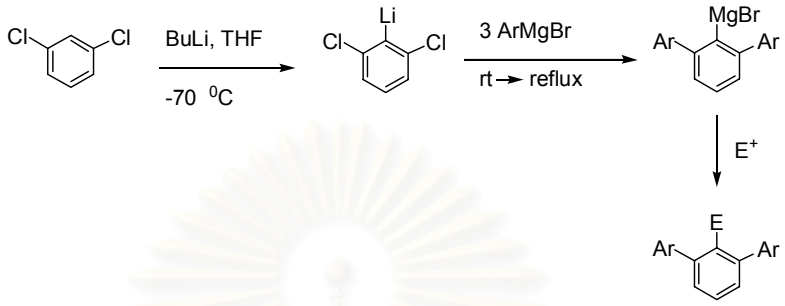
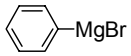
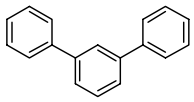
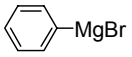
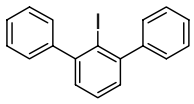
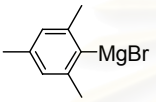
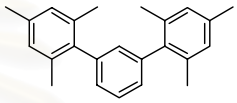
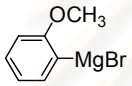
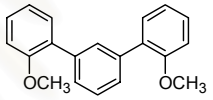
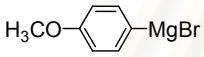
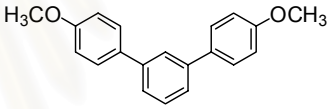
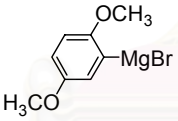
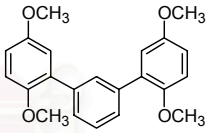
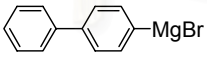
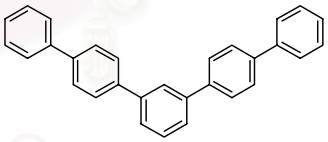
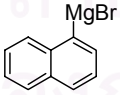
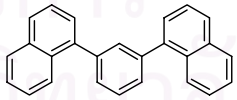


Figure 1.5 *m*-Terphenyls via 2,6-dichlorophenyllithium followed by Grignard reagent

In 1988 Kress and Leanna reported[14] that 2,6-dichlorophenyllithium could be prepared by regioselective lithiation of 1,3-dichlorobenzene with butyllithium (BuLi) in THF at – 70 ºC and that such solutions were stable below -50 ºC. The resulted intermediate reacted with aryl Grignard reagents at room temperature or reflux to give *m*-terphenyls. (Table 1.4)

Table 1.4 *m*-Terphenyls from 2,6-dichlorophenyllithium and Aryl-Grignard reagents

Entry	ArMgBr	Conditions	product	yield(%)
1		rt, 24 h		73
2		rt, 24 h; reflux,3 h		57
3		rt, 13 h ; reflux, 3 h		74
4		rt, 13 h ; reflux, 3 h		93
5		reflux, 12 h; rt, 48 h		60
6		rt,14 h ; reflux, 4 h		82
7		rt, 24 h ; reflux,3 h		65
8		rt, 24 h ; reflux,3 h		63

Method B

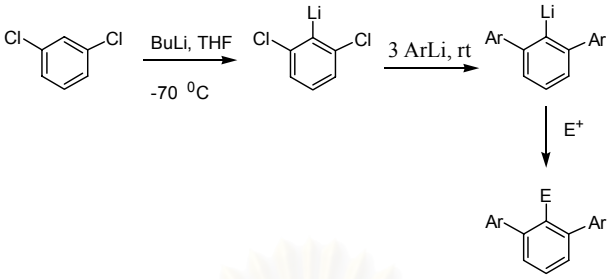
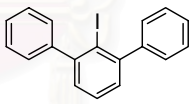
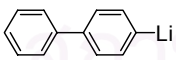
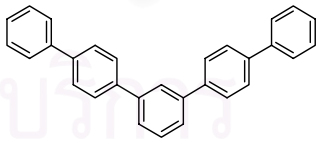
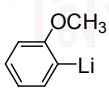
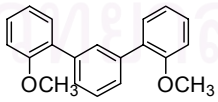
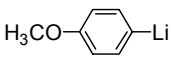
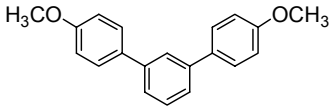


Figure 1.6 *m*-Terphenyls from 1,3-dichlorobenzene and aryllithium

The intermediate 2,6-dichlorophenyllithium was obtained by lithiation of 1,3-dichlorobenzene in THF. By changing the solvent to diethyl ether one could obtain *m*-terphenyls directly from 1,3-dichlorobenzene and excess of an aryllithium at room temperature. (Table 1.5)

Table 1.5 *m*-Terphenyls from 2,6-dichlorophenyllithium and Aryllithiums

entry	ArLi	Conditions	product	yield(%)
1		rt,15 h		55
2		rt, 24 h		63
3		rt, 48 h		73
4		rt, 7 h		52

In 1995, Tagat, Barton and co-workers[15] found novel compounds which inhibited the synthesis of interleukin-6, a pleiotropic cytokine involved in several inflammatory and some tumorogenic pathways. They found that SCH-21418 (**2**) had good inhibitory activity. Subsequently a systematic synthetic study revealed that the corresponding meta-terphenyls (**3**) also had comparable activity. (Figure 1.7)

SCH-21418 (**2**) SCH-53020 (**3**)

Figure 1.7 Structures of SCH-21418 and SCH-53020

In 1997, Protasiewicz and co-workers[16] reported the synthesis and structural characterization of the stable diphosphene DmpP=PDmp (Dmp = 2,6-dimesitylphenyl) (Figure 1.8). Many new and exciting main group and organometallic compounds have been isolated using the steric umbrella afforded by the Dmp system.

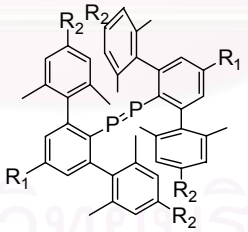


Figure 1.8 Structure of DmpP=PDmp

In 2000 Pietschnig[17] achieved the synthesis of terphenyl silanes and investigated their reduction behavior toward the unprecedent formation of unsaturated silicon-silicon compounds. (Figure 1.9)

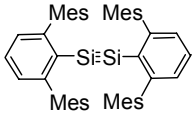


Figure 1.9 Structure of silicon-silicon triple bond containing compound

In 2003 Schrock and Yandulov[18] found a success on the reduction of nitrogen to ammonia at room temperature and 1 atmosphere with molybdenum catalysts that contained tetradentate $[HIPTN_3N]^{3-}$ triamidoamine ligands, where $[HIPTN_3N]^{3-}$ is $[\{3,5\text{-}(2,4,6\text{-}i\text{-}Pr_3C_6H_2)_2C_6H_3NCH_2CH_2\}_3N]^{3-}$ in heptane. (Figure 1.10) Slow addition of the proton source [{2,6-lutidinium}{BAr'_4}, where Ar' is 3,5-$(CF_3)_2C_6H_3$] and reductant (decamethyl chromocene) was critical for achieving high efficiency.

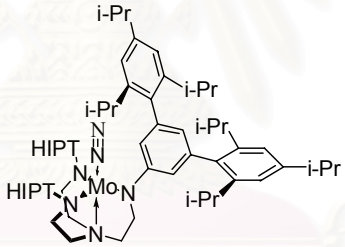


Figure 1.10 Structure of Schrock's molybdenum catalysts

In 2001 and 2003 Rabe and coworkers were interested in the organolanthanide chemistry of terphenyl ligand systems[19] because this type of sterically demanding ligand was found to be suitable for the stabilization of main group element complexes in unusual coordination geometries and unprecedented bonding situations that are not readily accessible with other ligands. They reported earlier the synthesis and structural characterization of two novel terphenyl derivatives of the lanthanide element ytterbium, thulium and yttrium of general composition $DnpLnCl_2(THF)_2$ [Dnp = 2,6-di(1-naphthyl)phenyl], (Ln = Yb, Tm, Y). These represented examples of novel chiral (racemic) organometallic complexes of the lanthanide elements ytterbium and thulium and the group 3 element yttrium. The molecular structures of monomeric complexes

exhibit distorted trigonal-bipyramidal coordination environments at the metal center, with the two oxygen atoms of the tetrahydrofuran ligands occupying the axial positions of a trigonal-bipyramidal coordination. Related interesting structures included novel donor-functionalized terphenyl derivatives[20] of trivalent ytterbium, yttrium and samarium of composition $[DanipYb(\mu_2\text{-}Cl)_2(\mu_3\text{-}Cl)Li(THF)]_2$ and $[DanipLn(\mu_2\text{-}Cl)_2(\mu_2\text{-}Cl)Li(THF)_2]_2$ (Ln = Y, Sm) [Danip = 2,6-di(*o*-anisol)phenyl] and a number of other 2,6-di(*o*-anisol)phenyl–based bis(amide) and bis(alkoxide) compounds of ytterbium, yttrium and samarium.[21]

In 2004 Protasiewicz and Smith[22] showed particular interest on the effect of phosphine selection as ligands on catalysis by metal complexes. Some key phosphine properties to be considered are cone angle, bite angle, and basicity. Structural and catalytic effects of unusually bulky phosphines are a topic of their current investigation. The *m*-terphenyl scaffold has been used to access a variety of interesting molecular geometries and coordination environments.

The chemistry of capsule-shaped macromolecules that can complex with neutral organic guests has been receiving increasing attention in the field of supramolecular chemistry. Among the different building blocks for these molecules have been widely employed as versatile units with a well-defined structure and easy accessibility. Although the capsule-type molecules by the combination of such units have been shown to have many outstanding characteristics as host molecules, they are at a disadvantage with respect to functional of the endohedral space because it is difficult to fix an inwardly-directed functional group in their cavity.

In 1995 Okazaki and coworkers[23] have reported the synthesis and application of bowl-shaped macrobicyclic cyclophanes with an intracavity functionality. It would provide an opportunity to study the chemistry of the inner space of molecular capsules not only as a complexing site but also as the reaction environment of the endohedral functionality. Molecules were base on a *m*-terphenyl unit, which appeared to be a versatile building block for the bottom moiety of a molecular lantern.

In 1995 Hart and Rajakumar[24] described a short route to new pyridinophanes that incorporated a *m*-terphenyl moiety which may contain intra-annularly directed functionality. They were used as model systems to study diastereo- and enantioselectivity in certain biochemically important reactions. A short, efficient synthesis of *m*-terphenyl-based cyclophanes with one or more functional groups

directed inward was described. Cyclophanes and molecular clefts with functionality directed toward the interior of the molecule can function as selective hosts.

In 1997 Rajakumar[25,26] described a simple and short convergent synthesis to new benzimidazolophanes that incorporated *m*-terphenyl moiety.

From these literatures, it could be envisioned the growing importance of the *m*-terphenyl compounds in the fields of organic synthesis and organometallics. Therefore, the thorough study on the synthetic method should take the first priority to consider. The easy efficient procedure and economical substrates would be sought after, which brought us to the current focus of this research.

1.5 Objectives

1. To develop the methodology to synthesize *m*-terphenyl derivatives by Hart reaction from either 3,5-dibromo-4-iodotoluene or 1,3-dichlorobenzene reacting with excess phenyl Grignard reagent.
2. To synthesize *m*-terphenyl derivatives with functional groups situated between the side phenyl rings after quenching the Hart reactions with appropriate electrophiles.

CHAPTER II

EXPERIMENTAL SECTION

2.1 Materials and Equipment

2.1.1 Materials

All materials were standard analytical or reagent grade purchased from commercial sources and used without further purification. Commercial grade acetone, hexanes, dichloromethane and ethyl acetate were distilled before use. Tetrahydrofuran (THF) was dried by refluxing with metallic sodium and benzophenone under nitrogen atmosphere and distilled before use. The progress of the reactions was followed by thin layer chromatography (TLC), carried out on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 F_{254}, 1 mm). Chromatographic separations were performed on silica gel column (Scharlau GE 0049 Silica gel 60, 63-200 μm).

2.1.2 Analytical Instrument

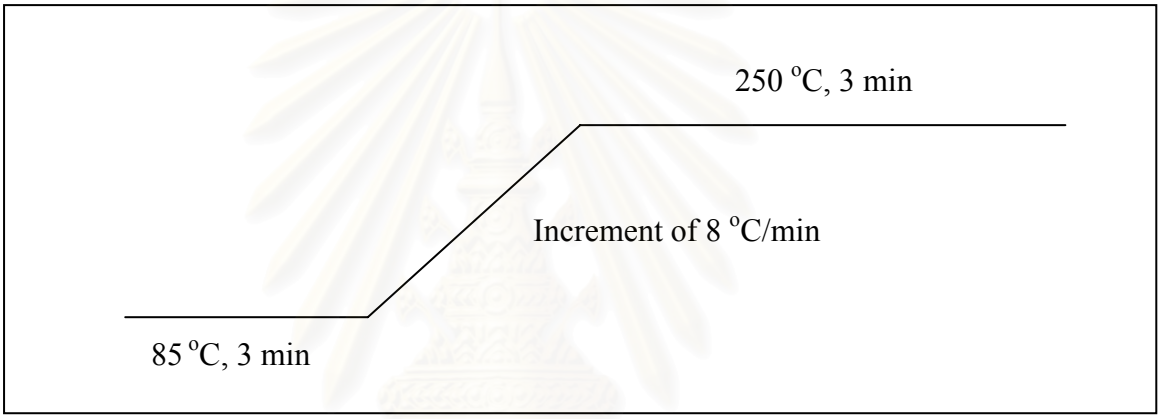
Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury + 400 NMR spectrometer operating at 400 MHz (^{1}H). Chemical shifts (δ) are reported in parts per million (ppm) using a residual proton signal of the solvent as internal reference. The melting point apparatus was Electrothermal 9100. Gas Chromatographic analysis was carried out on a Shimadzu Gas Chromatograph GC-16A instrument equipped with flame ionization detector (FID) with nitrogen as carrier gas, and a capillary column type of DB-1 (30 m ×0.25 mm). GC/MS characterizations were performed at 3 sources: The Varian CP-3800 Gas Chromatograph and Varian Saturn 2200 GC/MS located at Department of Chemistry, Faculty of Science, Chulalongkorn University; the Agilent Technologies 6890N GC system, Agilent 5973 Network Mass Selective Detector and Agilent 7683 Series Injector which was located at Thailand Institute of Scientific and Technological

Research; and the GCQ-Mass Spectroscopy Finnigan Mat which was located at Chulabhorn Research Institute.

2.1.3 Gas chromatographic method for the determination of GC yield.

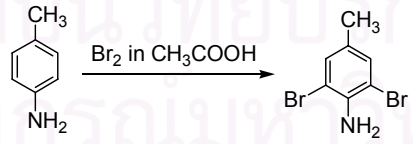
The method made use of a Shimadzu GC-16A Gas Chromatograph equipped with flame ionization detector (FID) with nitrogen as carrier gas and a capillary column type of DB-1 (30 m × 0.25 mm). The GC temperature program was shown in

Figure 2.1 The GC temperature program for liquid products



2.2 Experimental Procedures

2.2.1 Preparation of 2,6-dibromo-4-methylaniline

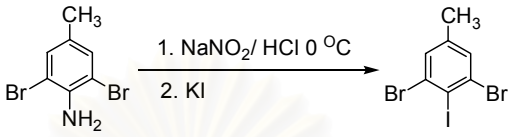


4

p-toluidine (3.5 g, 0.33 mol) was dissolved in 20 mL of glacial acetic acid in an ice bath. Bromine in glacial acetic acid (1:1) was slowly added until the brown color of bromine persists. This mixture was poured into 50 mL of water and the precipitates were filtered off. After filtration, the yellow solid was obtained and purified by column chromatography (hexanes) to give the desired product as a white

solid (8.17 g, 3.08 × 10^{-2} mol, 93.7%) (mp.77-78 °C) (lit. mp. 78 ºC).[27] ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.30 (3H, s, C-C<u>H</u>$_3$), 7.35 (2H, s, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 20 (<u>C</u>H$_3$-Ar), 109 (<u>C</u>-Br), 129, 132, 140 (Ar).

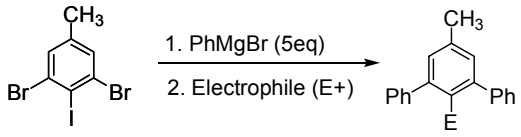
2.2.2 Preparation of 3,5-dibromo-4-iodotoluene



4 **5**

To a solution of 2,6-dibromo-4-methylaniline (2 g, 8 × 10^{-3} mol) in 3.5 mL of dilute HCl (HCl : H_2O = 1 : 1) was added dropwise at 0 °C a solution of sodium nitrite (0.625 g, 0.009 mol) in 5 mL of water. After being stirred for 30 min, the resulted diazonium solution was poured through a glass wool filter into a chilled solution of potassium iodide (1.51 g, 0.001 mol) in 5 mL of water. The solution was stirred vigorously for 1 h, then 2-3 mL of CH_2Cl_2 and 3-5 mL of 10% $NaHSO_3$ were added successively. The mixture was extracted with more CH_2Cl_2 and the combined organic layer was separated, washed with 5% NaOH, water and then dried with anhydrous $MgSO_4$. The white crystal residue was obtained after solvent removal and was further purified by column chromatography (hexane) to give the desired product (3.90 g, 1.04 × 10^{-2} mol, 70%) (mp 97 °C) (lit. mp 96-97.5 °C)[28] ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.30 (3H, s, C-C<u>H</u>$_3$), 7.30-7.46 (2H, s, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 21 (<u>C</u>H$_3$-Ar), 105 (<u>C</u>-I), 131, 132, 141 (Ar); mass spectrum(EI): *m/e* 376, 297, 170, 89.

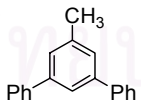
2.2.3 General procedures for the preparation of *m*-terphenyl derivatives using dibromoiodotoluene



6

Phenylmagnesium bromide solution was prepared from bromobenzene (3.5 mL, 2.12×10^{-2} mol) and magnesium turnings (0.55 g, 2.26×10^{-2} mol) in 20 mL of dried THF under nitrogen atmosphere. A solution of 3,5-dibromo-4-iodotoluene (0.70 g, 4.48×10^{-3} mol) in 15 mL of dried THF was slowly added over 20 min from an addition funnel. The reaction mixture was stirred for 3 h and quenched by an excess amount of selected electrophile reagent, approximately 10 equivalent. The solution was stirred for another 1 h, then 5-10 mL of water was added. The aqueous solution was extracted twice with ether. The combined organic layer was washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (hexane). Using this method, the following compounds were prepared:

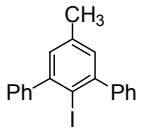
2.2.3.1 3,5-diphenyltoluene



6a

The reaction mixture was quenched by 10 mL of 10% H_2SO_4. 3,5-diphenyltoluene was obtained as a white solid after purification (0.76 g, 3.11×10^{-3} mol, 59%) (mp 129-130 °C) (lit. mp. 131.4-131.9 ºC)[29]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.60 (3H, s, C-C<u>H</u>$_3$), 7.20-7.80 (13H, m, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 21 (<u>C</u>H$_3$-Ar), 124, 127, 129, 139, 141, 142 (Ar); mass spectrum(EI): *m/e* 165, 228, 244.

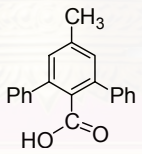
2.2.3.2 3,5-diphenyl-4-iodotoluene



3b

The reaction mixture was quenched by I_2 (3.37 g, 1.33 × 10^{-2} mol). 3,5-diphenyl-4-iodotoluene was obtained as a white solid after purification (0.50 g, 1.35 × 10^{-3} mol, 73%) (mp 153-154 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.40 (3H, s, C-C<u>H</u>$_3$), 7.20-7.60 (12H, m, Ar-<u>H</u>); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 21 (<u>C</u>H$_3$-Ar), 99 (<u>C</u>-I), 127, 128, 129, 130, 137, 146, 148 (Ar); mass spectrum(EI): *m/e* 165, 228, 243, 370, 371.

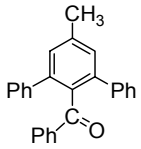
2.2.3.3 2,6-diphenyl-4-methylbenzoic acid



6c

The reaction mixture was quenched by 0.5 kg of dry ice (CO_2). The product was obtained as a white solid but its characterization data did not correspond to the desired product **6c**.

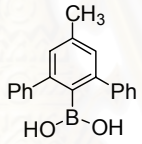
2.2.3.4 2,6-diphenyl-4-methyl benzophenone



6d

The reaction mixture was quenched by methyl benzoate (3.5 mL, 1.83×10^{-2} mol). The product was obtained as yellow solid but its characterization data did not correspond to the desired product **6d**.

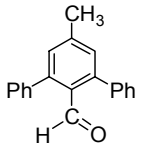
2.2.3.5 2,6-diphenyl-4-methyl benzene boronic acid



6e

The reaction mixture was quenched by trimethyl borate (15 mL, 9.15×10^{-2} mol). The product was obtained as white solid but its characterization data did not correspond to the desired product **6e**.

2.2.3.6 2,6-diphenyl-4-methylbenzaldehyde

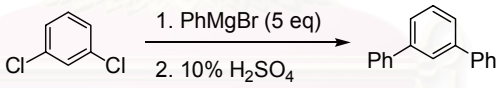


6f

The reaction mixture was quenched by ethyl formate (5 mL, 3.66×10^{-2} mol). The product was obtained as mixture of a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.70 (3H, s, C-C<u>H</u>$_3$), 7.20-8.00 (12H, m, Ar-<u>H</u>), 10.00 (1H, s, O=C-<u>H</u>). mass spectrum(EI): *m/e* 165, 228, 257, 272. The product showed evidence of the presence of the desired product but cannot yet be successfully separated and purified.

2.2.4 General procedures for preparation of *m*-Terphenyl Derivatives using 1,3-dichlorobenzene

2.2.4.1 The variation of reaction time



7a

To a 100 mL three neck round bottom flask equipped with a magnetic bar was added magnesium turnings (0.55 g, 2.26×10^{-2} mol) in 10 mL of dried THF under nitrogen atmosphere and slowly added a solution of bromobenzene (3.5 mL, 2.12×10^{-2} mol) in dried THF 10 mL from an addition funnel. The mixture was stirred until the formation of Grignard reagent completed which may need a gentle heating. A solution of 1,3-dichlorobenzene (0.63 g, 4.28×10^{-3} mol) in 10 mL of dried THF was slowly added at RT over 20 min from another addition funnel. The reaction mixture was stirred for 7 h during which a 2 mL aliquot of the solution was withdrawn by syringe after an hour and at every hour. The withdrawn solutions were quenched by 3 mL 10% H_2SO_4, and 5-10 mL of water, and then the aqueous solution was extracted twice with a small amount of ether. The combined organic layer was washed with

water and dried with anhydrous sodium sulfate. The solvent was evaporated to give crude mixture of the product. Each crude mixture was dissolved with 8 mL of ether and added anthracene standard solution (see Appendix) 2 mL in 10 mL volumetric flask. 2μL of this solution was injected into GC to measure the relative concentration of the desired components. The values obtained were used to calculate % yield of the product at various reaction time. (Table 2.1)

Table 2.1 % Yield (GC) of withdrawn solutions at various reaction time

Reaction Time (h)	% GC yield		average yield (%)
	exp.no.1	exp.no.2	
1	17.0	8.6	12.8
2	19.7	17.6	18.7
3	28.2	33.0	30.6
4	23.0	19.9	21.5
5	23.9	21.9	22.9
6	12.1	22.1	17.1
7	8.4	21.7	15.1

2.2.4.2 The variation of 1,3-dichlorobenzene concentration

In this section, the reaction followed the similar procedure as 2.2.4.1 except that no solution was withdrawn and reaction time was kept at 3 h. The amount of 1,3-dichlorobenzene and THF were varied according to Table 2.2 together with the corresponding equivalents of other reagents. The whole reaction mixture was quenched and separated the product in the usual manner. The results are shown in Table 2.2

Table 2.2 % Yield (GC) of reaction at various concentrations of 1,3-dichlorobenzene

1,3-dichlorobenzene (g)	THF (mL)	Concentration (M)	% GC yield			% Isolated yield		
			exp. no.1	exp. no.2	Average	exp. no.1	exp. no.2	Average
1.23	30	0.29	43.5	47.3	45.4	14.9	13.0	14.0
0.63	30	0.15	28.2	33.0	30.6	10.7	11.8	11.3
0.63	60	0.07	12.3	1.6	7.0	trace	trace	trace

2.2.4.3 The variation of reaction temperature

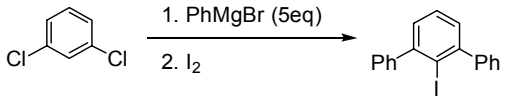
In this section, the reaction followed the similar procedure as shown in 2.2.4.2 and use 1,3-dichlorobenzene 0.15 M. The reaction was repeated by keeping the temperature of the mixture during the addition of 1,3-dichlorobenzene at -10 ºC by an ice-salt bath. The results are compared with the room temperature addition in Table 2.3

Table 2.3 % Yield (GC) of reaction at various temperature during addition of 1,3-dichlorobenzene

Temperature during addition of 1,3-dichlorobenzene	% GC yield			% Isolated yield		
	exp. no.1	exp. no.2	average	exp. no.1	exp. no.2	average
RT	28.2	33.0	30.6	10.7	11.8	11.3
-10 ºC	35.9	36.9	36.4	14.8	13.1	14.0

The *m*-terphenyl product was obtained as white solid (mp 85 °C) (lit. mp 89 °C).[13] ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30-7.90 (14H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 126, 127, 129, 129.5, 141, 142 (Ar); mass spectrum(EI): *m/e* 154, 188, 230.

2.2.4.4 2,6-diphenyliodobenzene



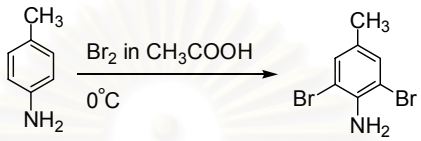
7b

The reaction followed the similar procedure as 2.2.4.2 using 1,3-dichlorobenzene 0.63 g, THF 30 mL and reaction time was kept at 3 h and quenched reaction by I_2 (3.37 g, 1.33×10^{-2} mol) instead of 10% H_2SO_4, then 15 mL of water was added. The aqueous solution was extracted twice with ether. The combined organic layer was washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (hexane). The 2,6-diphenyliodobenzene was obtained as a white solid (0.30 g, 8.43×10^{-4} mol, 23 %) (mp 109-110 °C) (lit. mp. 113.5-115 °C).[13] ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.10-7.60 (14H, m, Ar); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 100 (C-I), 127, 128, 130, 138, 148 (Ar); mass spectrum(EI): *m/e* 154, 188, 230, 280, 314, 356.

CHAPTER III

RESULTS AND DISCUSSION

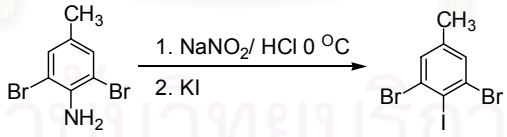
3.1 The synthesis of 2,6-dibromo-4-methylaniline



4

The product was obtained as a white solid in 94% yield. The reason for any lost of the product may arise from the fact that *p*-toluidine and the aniline derivative product can be easily oxidized by air. The temperature of the reaction was difficult to control. This reaction is exothermic, which could accelerate oxidation and other side reactions.

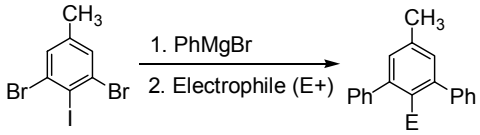
3.2 The synthesis of 3,5-dibromo-4-iodotoluene



4 **5**

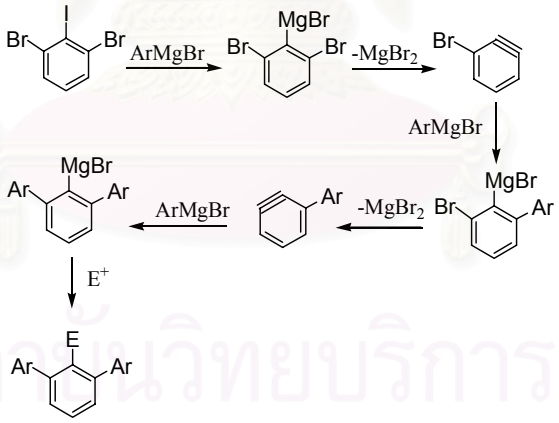
3,5-Dibromo-4-iodotoluene was readily prepared in high quantity (white solid, 70% yield) from 2,6-dibromo-4-methylaniline via diazotization and substitution by iodide ion. The intermediate diazonium salt could react with water to give phenol derivatives as a minor product, which was assumed to be the main reason for poorer yield. In this step, the side reaction toward phenol could be increased with the temperature, hence further affected the yield of the product.

3.3 The synthesis of *m*-terphenyl derivatives using dibromoiodotoluene



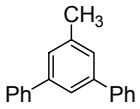
5 **6**

m-Terphenyl can be synthesized by Hart reaction.[10] (Scheme 3.1) The mechanism of the reaction starts with metal-halide exchange of carbon-iodine bond in 2,6-dihaloiodobenzene and one equivalent of Grignard reagent. β-Elimination by the resulting carbon-metal bond gave bromobenzyne. Nucleophilic addition of another equivalent of Grignard reagent onto bromobenzyne at *meta* position to the bromo group provided the second Grignard reagent, which repeated another β-elimination to give an arylbenzyne. Addition of the third Grignard reagent and final quenching by selected electrophile yielded the corresponding *m*-terphenyl derivatives.



Scheme 3.1 The mechanism of Hart reaction of 2,6-dihaloiodobenzene

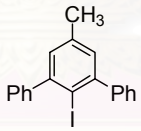
3.3.1 3,5-diphenyltoluene



6a

Hart reaction of 3,5-dibromo-4-iodotoluene with Grignard reagent in THF was quenched by 10% H_2SO_4. The product mixture contained 3,5-diphenyltoluene and some impurities as determined by thin-layer chromatography. After purification by column chromatography, one of the identifiable byproducts was biphenyl. This side-product was known to have arisen from self-coupling of the Grignard reagent. Moreover, small amounts of phenol was found, possibly from air oxidation of the Grignard reagent. The 3,5-diphenyltoluene was isolated from the reaction mixture and purified as white solid in 59% yield.

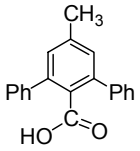
3.3.2 3,5-diphenyl-4-iodotoluene



6b

Hart reaction of **5** with excess Grignard reagent was quenched by I_2. 3,5-Diphenyl-4-iodotoluene product was isolated from the reaction mixture and purified as a white solid in 73% yield. In this case, iodobenzene was observed as the major product, which was produced by the rest of the unreacted phenyl Grignard reagent quenched with I_2. Small amounts of the usual byproducts, biphenyl and phenol, were also detected.

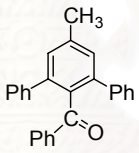
3.3.3 2,6-diphenyl-4-methylbenzoic acid



6c

2,6-Diphenyl-4-methylbenzoic acid could not be obtained from the reaction of **5** with Grignard reagent and quenching with dry ice (CO_2). In this case only the protonic quenched product **6a**, presumably arises from the reaction with the condensed ice-water around a pieces of dry ice.

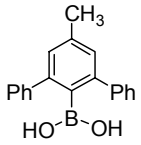
3.3.4 2,6-diphenyl-4-methylbenzophenone



6d

Likewise, the reaction of **5** with Grignard reagent and quenching by methyl benzoate did not give the 2,6-diphenyl-4-methylbenzophenone. Instead, only small amounts of the benzophenone was found and determined by analysis of their ^{1}H NMR spectra. The ^{1}H NMR spectrum of benzophenone revealed one broad signal of aromatic protons at 7.30 ppm. MS spectrum showed characteristic molecular ion *(m/z)* for benzophenone at 183 (M+1). In this case no reaction of **5** with Grignard reagent was detected, only products arising from methyl benzoate reacted directly with Grignard reagent were obtained.

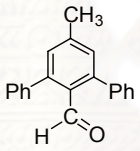
3.3.5 2,6-diphenyl-4-methylbenzene boronic acid



6e

The reaction of **5** with Grignard reagent and quenching by trimethyl borate is also difficult. The reaction gave only **6a** which was the product often obtained from excess moisture in the quenching reagent. The ^{1}H NMR spectrum and MS spectrum confirmed the structure of **6a**.

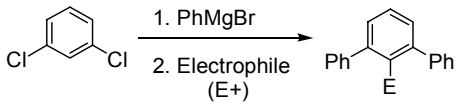
3.3.6 2,6-diphenyl-4-methylbenzaldehyde



6f

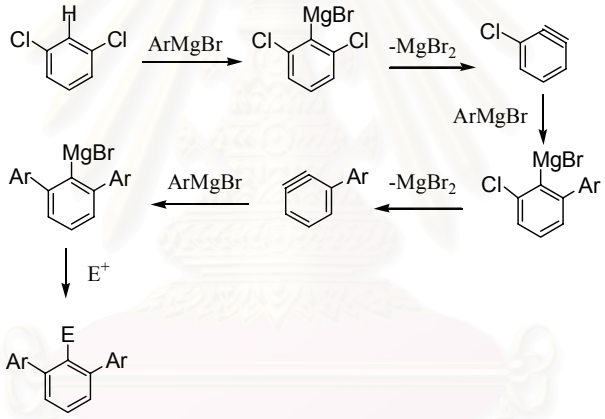
Likewise, the reaction of **5** with Grignard reagent and quenching by anhydrous DMF did not give the 2,6-diphenyl-4-methylbenzaldehyde and only the moisture quenched 3,5-diphenyltoluene **6a** was obtained. Changing the electrophile quenching reagent to ethyl formate gave a very low yield of 2,6-diphenyl-4-methylbenzaldehyde product, observed in the ^{1}H NMR spectrum showing the characteristic singlet signal associated with the aldehyde proton at 10 ppm. (Figure A-13, Appendix). The MS spectrum showed a signal of mass 272, corresponding to the desired product 2,6-diphenyl-4-methylbenzaldehyde **6f** (Figure A-14, Appendix). Because the product **6f** was obtained in very small amount, mixed with many other major components which were very difficult to differentiate, the isolation process was not pursued.

3.4 The synthesis of *m*-terphenyl derivatives using 1,3-dichlorobenzene



7

m-Terphenyl can be synthesized by another route of Hart reaction starting from 1,3 dichlorobenzene.[13] The mechanism was the same as the reaction of 2,6-dibromoiodobenzene except that the initiation step was acid-base reaction of the arene proton between 2 chloro substituents in 1,3-dichlorobenzene and one equivalent of Grignard reagent. (Scheme 3.2)



Scheme 3.2 The mechanism of Hart reaction of 1,3 dichlorobenzene

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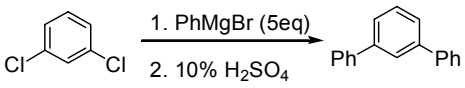
3.4.1 *m*-Terphenyl



7a

Hart reaction of 1,3-dichlorobenzene with Grignard reagent in THF was quenched by 10% H_2SO_4. The product mixture contained *m*-terphenyl and some impurities as determined by thin-layer chromatography. After purification by column chromatography, one of the identifiable byproduct was biphenyl. This side-product was known to arise from self-coupling of the Grignard reagent. Moreover, a small amount of phenol was found, possibly from air oxidation of the Grignard reagent. The *m*-terphenyl was isolated from the reaction mixture and purified as white solid in 14% yield.

A variety of conditions were examined while identifying the best condition for the synthesis of *m*-terphenyl.

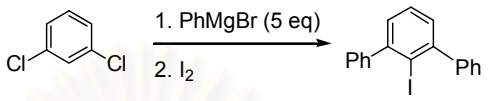
The data shown in Table 2.1 revealed that the synthesis of *m*-terphenyl could have completed in about 3 hours. It was found that after 3 hours, %yield determined from GC decreased. The reason was assumed to be the coupling of the excess Grignard reagent with the arylmagnesium intermediates that would have gone to be the product after quench.

Table 2.2 showed the effect of substrate concentration. It was found that at low concentration, the reaction may not proceed to completion. When the concentration of the substrate in the reaction was increased, the product was obtained in higher yields, supporting the involvement of multimolecular nature of the reaction mechanism.

The data shown in Table 2.3 suggested that the reaction proceeded more efficiently when adding the substrate to the prepared Grignard reagent at low temperature (-10 °C). The reason for this efficiency may be because: low temperature slowed down the self-coupling of Grignard reagent and undesired metal-chloride

exchange to the 1,3-dichlorobenzene while still allowed the fast deprotonation of the substrate that initiated the reaction. As a result, the starting material was more consumed toward the expected product at low temperature.

3.4.2 2,6-diphenyl iodobenzene



7b

Hart reaction of 1,3-dichlorobenzene with excess Grignard reagent was quenched by I_2. 2,6-Diphenyliodotoluene product was isolated from the reaction mixture and purified as white solid in 23% yield. In this case, iodobenzene was observed as the major product, which was produced by the rest of the unreacted phenyl Grignard reagent quenched with I_2. Small amounts of the usual byproducts, biphenyl and phenol, were also detected.

CHAPTER IV

CONCLUSION

The study of Hart reaction for the syntheses of *m*-terphenyl derivatives were performed in a one-pot fashion using an excess amount of phenyl Grignard reagent reacting with 3,5-dibromo-4-iodotoluene. Working up the reaction mixtures by 10% H_2SO_4 and I_2 give 59% of 3,5-diphenyltoluene and 73% of 3,5-diphenyl-4-iodotoluene respectively. Working up by dry ice and trimethyl borate only gave the moisture quenched 3,5-diphenyltoluene as determined by ^1H NMR and MS spectra. The reaction worked up by methyl benzoate gave only benzophenone. Only a small amount of **6f** was found when working up with ethyl formate. This potential product has not yet been isolated.

Another study of Hart reaction used 1,3-dichlorobenzene reacting with excess phenyl Grignard reagent. Working up the reaction mixtures by 10% H_2SO_4 and I_2 gave 30% yield of *m*-terphenyl and 23% yield of 2,6-diphenyliodobenzene, respectively.

Investigations had been carried out to search for efficient method to prepare *m*-terphenyl derivatives from 1,3-dichlorobenzene. The work had focused on the variations of the reaction time, temperature and substrate concentration. Monitoring by GC, the *m*-terphenyl product increased noticeably to the best yield when the reaction temperature was kept at -10 °C during the addition of the 1,3-dichlorobenzene into the Grignard reagent and subsequently ran the reaction at reflux for 3 hours. Furthermore, when higher concentration of the substrate was used, the reaction was found to proceed more efficiently.

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Appendix

A-1. The calculation of yields from Gas Chromatographic analysis

The product mixtures were analyzed by Gas Chromatography using anthracene as an internal standard.

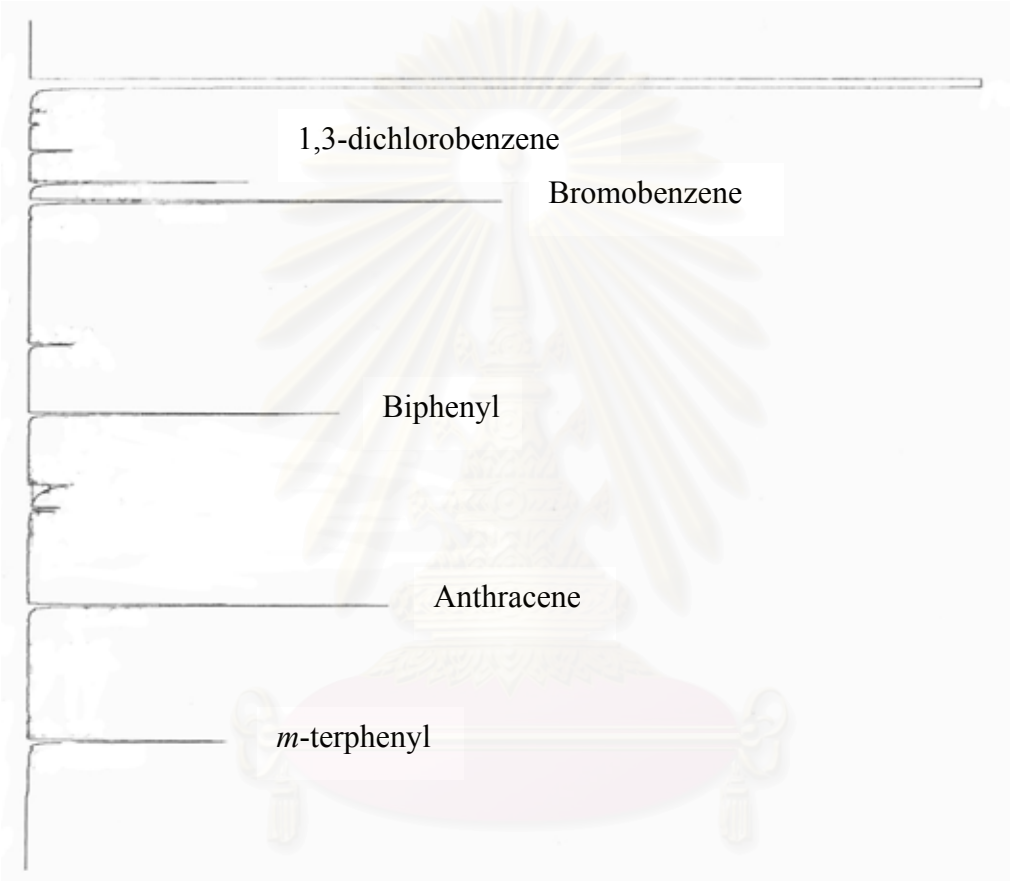

Figure A-1 Gas Chromatogram of *m*-terphenyl product and anthracene internal standard for calculation.

The calculation of response ratio of *m*-terphenyl product and anthracene internal standard:

Using peak area obtained from GC analysis

A : amount of *m*-terphenyl (mol)

B : amount of anthracene (mol)

D : peak area of *m*-terphenyl

E : peak area of anthracene

The response ratio (R) between *m*-terphenyl and anthracene from GC:

$$R = \frac{A}{B} \times \frac{E}{D}$$

The average response ratio of *m*-terphenyl and anthracene was found to be 1.14

The concentration of *m*-terphenyl from GC experiment $= R \times A$

$$= R \times \frac{D \times B}{E}$$

Example:

1. Anthracene (0.57 g) was dissolved in 50 mL volumetric flask yielding 0.064 M solution
2. 1 mL of the concentrated anthracene solution was transferred to 10 mL volumetric flask. The dried crude mixture of *m*-terphenyl product was added and adjusted the volume of the solution to 10 mL by ether.
3. Inject 2 μL of the above solution into GC and record the peak areas of *m*-terphenyl (D) and anthracene (E).
4. Calculate the concentration of *m*-terphenyl using the response ratio.
5. Calculate the quantity of *m*-terphenyl in mole and calculate % yield from:

$$\frac{calculate\ mole\ of\ \ product}{mole\ of\ \ substrate\ (1,3-dichlorobenzene)} \times 100 = \%\ yield\ of\ \ product$$

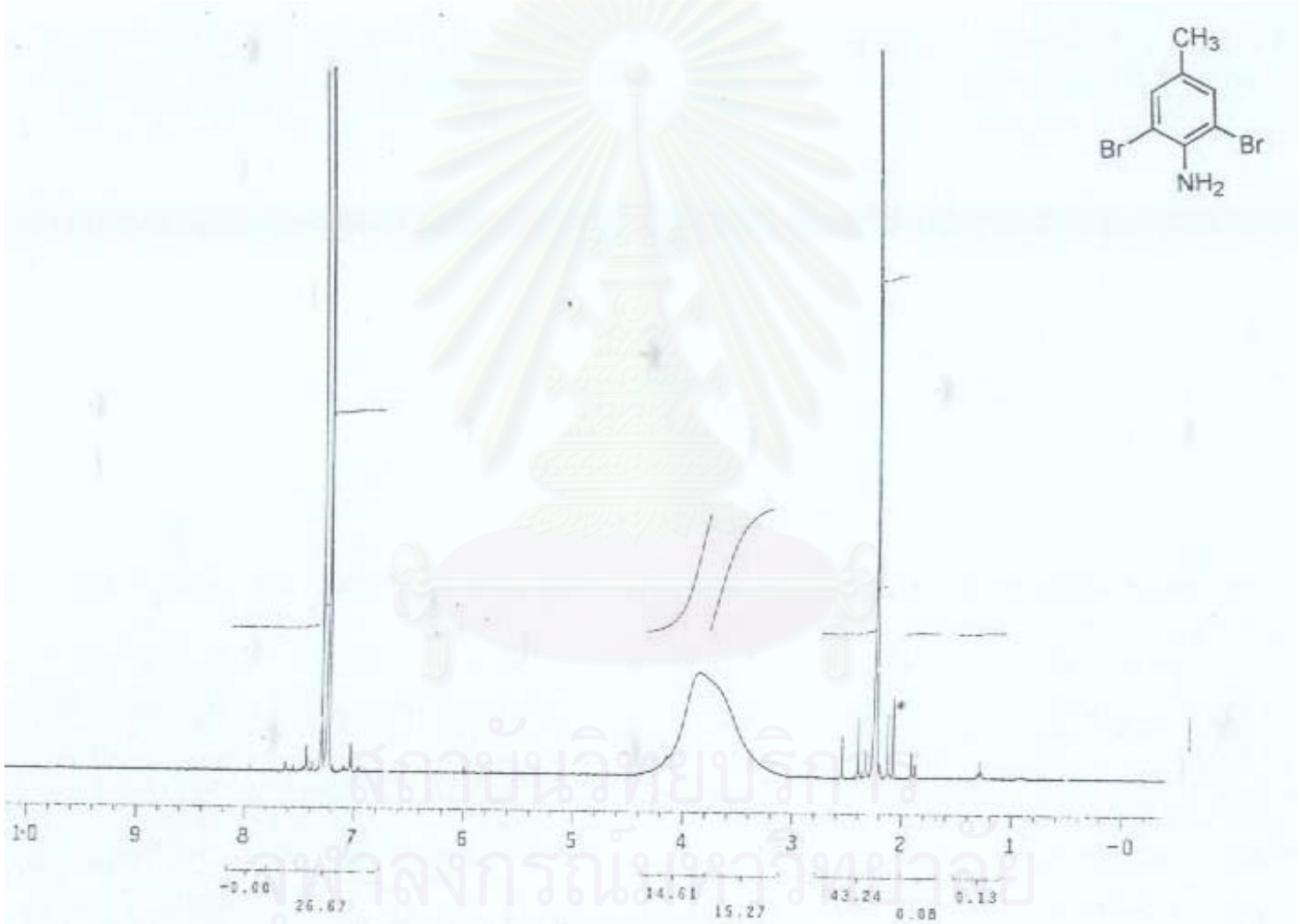

Figure A-2 The ^{1}H-NMR spectrum of 4

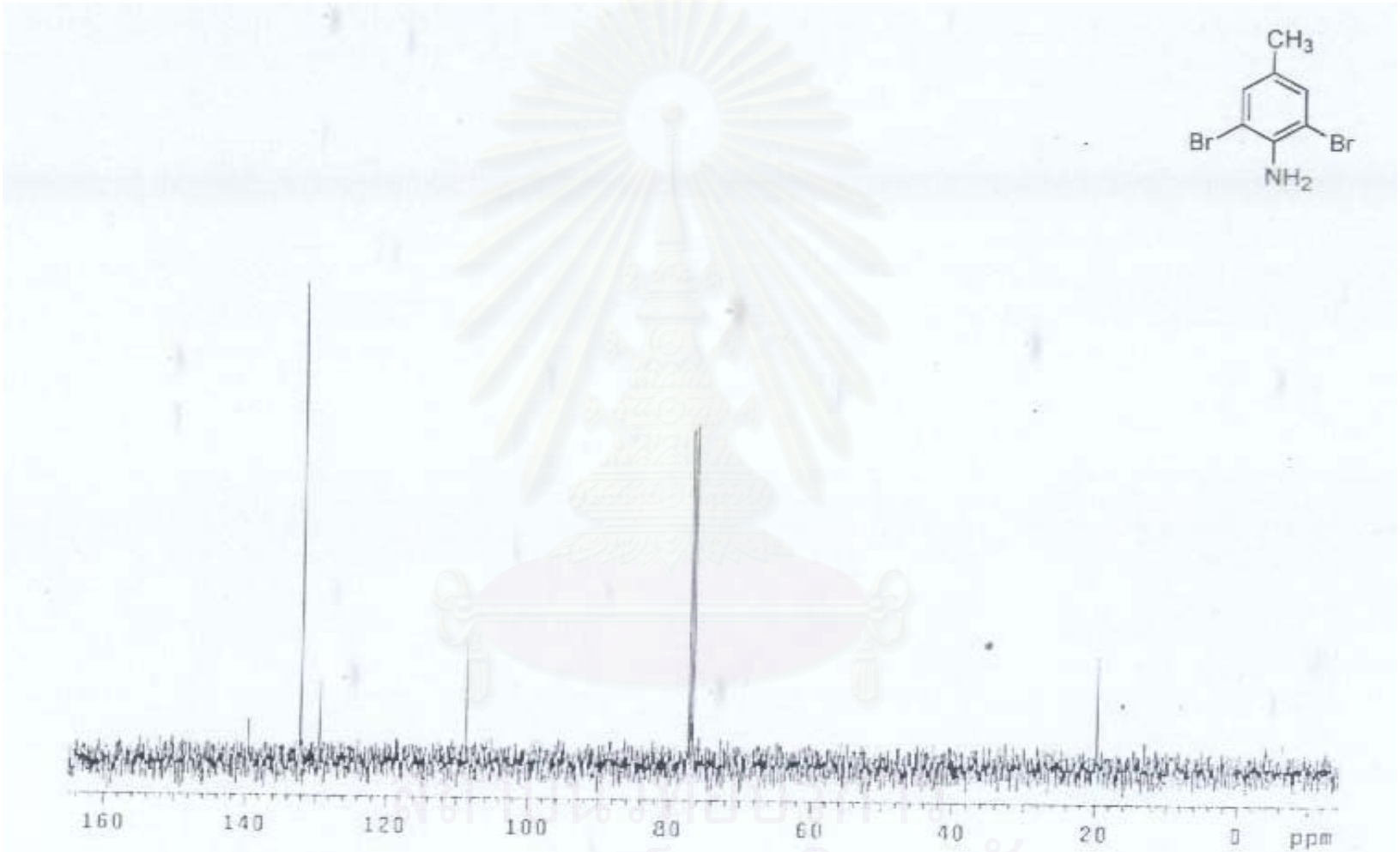

Figure A-3 The ^{13}C-NMR spectrum of 4

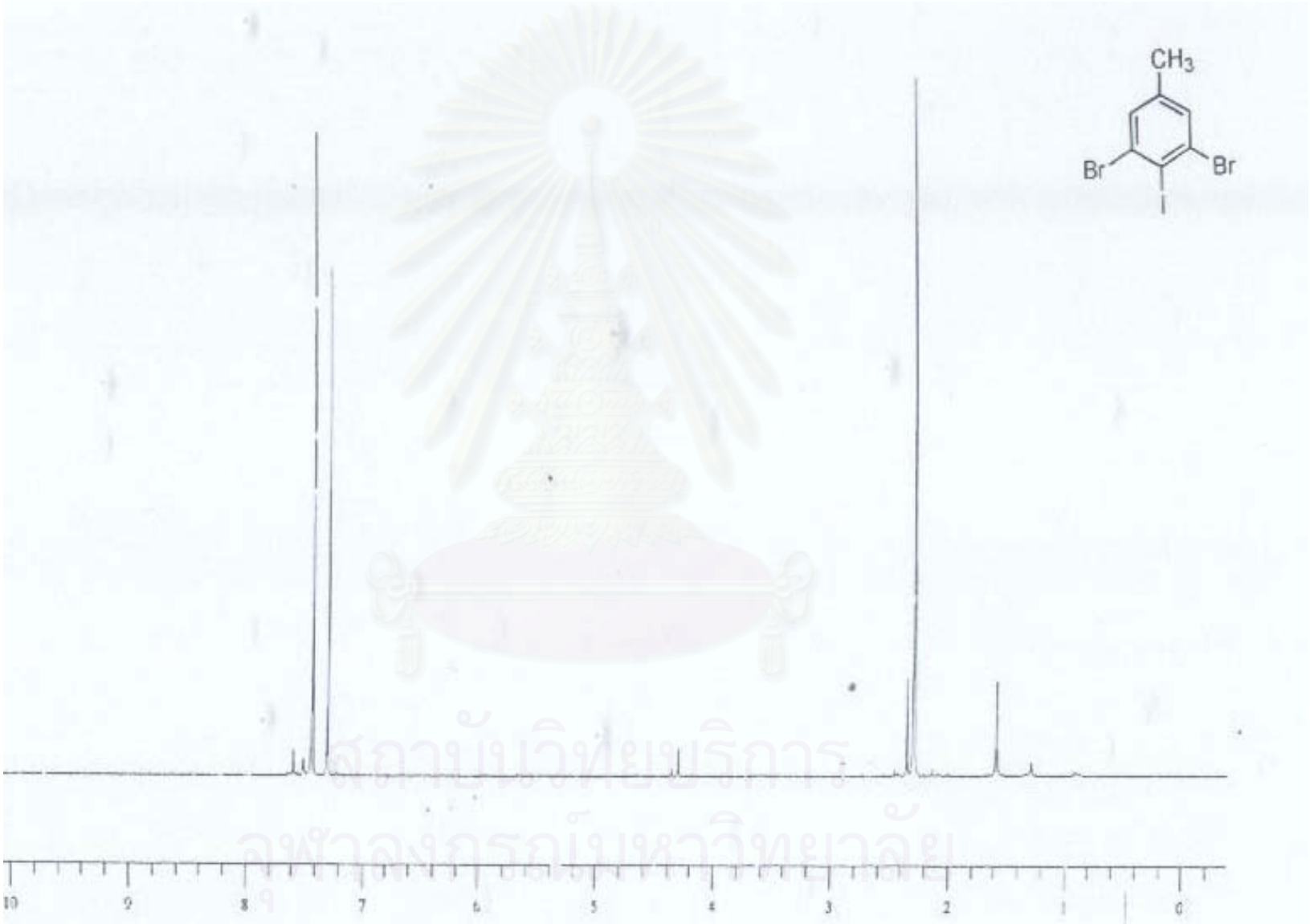

Figure A-4 The ^{1}H-NMR spectrum of **5**

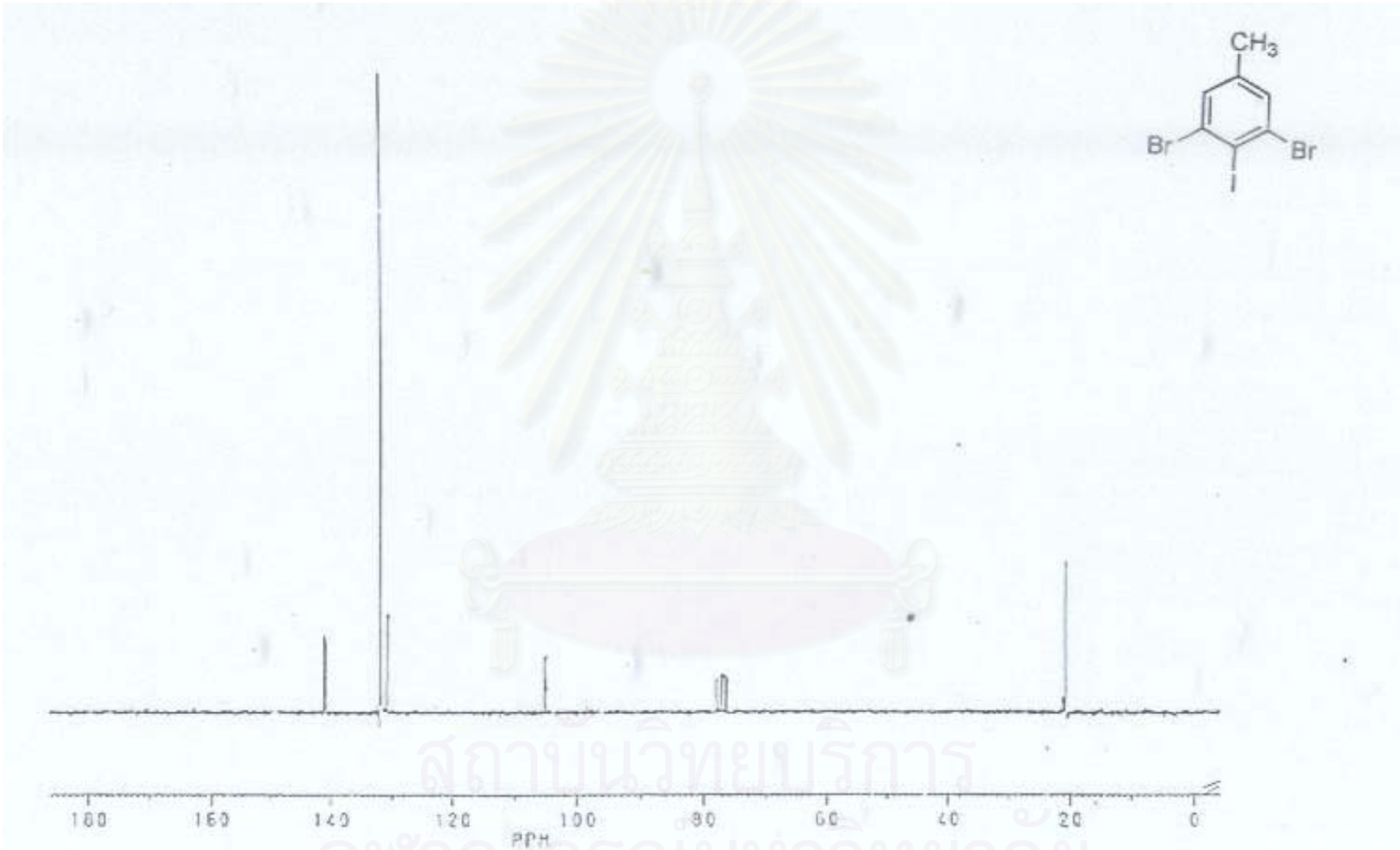

Figure A-5 The ^{13}C-NMR spectrum of **5**

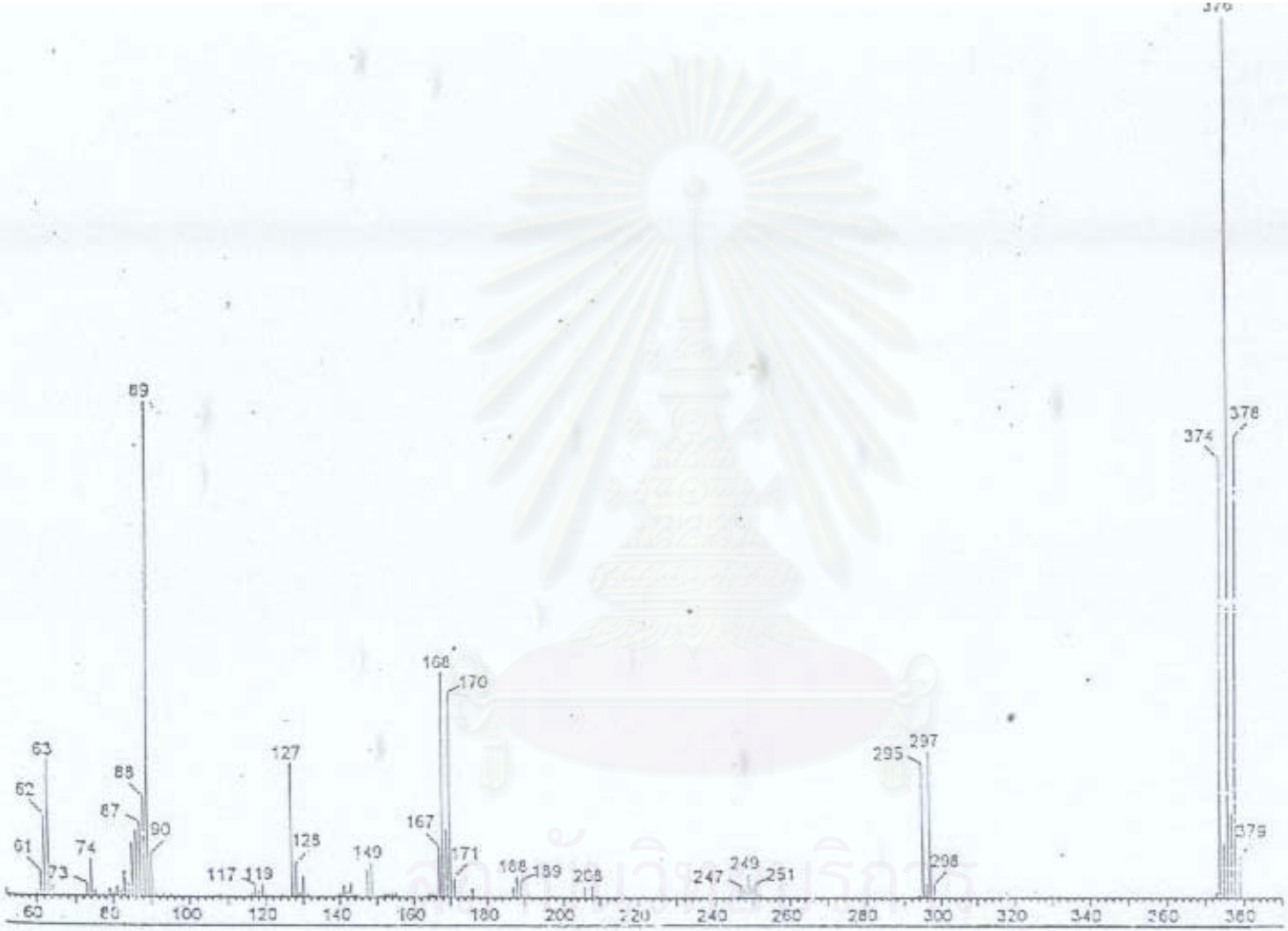

Figure A-6 The MS spectrum of **5**

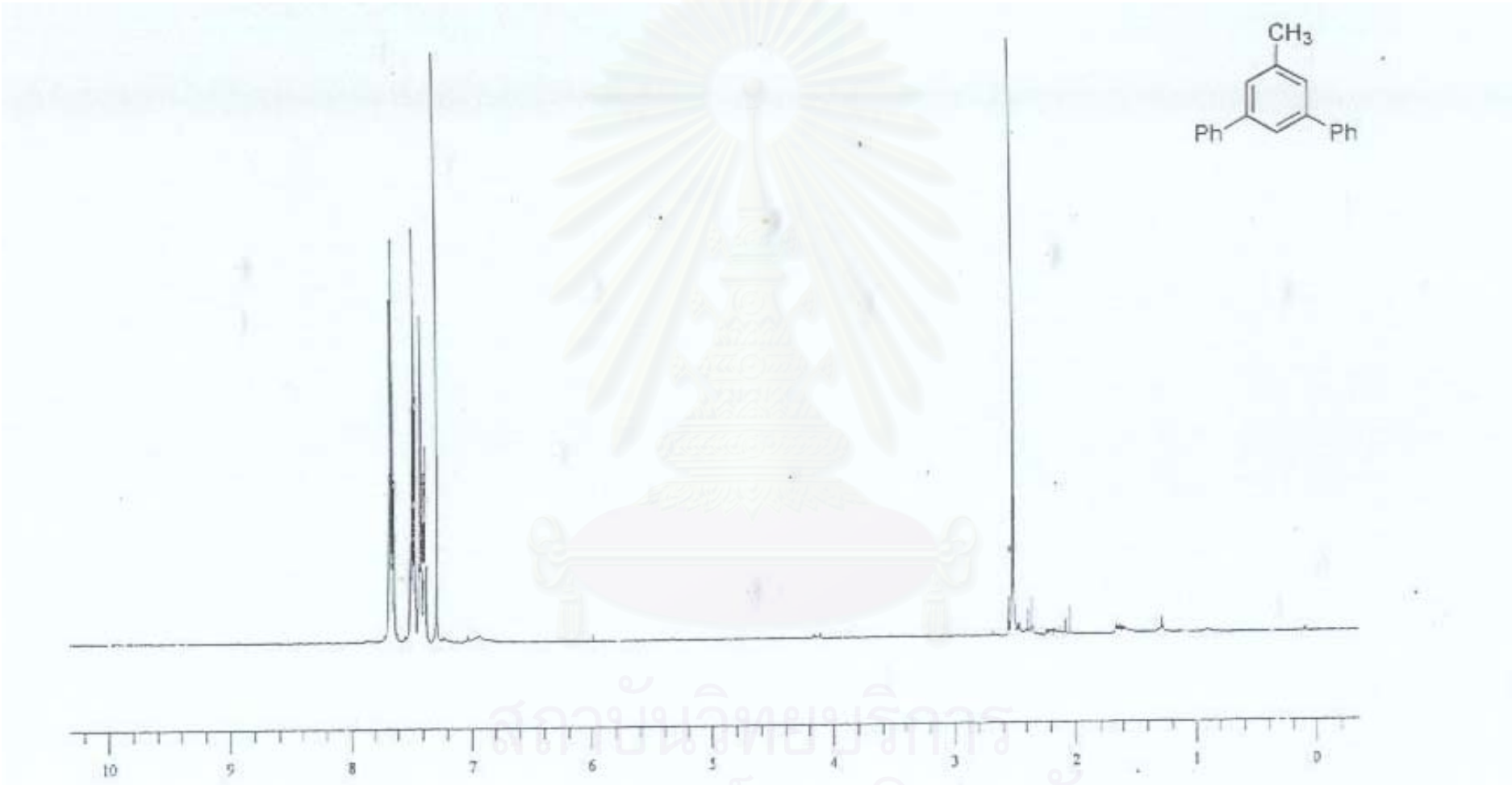

Figure A-7 The ^{1}H-NMR spectrum of 6a

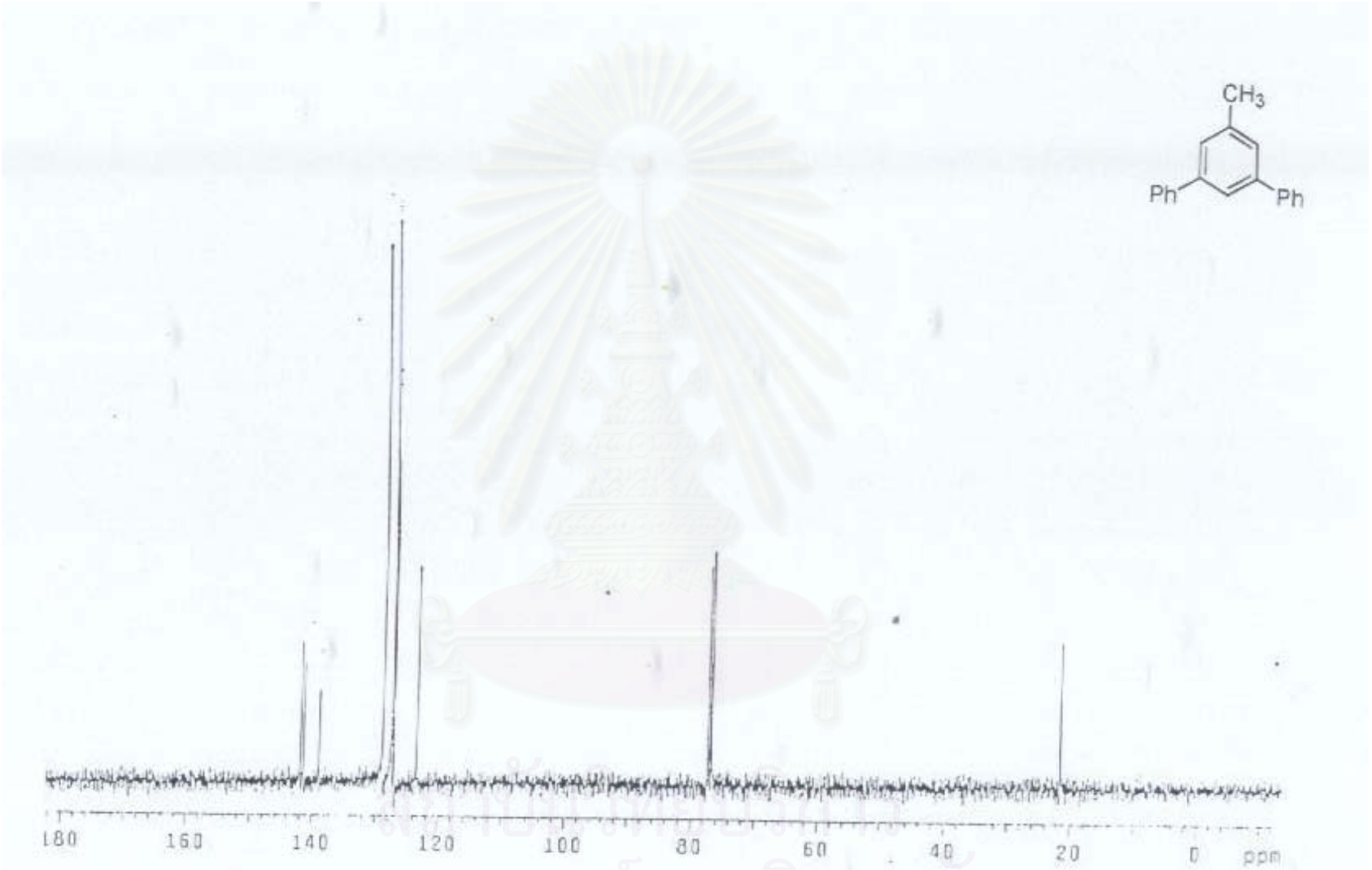

Figure A-8 The ^{13}C-NMR spectrum of 6a

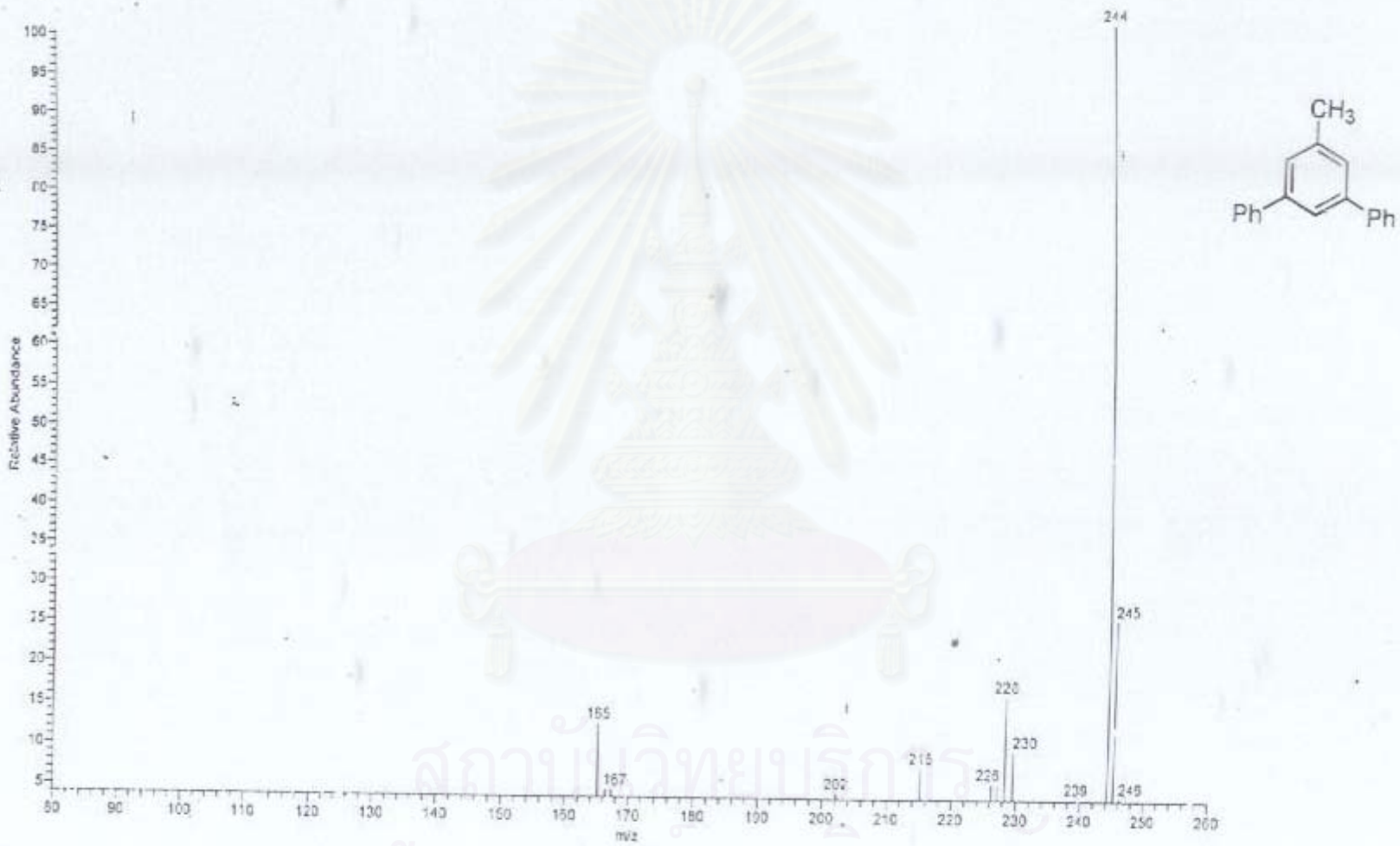

Figure A-9 The MS spectrum of **6a**

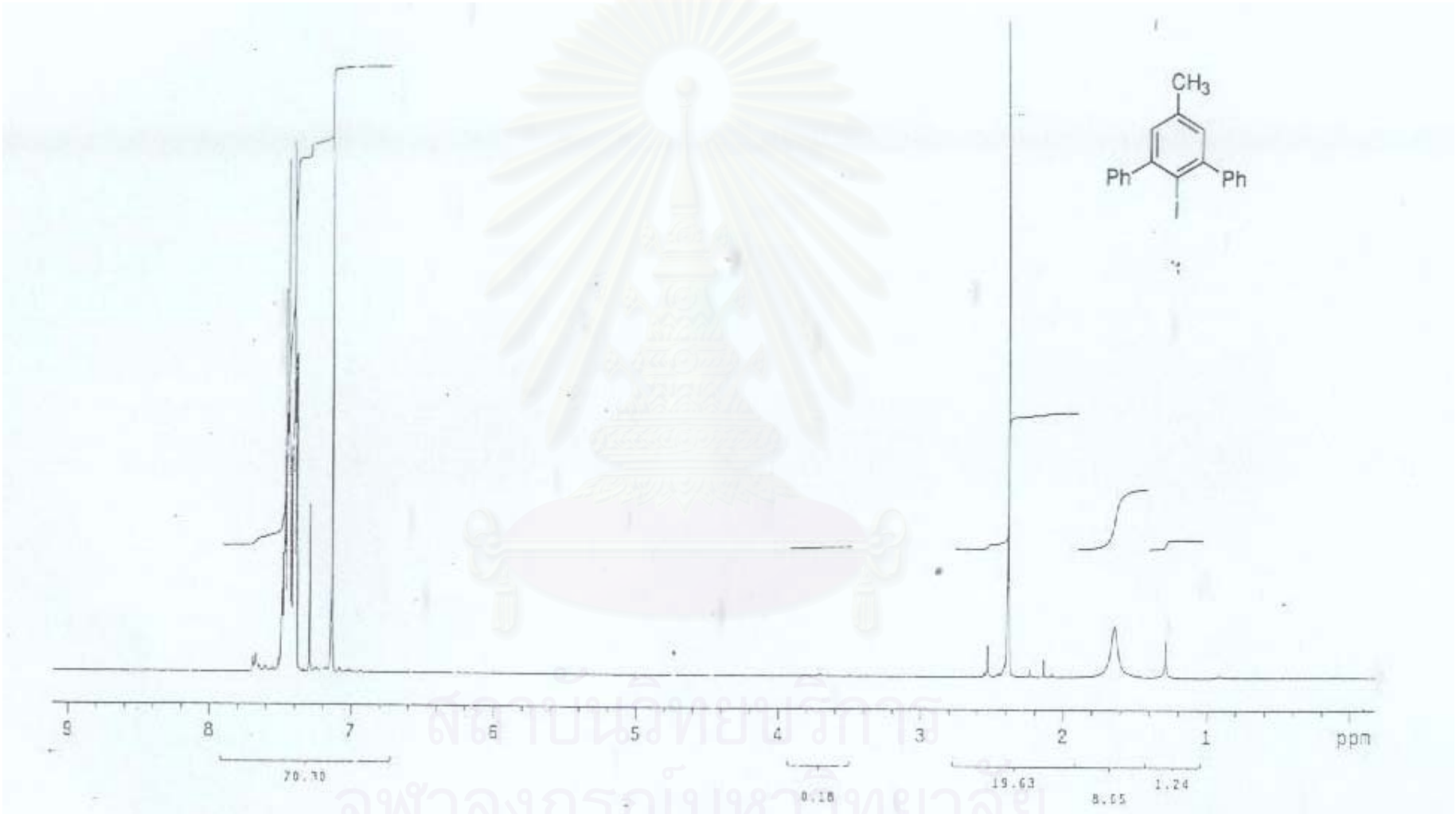

Figure A-10 The ^{1}H-NMR spectrum of **6b**

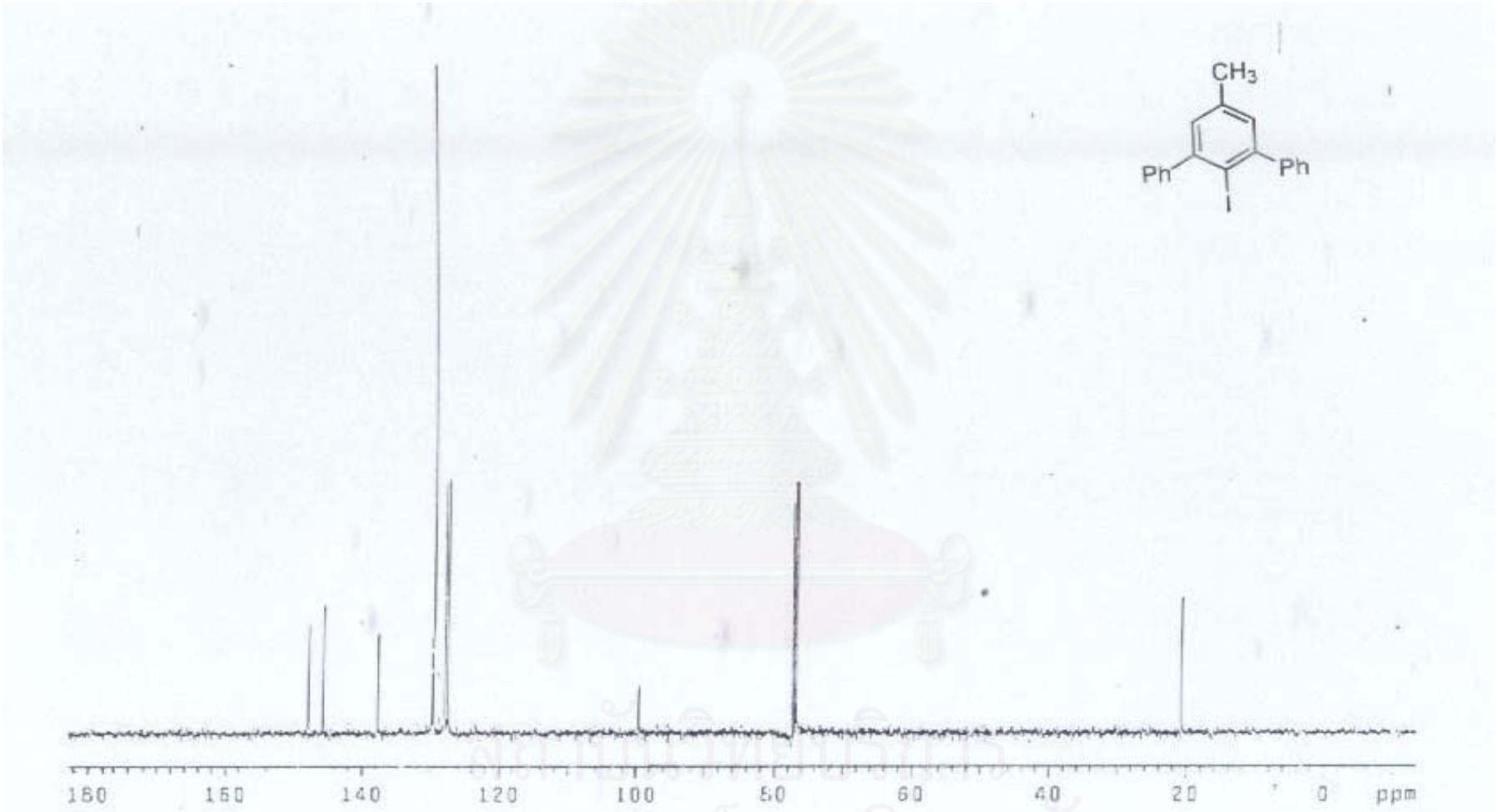

Figure A-11 The ^{13}C-NMR spectrum of 6b

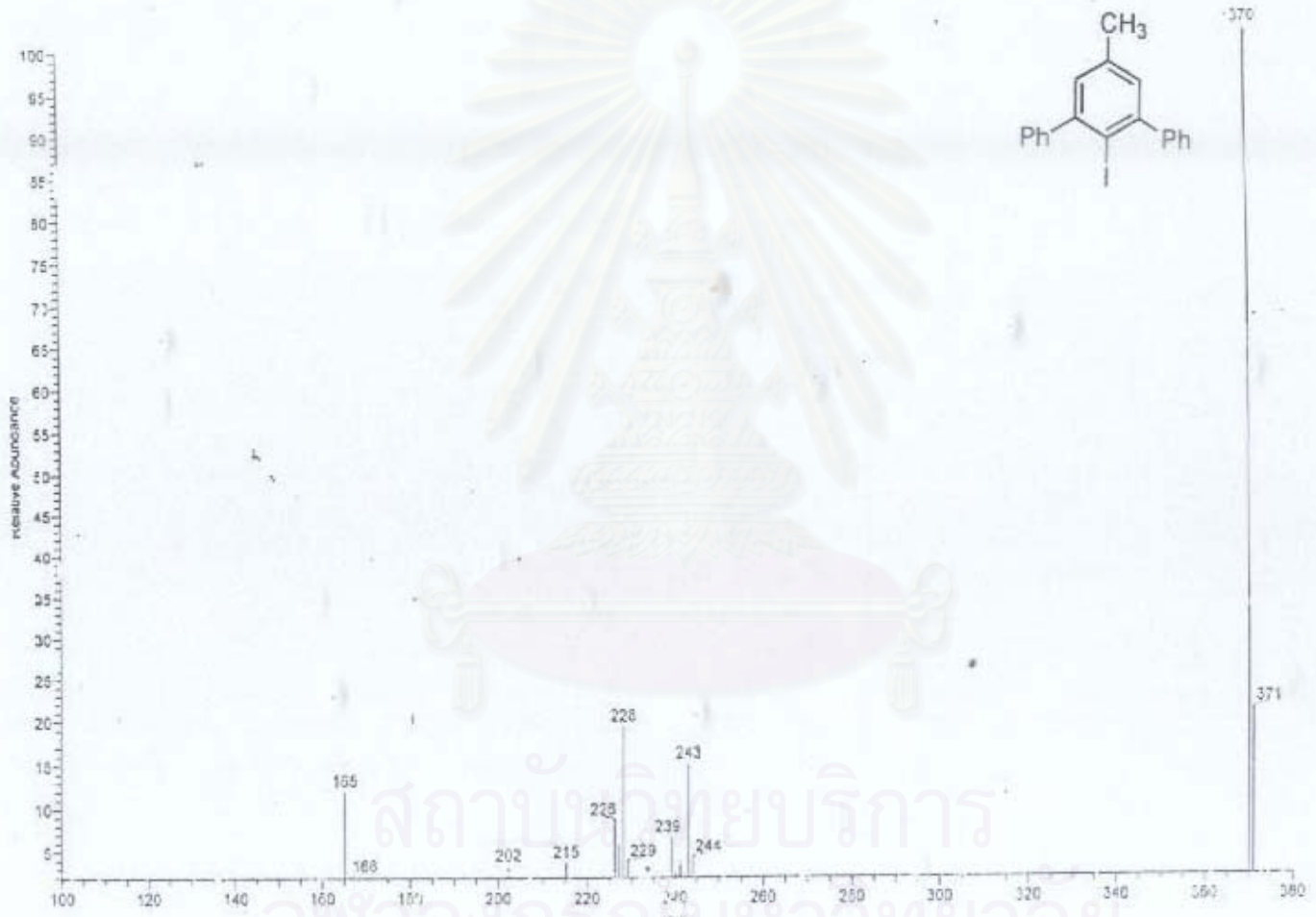

Figure A-12 The MS spectrum of **6b**

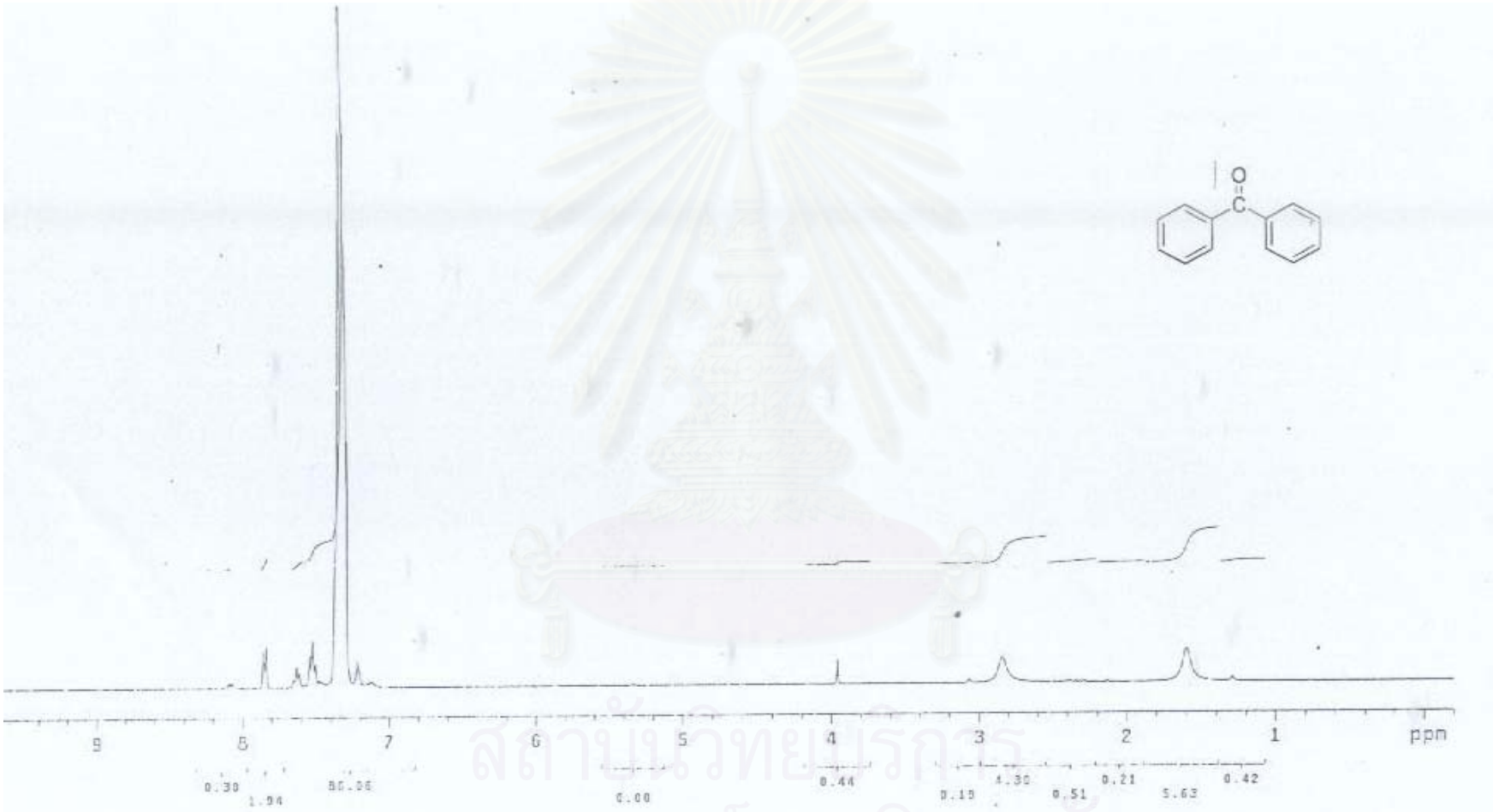

Figure A-13 The ^{1}H-NMR spectrum of undesired product from the attempted synthesis of **6d**

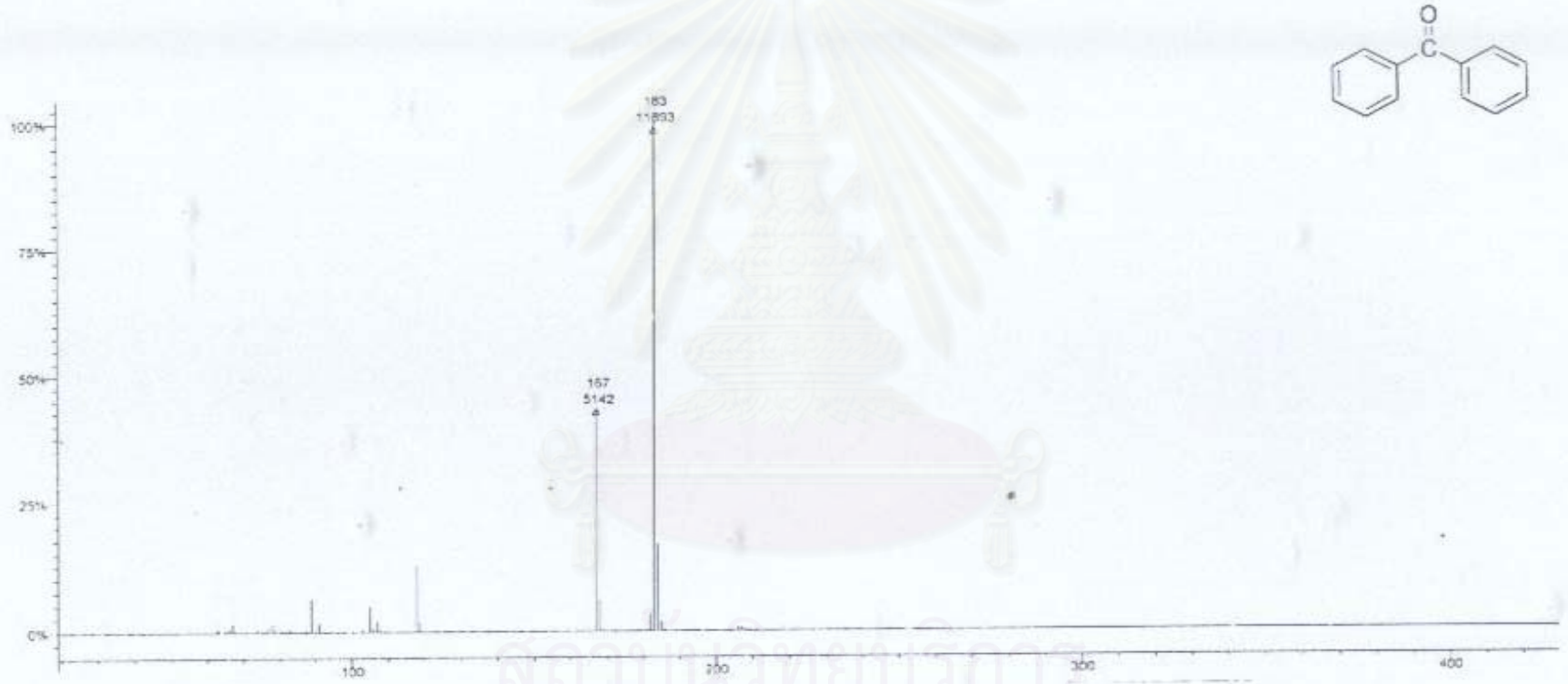

Figure A-14 The MS spectrum of undesired product from the attempted synthesis of **6d**

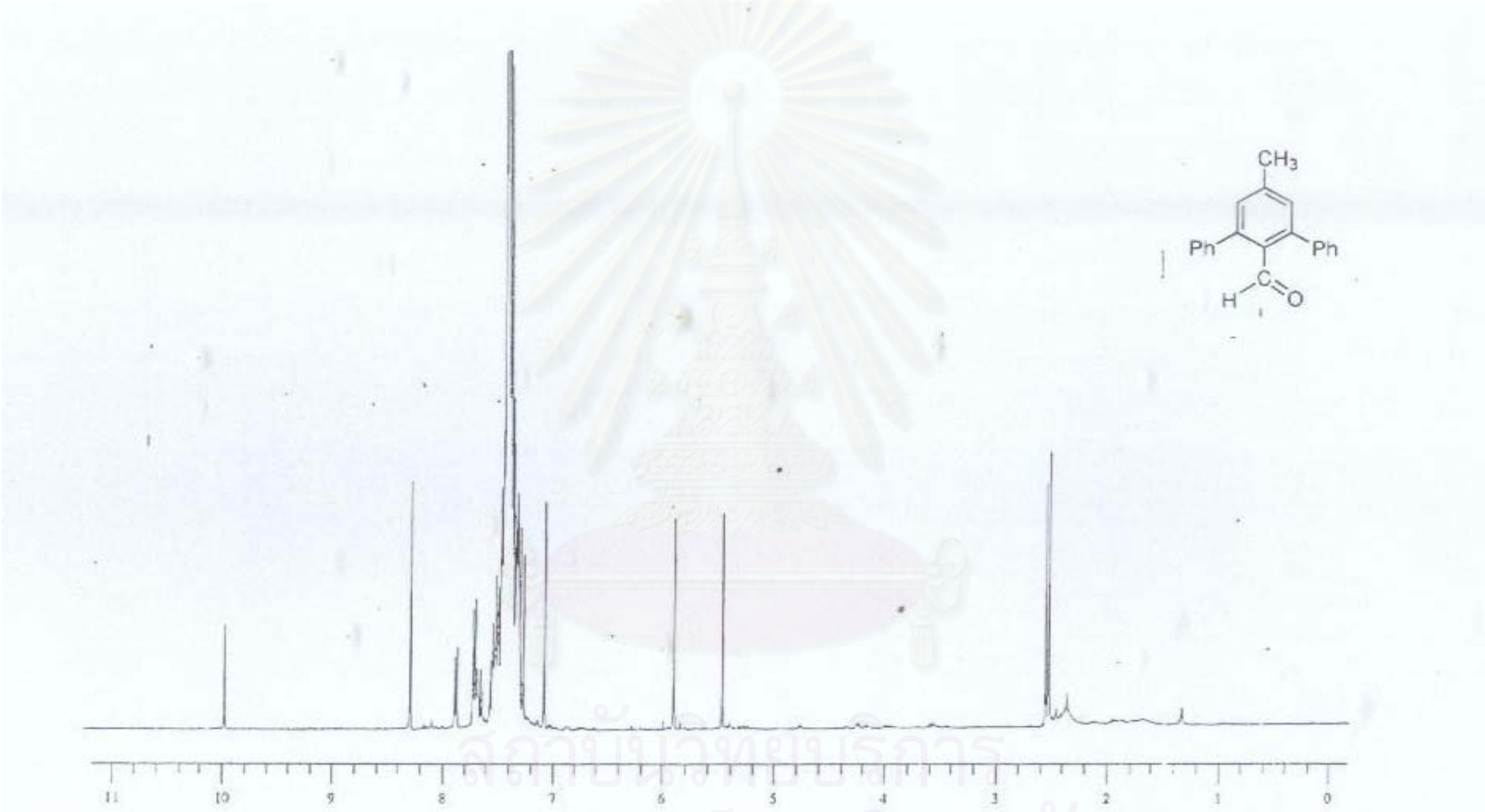

Figure A-15 The ^{1}H-NMR spectrum of the crude mixture upon the synthesis of **6f** quenched with ethyl formate

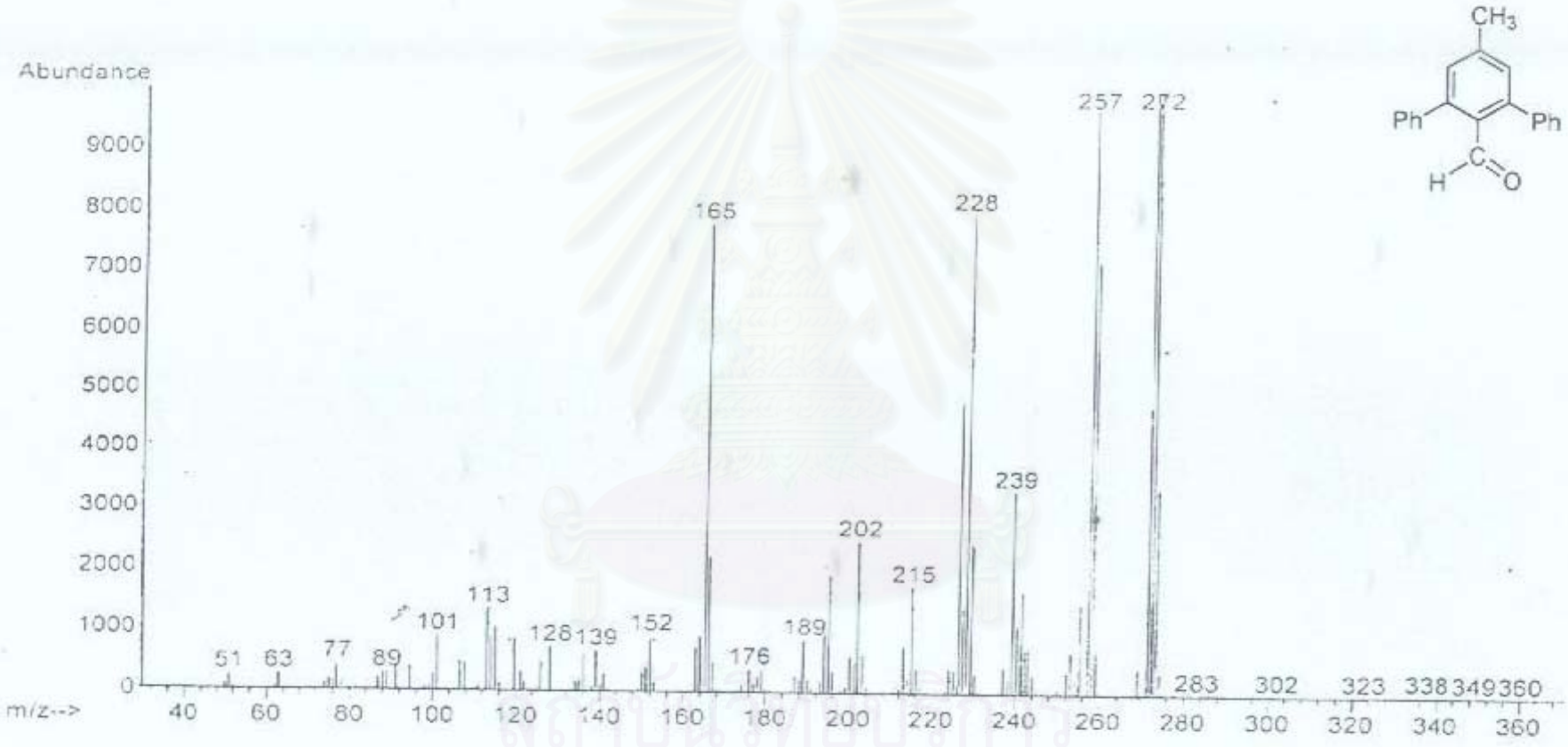

Figure A-16 The MS spectrum of the crude mixture upon the synthesis of **6f** quenched with ethyl formate

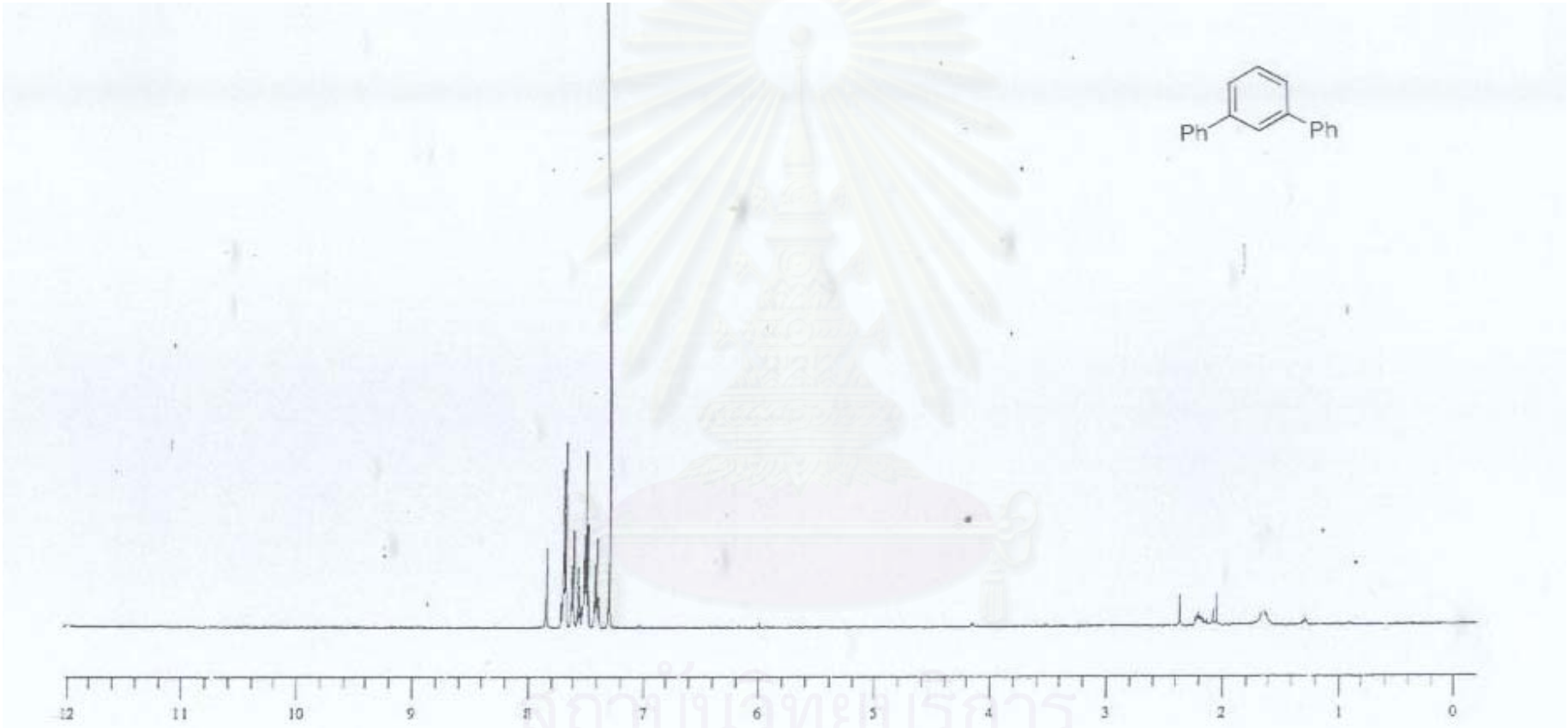

Figure A-17 The ^{1}H-NMR spectrum of 7a

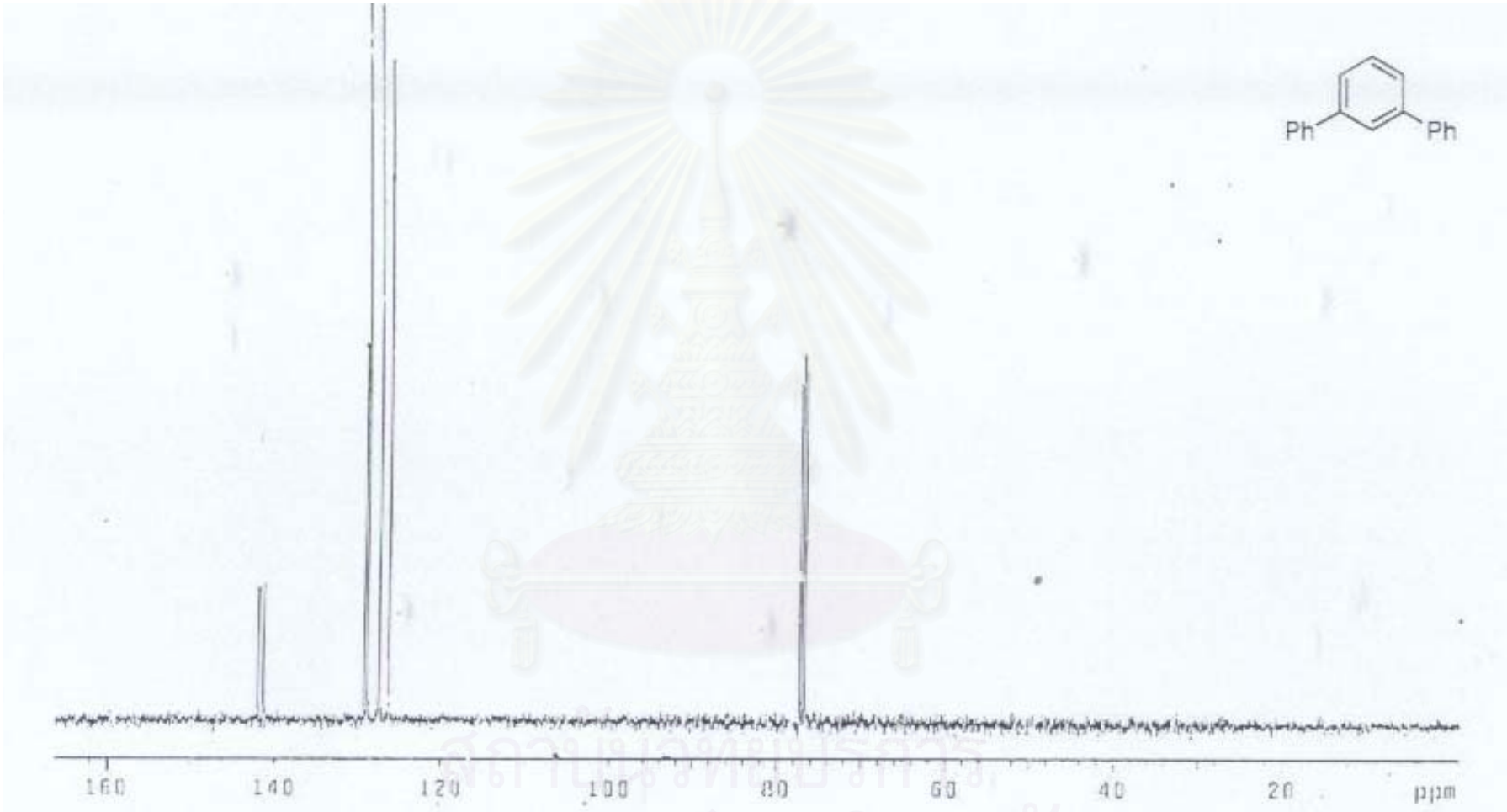

Figure A-18 The ^{13}C-NMR spectrum of **7a**

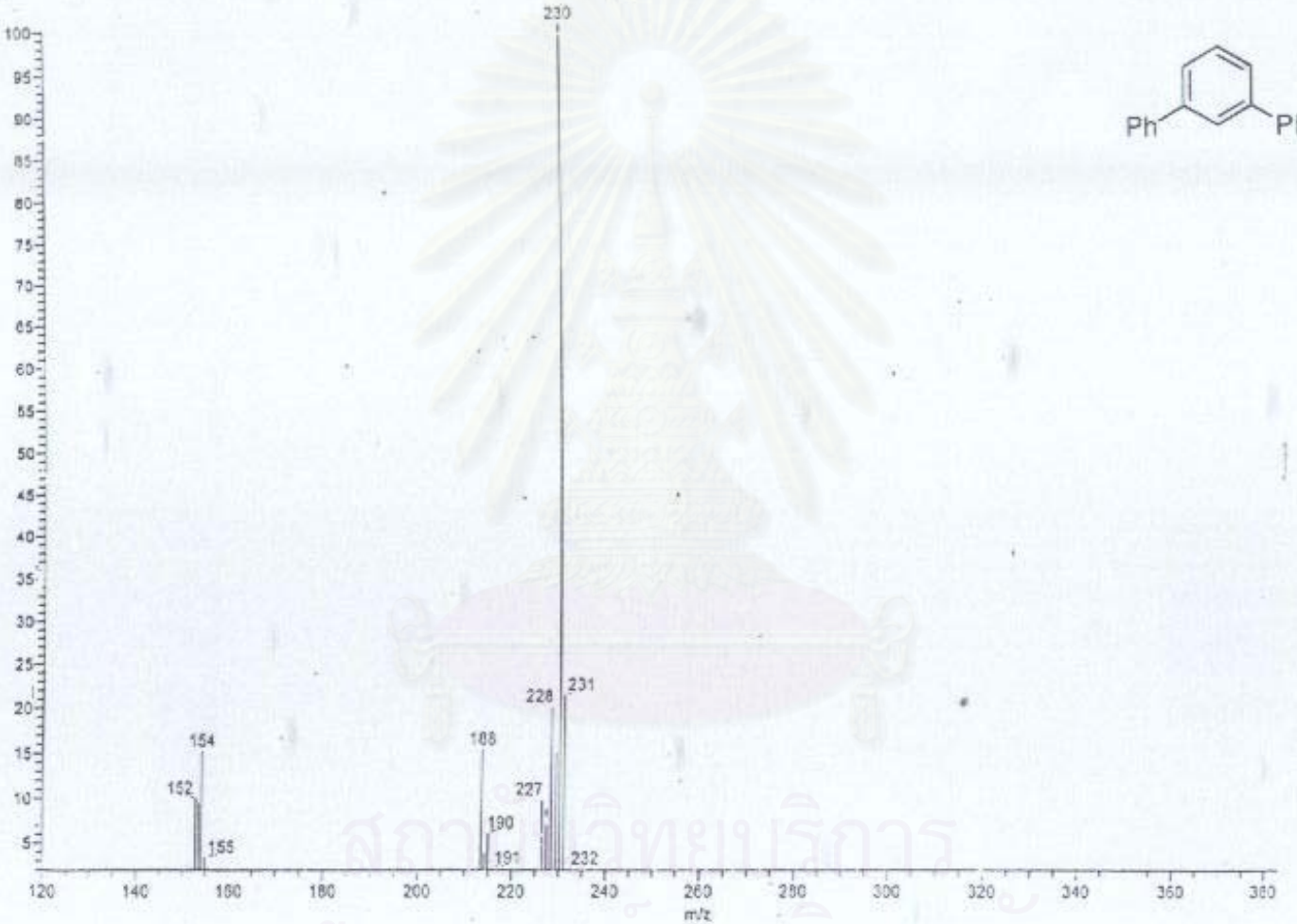

Figure A-19 The MS spectrum of 7a

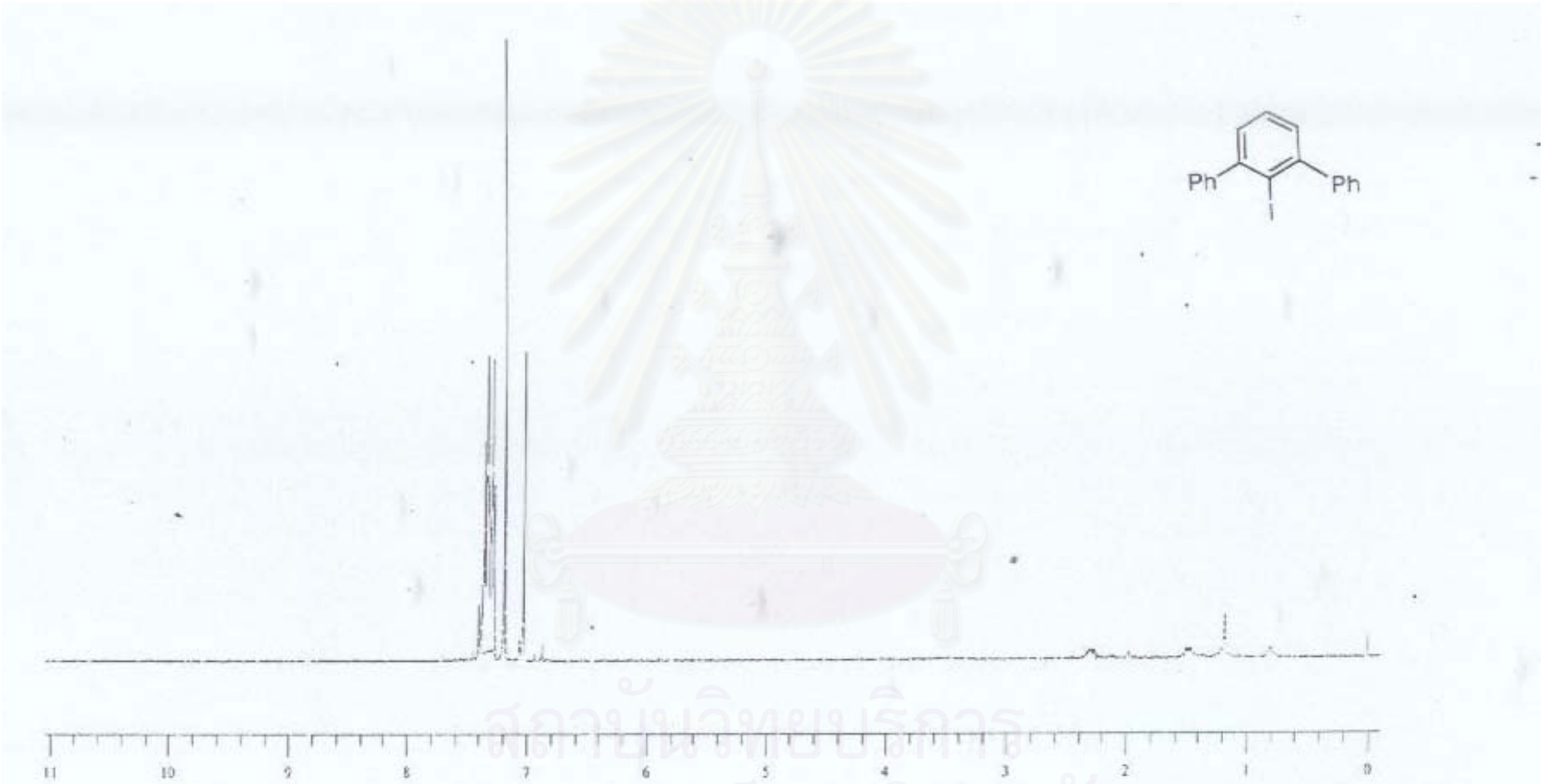

Figure A-20 The ^{1}H-NMR spectrum of **7b**

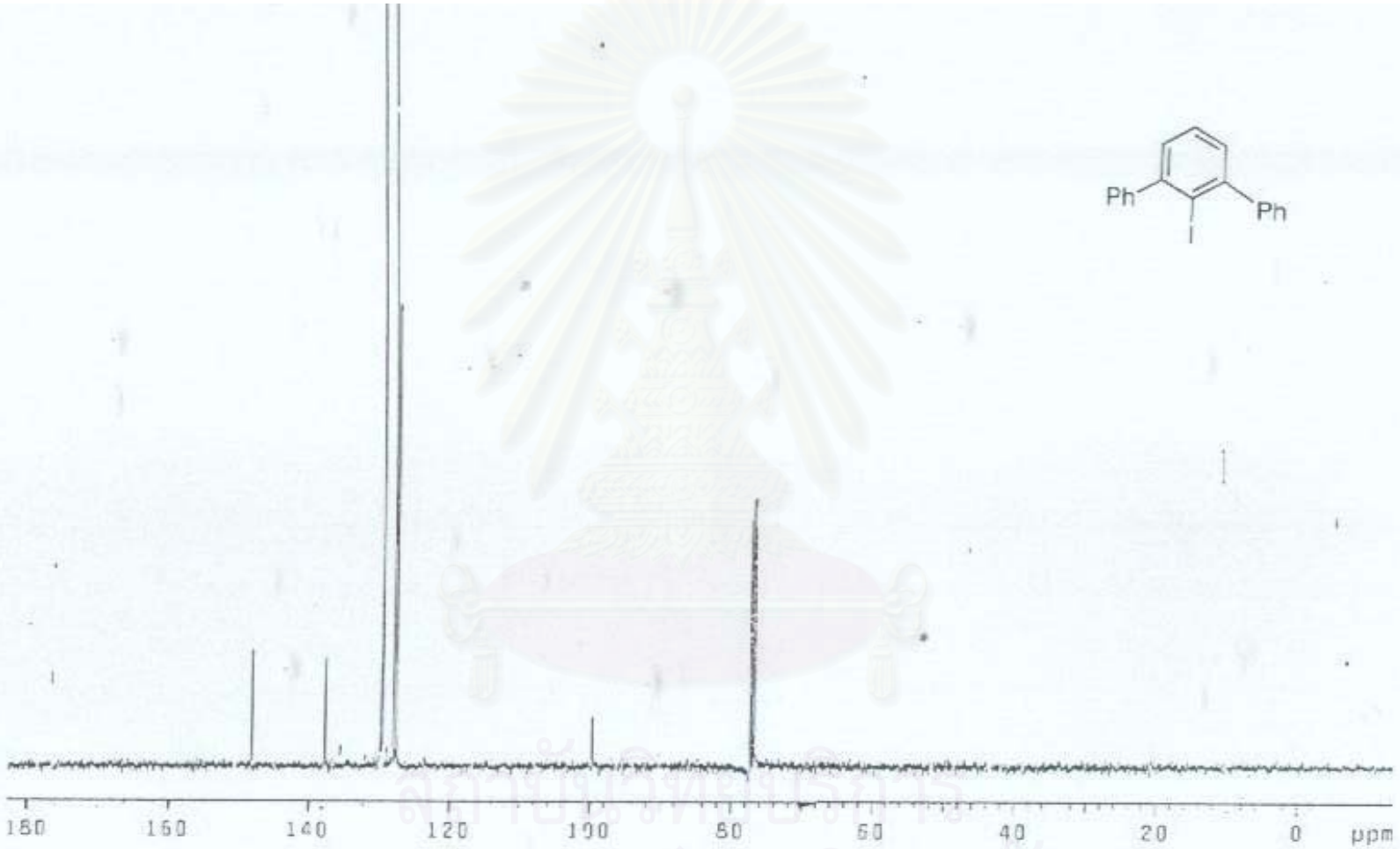

Figure A-21 The ^{13}C-NMR spectrum of 7b

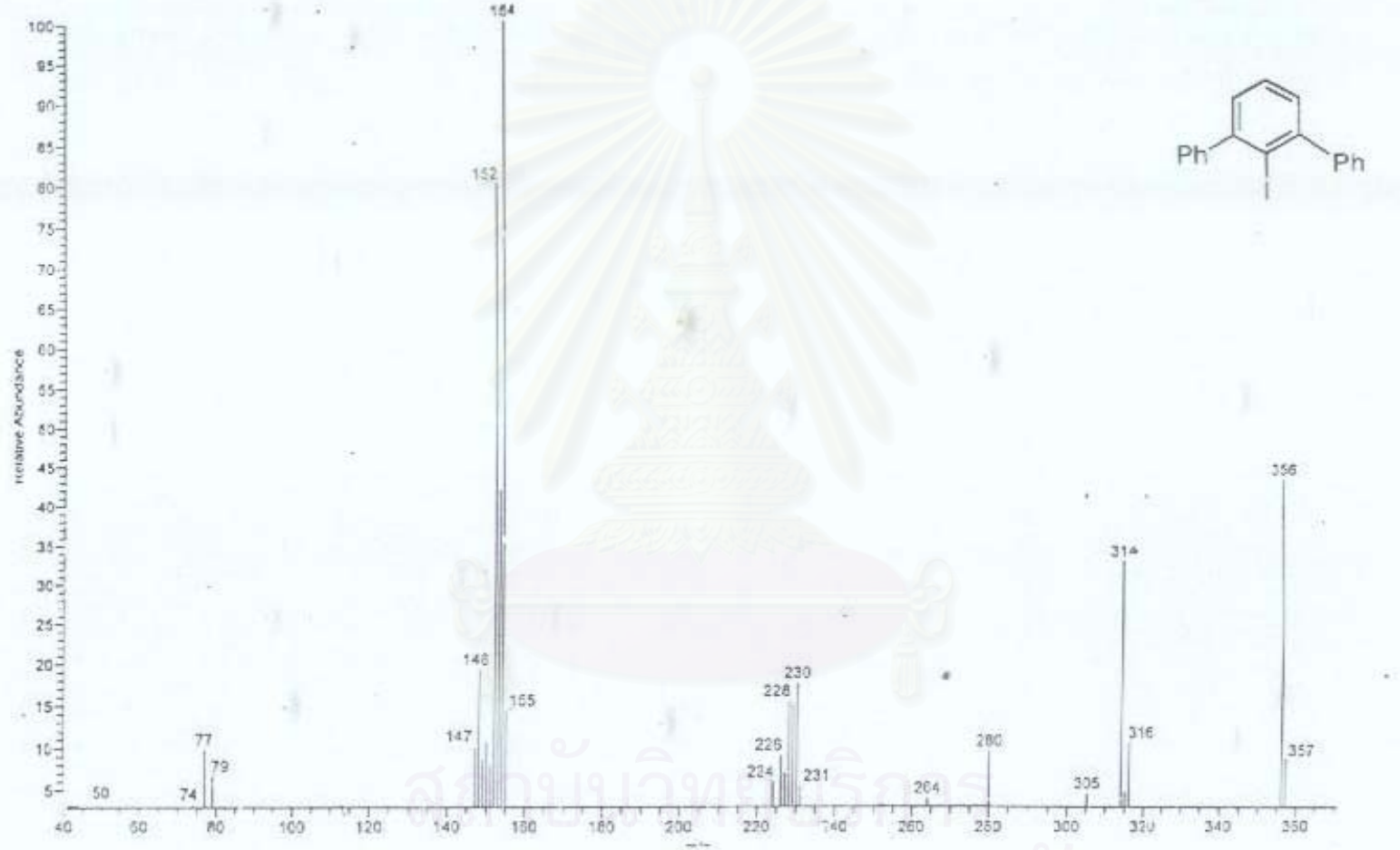

Figure A-22 The MS spectrum of **7b**

VITAE

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