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SYNTHESIS OF FIRST GENERATION OF POLY(ALKYL ARYL ETHER) DENDRIMER USING HEXASUBSTITUTED BENZENE CORE STRUCTURE

Miss Piyarat Charoenkan

A Thesis Submitted in Partial Fulfillment of the Requirements
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Thesis Title	SYNTHESIS OF FIRST GENERATION OF POLY (ALKYL ARYL ETHER) DENDRIMER USING HEXASUBSTITUTED BENZENE CORE STRUCTURE
By	Miss Piyarat Charoenkan
Field of Study	Petrochemistry and Polymer Science
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งานวิจัยนี้เป็นการศึกษาการสังเคราะห์อนุพันธ์ของสารที่มีโครงสร้างเป็นวงเบนซีนที่มีหมู่แทนที่ทั้งหกตำแหน่งที่จะนำไปสู่สารประกอบเดนดริเมอร์ โดยสารประกอบ 1,3,5-ไตรฟอร์มิล-2,4,6-ไตรไฮดรอกซีเบนซีน 28 สามารถทำการสังเคราะห์โดยปฏิกิริยาไรเมอร์-ทีมานโดยใช้ฟลอโรกลูซินอลเป็นสารตั้งต้นทำปฏิกิริยากับไดคลอโรคาร์บีนที่ได้จากโซเดียมไฮดรอกไซด์และคลอโรฟอร์ม หลังจากปฏิกิริยาไฮโดรไลซิสได้สารประกอบ 28 ในปริมาณ 59% ในขณะที่สารประกอบ 1,3,5-ไตรแอเซติล-2,4,6-ไตรไฮดรอกซีเบนซีน 29 สังเคราะห์โดยใช้ฟลอโรกลูซินอลทำปฏิกิริยากับแอเซติลคลอไรด์เกิดปฏิกิริยาเอสเทอร์ที่ออกซิเจนทั้งสามอะตอม จากนั้นเกิดการจัดเรียงโมเลกุลใหม่ของฟรีส์ได้ผลิตภัณฑ์ที่ต้องการในปริมาณ 85% สารประกอบ 29 ถูกปรับเปลี่ยนหมู่ฟังก์ชันเพื่อให้มีรูปโครงสร้างเป็นแบบ *ababab* โดยทำปฏิกิริยาแอลคิลเลชันบนหมู่ฟีนอลิกไฮดรอกซีได้สารประกอบ 30 ปริมาณ 75% สารประกอบ 31 ปริมาณ 65% สารประกอบ 32 ปริมาณ 56% และสารประกอบ 33 ในปริมาณ 44% ตามลำดับ สารประกอบเจเนอเรชันที่ 1 ของพอลิแอลคิลแอริลอีเทอร์เดนดริเมอร์ 44 ได้จากปฏิกิริยาระหว่างสารประกอบ 32 กับ 3,5-ไดเมทอกซีฟีนอลแล้วตามด้วยปฏิกิริยาดีเมทิลเลชันได้ผลิตภัณฑ์เป็นของผสม

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต ปิยรัตน์ เจริญกัณฑ์

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PIYARAT CHAROENKAN: SYNTHESIS OF FIRST GENERATION OF POLY(ALKYL ARYL ETHER) DENDRIMER USING HEXASUBSTITUTED BENZENE CORE STRUCTURE. THESIS ADVISOR: ASST. PROF. YONGSAK SRITANA-ANANT, Ph.D., 108 pp.

The synthesis of hexasubstituted benzene derivatives towards a dendrimer is the main focus of this research. 1,3,5-Triformyl-2,4,6-trihydroxybenzene **28** was synthesized by Reimer-Tiemann reaction using the phloroglucinol starting material reacting with dichlorocarbene generated from sodium hydroxide and chloroform. After hydrolysis, compound **28** was obtained in 59% yield. 1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** was synthesized using phloroglucinol reacting with acetyl chloride which went through triple *O*-acylations and then Fries rearrangement to become the desired product in 85% yield. Compound **29** was modified into the *ababab* geometry by alkylations on the phenolic hydroxy groups, giving compounds **30**, **31**, **32** and **33** in 75, 65, 56 and 44% yields, respectively. The potential first generation of poly(alkyl aryl ether) dendrimer **44** was obtained from the reaction of compound **32** with 3,5-dimethoxyphenol followed by demethylations to provide a mixture of products.

Field of Study : Petrochemistry and Polymer Science Student's Signature P. Charoenkan
Academic Year : 2008 Advisor's Signature

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LIST OF ABBREVIATIONS

^{13}C-NMR	: carbon-13 nuclear magnetic resonance spectroscopy
^{1}H-NMR	: proton nuclear magnetic resonance spectroscopy
anh.	: anhydrous
Ar	: aryl
bend	: bending vibration (IR)
$CDCl_3$	: deuterated chloroform
CH_2Cl_2	: methylene chloride
$CHCl_3$	: chloroform
cm^{-1}	: unit of wavenumber (IR)
d	: doublet (NMR), day(s)
DMF	: *N*,*N*-dimethylformamide
DMSO-d_6	: hexadeuterated dimethyl sulfoxide
eq	: equivalent (s)
EtOAc	: ethyl acetate
EtOH	: ethanol
g	: gram (s)
G1	: first generation
h	: hour (s)
Hz	: hertz (s)
IR	: infrared spectroscopy
J	: coupling constant
M	: molar (s)
m	: multiplet (NMR)
m.p.	: melting point
m/z	: mass per charge ratio
MALDI-TOF	: matrix assisted laser desorption ionization-time of flight
MeCN	: acetonitrile
MeOH	: methanol
mg	: milligram (s)

mL	: milliliter (s)
mM	: millimolar (s)
mmol	: millimole (s)
MS	: mass spectrometry
NBS	: *N*-bromosuccinimide
nm	: nanometer (s)
NMR	: nuclear magnetic resonance spectroscopy
^{o}C	: degree Celsius
Ph	: phenyl
ppm	: parts per million (unit of chemical shift)
q	: quartet (NMR)
RT	: room temperature
s	: singlet (NMR)
st	: stretching vibration (IR)
t	: triplet (NMR)
TLC	: thin layer chromatography
TMSCl	: chlorotrimethylsilane
δ	: chemical shift

CHAPTER I

INTRODUCTION

Dendrimers are a class of highly branched synthetic polymers that form spherical macromolecules that can be reliably synthesized to a specific physical size in a highly reproducible manner. Dendrimers of different generations are chemically related to each other, allowing the study of molecular size without the interfering variable of different chemical structures. The name dendrimer originates from Dendron, meaning “tree” in Greek, and references the structure of these molecules that branch outward from the core molecule. Dendrimeric structure can be devided into three distinct regions: the core, the interior (or branches), and periphery (surface groups) [1].

The first synthesized dendrimers were polyamidoamines (PAMAM). They are also known as starburst dendrimers. The term “starburst” is a trademark of the Dow Chemicals Company. Ammonia is used as the core molecule. Nowadays dendrimers are commercially available. Dendritech^{TM} (U.S.A.) manufactures PAMAM dendrimers. They are based on either an ethylenediamine (EDA) core or ammonia core and possess amino groups on the surface. They are usually sold as a solution in either methanol or water. DSM (Netherlands) has developed production of poly(propylene imine) (PPI) dendrimers. They are currently available under the name Astramol^{TM}. Butylenediamine (BDA) is used as the core molecule. The repetitive reaction sequence involves Michael addition of a primary amino group to acrylonitrile followed by hydrogenation of nitrile groups to primary amino groups [2].

1.1 Synthesis of dendrimers

1.1.1 Divergent method

Two main strategies for the synthesis of dendrimers have been described. The first method, based on the divergent approach pioneered by Tomalia [3-4] and Newkome [5-6]. Dendrimer grows outwards from a polyfunctional core molecule.

The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built layer after layer (**Figure 1.1**). Problems could occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion, large excess of reagents is required. It causes some difficulties in the purification of the final product [7].

1.1.2 Convergent method

The second method, named the convergent approach and described by Hawker and Fréchet [8-9], involves the construction of macromolecules starting at the periphery of the dendrimer. The dendrimer is constructed stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a polyfunctional core molecule (**Figure 1.1**). The convergent growth method has several advantages. It is relatively easy to purify the desired product and the occurrence of defects in the final structure is minimized. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because of the steric problems occurred in the reactions of the dendrons and the core molecule [7].

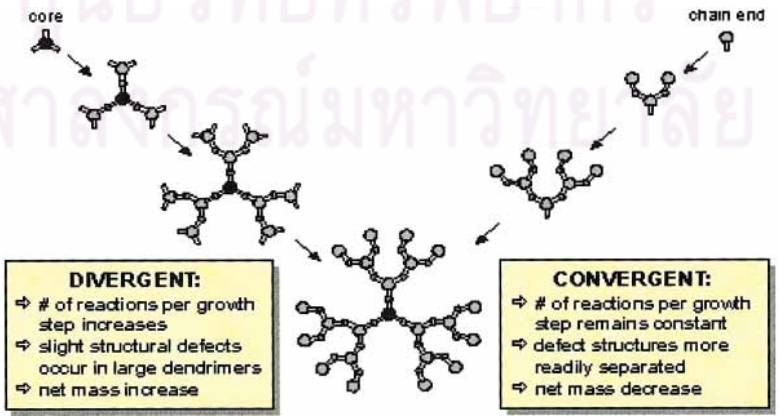


Figure 1.1 Dendrimer growth by the divergent and convergent methods

1.2 Dendritric copolymer

There are two or more different types of dendritic copolymers (**Figure 1.2**). Segment-block dendrimers are built with dendritic segments of different constitutions. They are obtained by attaching different wedges to one polyfunctional core molecule. Layer-block dendrimers consist of concentric spheres of differing chemistry. They are the result of placing concentric layers around the central core. Hawker and Fréchet [9] synthesised a segment-block dendrimer which had one ether-linked segment and two ester-linked segments. They also synthesized a layer-block dendrimer. The inner two generations were ester-linked and the outer three ether-linked.

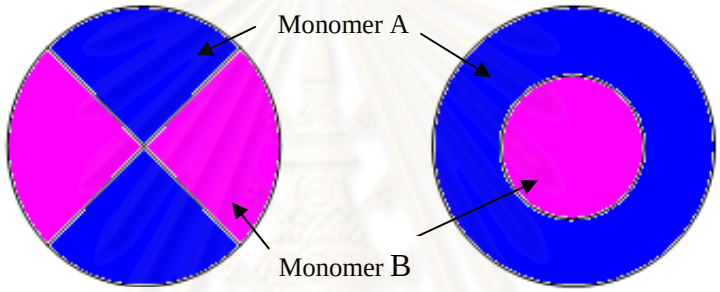


Figure 1.2 Dendritic copolymer: (a) segment-block dendrimer (b) layer-block dendrimer

1.3 Molecular structure and properties

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure [10]. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the “starburst effect” [11]. They are characterised by the presence of internal cavities and by a large number of reactive end groups (**Figure 1.3**).

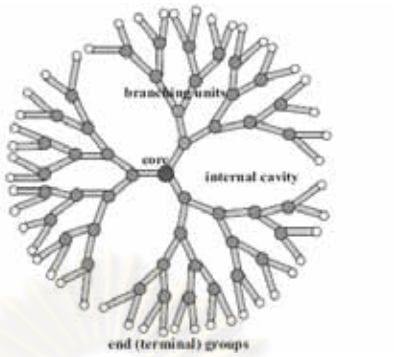


Figure 1.3 A fourth generation dendrimer

Dendrimers are unlike linear polymers, monodispersed macromolecules. The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.

Modification of core structure or functional groups on the periphery of a dendritic structure offers a convenient route to new dendrimers. Planar structure such as benzene has been widely used in dendrimers synthesis. Many researchers have selected 1,3,5-trisubstituted benzene **1** as the core while trisubstituted mesitylene **2** has been used only in few occasions.

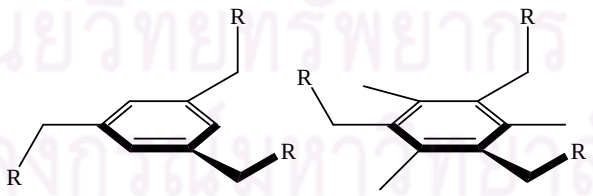


Figure 1.4 1,3,5-Trisubstituted benzene **1** and trisubstituted mesitylene **2**

1.4. Benzene core structure

1.4.1 1,3,5-Trisubstituted benzene core structure

In 1996, Chow and coworkers [12] synthesized polyether dendrimer up to the fourth generations. It was prepared by a convergent approach from readily available 4-tert-butylphenol, phloroglucinol and 1,3-dibromopropane. Using a three-step iterative synthetic sequence involving mono-*O*-alkylation of [Gn]-OH with excess 1,3-dibromopropane, bis-*O*-alkylation of the resulting compound with 5-benzyloxyresorcinol followed by hydrogenolysis with palladium catalyst, [G(n+I)]-OH of the next higher generation could be prepared in good yields. These dendritic sectors have good solubility properties and are inert in both acidic and basic media, and do not show any redox behaviour from -2.0 to +1.9 V. Hence, they are useful dendritic building blocks for the preparation of functional dendrimers.

In 1997, Chow and Mak [13] prepared the tartaric acid based layer-block chiral dendrimers. First generation layer-block dendrimers **3** and **4** have been prepared by a convergent synthetic procedure (**Figure 1.5**). These chiral layer-block dendrimers utilize 4-tertbutylphenoxy moieties as the surface groups and phloroglucinol as the branching junctures. Two different chiral units, which are derivatives of (D)- and (L)-tartaric acid, serve as the chiral linkers between the surface groups and the branching junctures, or between two branching junctures. The first layer-block dendrimer **3** has an outer chiral layer made up of six (L)-tartrate derived units and an inner chiral layer of three (D)-tartrate derived units. The second layer-block dendrimer **4** has an outer shell consisting of three (D)- and three (L)-chiral units and an inner shell of three (D)-chiral units. The molar rotation of these structurally flexible, low generation dendritic compounds is proportional to the number of chiral tartrate units in excess, with the chiroptical effect of a (D)-tartrate derived chiral unit cancelling that of an (L)-tartrate derived unit on a 1:1 basis. Circular dichroism studies, however, reveal that this cancellation effect is more effective when both the (D)- and (L)-chirons are situated within the same layer.

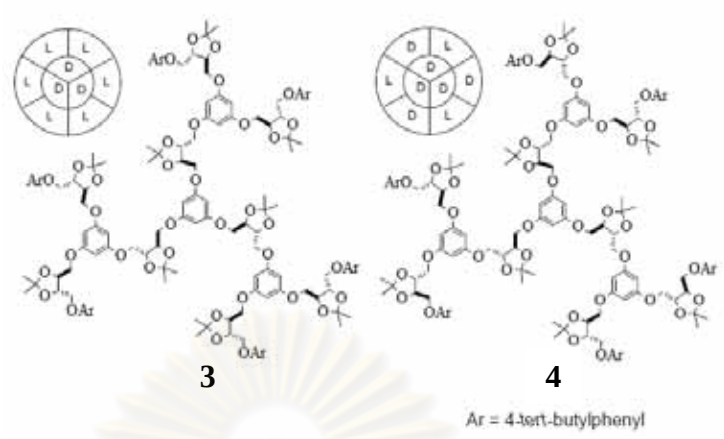
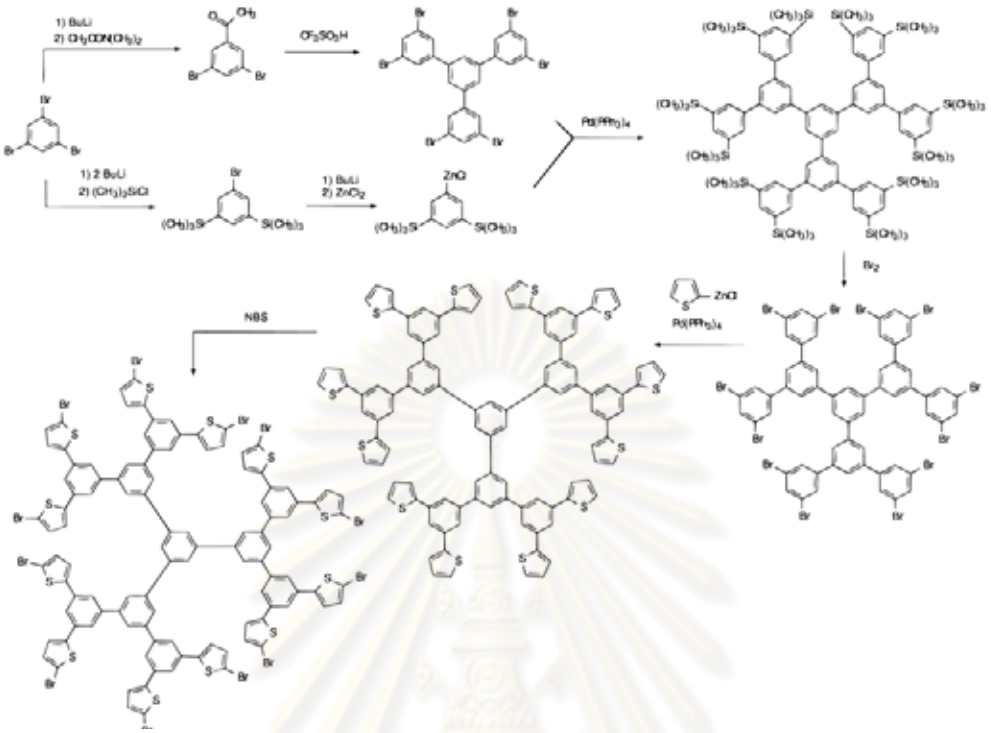


Figure 1.5 First generation layer-block dendrimers **3** and **4**

In 2000, Kim and Jung [14] were prepared ethynylsilane dendrimers. A dendritric macromolecule containing 144 phenylethylnyl groups was created. 1,3,5-Tris(dimethylvinyl)benzene as a core and bis(phenylethynyl)methylsilyl groups as progressing units were used. The first generation was obtained by the reaction of G0 with trichlorosilane and was followed by the phenylethynyl-group-containing generation by the reaction of lithium phenylacetylide. Using the continuous iterative reactions of trichlorosilane and lithium phenylacetylide, the dendritic molecule progressed to the second generation. For the formation of a less crowded model, the reaction of the first generation (G1-9PA) with dichloromethylsilane was allowed to progress to the 18 Si-Cl bonded second generation. After that, by the use of the two iterative reaction mechanisms, the fifth generation with 144 phenylethynyl groups containing the carbosilane dendrimer was prepared.

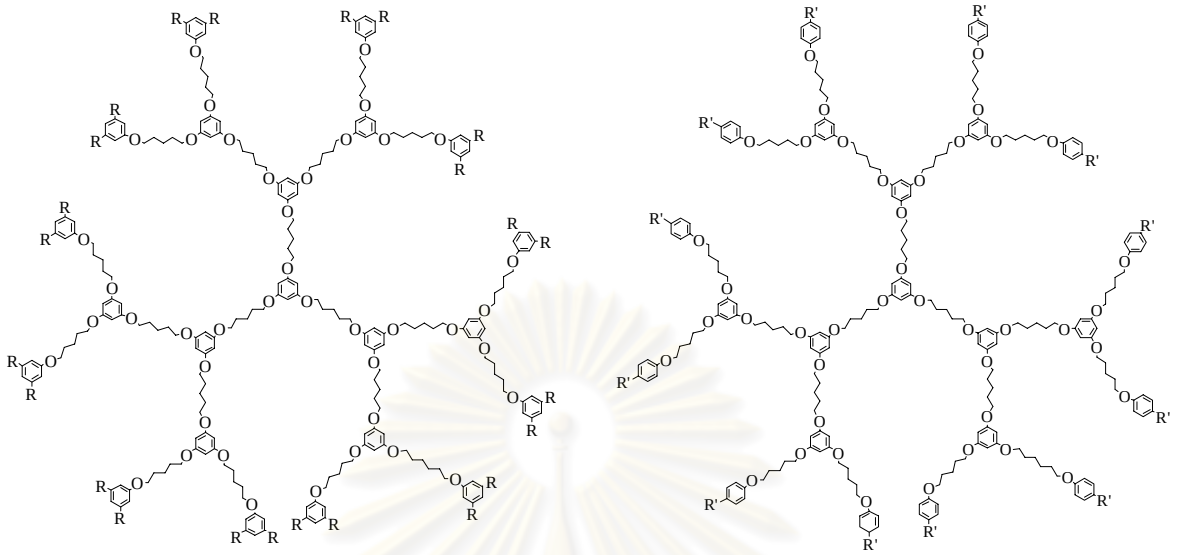
In 2000, Wang and coworkers [15] reported the synthesis and characterization of a polyphenylene dendrimer **5** in which its terminals functionalized with bromothiophene (**Scheme1.1**). The dendrimer was synthesized by a stepwise divergent approach using the palladium-catalyzed coupling reaction of aryl-zinc chloride and aryl bromide. The molecular weights of these dendrimers were determined by SEC.



5

Scheme 1.1 Synthesis of polyphenylene dendrimer **5**

In 2002, Nithyanandhan and Jayaraman [16] synthesized and characterized a group of poly(alky aryl ether) dendrimers. Dendrimers of up to fourth generations composed of a phloroglucinol core, branching components and pentamethylene spacers were synthesized by divergent growth methodology. A repetitive synthetic sequence of phenolic *O*-alkylation and debenzylation reaction are adopted for synthesis of these dendrimers. The peripheries of the dendrimers contain 6, 12, 24, and 48 phenolic hydroxyl groups, either in the protected or unprotected form, for the first, second, third, and forth generation, respectively. Because of the presence of hydrophilic exterior and relatively hydrophobic interior regions, alkaline aqueous solution of these dendrimers is able to solubilize an otherwise insoluble pyrene molecule. These supramolecular complexes can be precipitated upon neutralization of the aqueous solutions.



6 R = OH
7 R = OBn
8 R = CO_2Me

9 R´ = Br
10 R´ = PPh_2

Figure 1.6 Poly(alkyl aryl ether) dendrimers

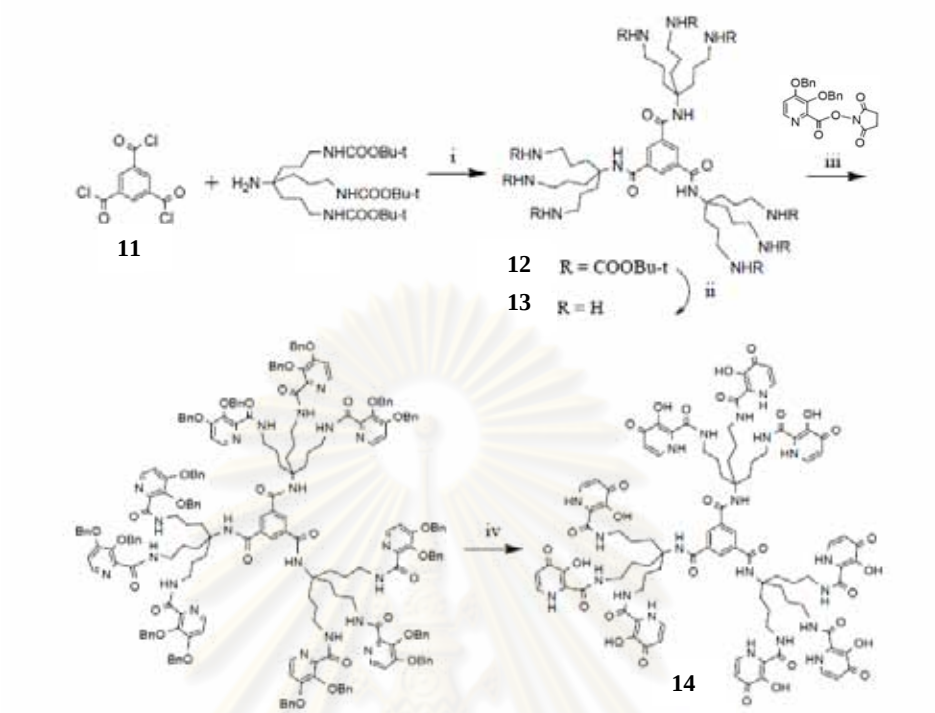
Water-soluble organic molecules, poly(alkyl aryl ether) dendrimers **6** and **8**, have been explored for their use as hosts of organic substrates in aqueous media by Kaanumalle and coworkers [17-18]. Prototypical photoreactions, namely, photo-Fries reaction of 1-naphthyl benzoate and 1-naphthyl phenyl ester and α-cleavage reaction of dibenzyl ketones and benzoin alkyl ethers, have been examined inside the dendritic environments. They found that a dendritic microenvironment not only restricts the mobility of radical intermediates but also rigidly encapsulates the substrate, intermediates, and products from “leaking” to the bulk environment. Comparative studies of the same photoreactions in micellar media demonstrate that dendritic media offer much better constrainment than the micelles.

Nithyanandhan and Jayaraman [19] synthesized a series of new triphenylphosphine functionalized poly(alkyl aryl ether) dendrimers. Zero, first, second and third generation dendrimers, carrying 3, 6, 12 and 24 triphenylphosphine units, were prepared and characterized. The new triphenylphosphine containing dendrimers **10** were assessed for their reactivity profiles and in this instance, the dendrimers were used as reagents to mediate Mitsunobu etherification reaction

between phenol and various primary, secondary and benzylic alcohols. In addition, dendritic poly-phenols were also tested in an *O*-benzylation reaction. A monomeric methoxy group attached triphenylphosphine acted as a control for comparison of reactivity profiles of dendrimers. It was observed that the etherification reaction was mediated efficiently by the dendritic reagent, and in addition, the dendritic phosphine oxide reagents could be recovered quantitatively by precipitation methods. The recovered dendritic phosphine oxides could be reduced subsequently to the corresponding phosphines and used as reagents for the Mitsunobu reaction, repetitively.

In 2006, they also functionalized poly(alkyl aryl ether) dendrimers with bromophenyl groups at their peripheries [20]. The new bromophenyl functionalized dendrimers **9** were assessed for their reactivities in C-heteroatom and C-C bond forming reaction. For this purpose, the bromophenyl functionalized dendrimers were converted quantitatively to their polylithiated derivatives, using n-BuLi in benzene. The polylithiated dendrimers were reacted either with D_2O or CO_2, to afford the corresponding deuterated or carboxylic acid functionalized dendrimers, respectively. The carboxylic acid functionalized dendrimers were modified further to the methyl esters during their characterizations.

In 2005, Zhou and coworkers [21] had aimed to design and synthesize of orally active iron(III) scavenging based on dendrimer. The synthesis of an iron(III)–selective hydroxylpyridinone terminated dendritic chelator based on a benzene tricarbonyl core **11** polyamine dendrimer is described. The dendrimer was found to possess an extremely high affinity for iron(III), namely the absolute stability constant (log K) = 34.8 and p[Fe^{3+}] = 30.6.



(i) CH_2Cl_2, 0 °C–rt, 6 h, 68% yield; (ii) 96% HCOOH, rt, 24 h, 95% yield; (iii) DMF, rt, 3 d, 83% yield; (iv) BCl_3, CH_2Cl_2, 0 °C–rt, 2 d, 88% yield

Scheme 1.2 Synthesis of dendritic chelator

1.4.2 Mesitylene core structure

In 2004, Sengupta and coworkers [22] reported a stilbene dendrimer prepared using rigid caltop-shaped dendrons derived from tetraphenylmethane. Dendrons reacted with 2,4,6-tris(bromomethyl)mesitylene **15,** a hexasubstituted benzene nucleus. In analogy to other hexasubstituted benzene derivatives, stilbene dendrimer is expected to adopt a conformation in which the three stilbenoid dendrons (alternate substituents) would remain on the same side of the benzene plane, that is, conformation I or III (**Figure 1.7**). Conformation I having an all *s-trans* orientation of the caltrops is believed to be the preferred one because conformations II and IV, having *s-cis* orientations of the ether linkages, would suffer from severe steric interactions between the stilbenoid caltrops (as in conformation II) or between the stilbenoid caltrops and the *ortho*-methyl groups of the central benzene ring (as in conformation IV). However, since conformations II and IV are less stable, it may be concluded that, irrespective of whether dendrimer prefers conformation I or III,

excimer formation in the dendrimer via pre-organization of the stilbene chromophores would be highly disfavored.

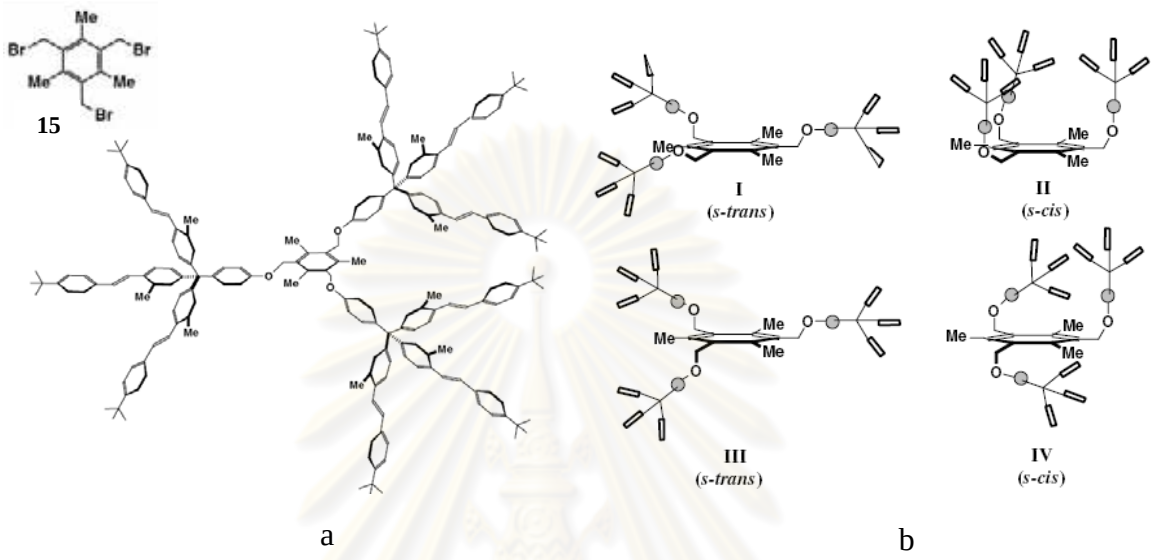


Figure 1.7 Stilbene dendrimer: (a) 2,4,6-tris(bromomethyl)mesitylene **15** and stilbene dendrimer (b) Conformational analysis of the dendrimer

The absorption maximum of the dendrimer was found at λ_{max} 319 nm with a high molar extinction coefficient [$\varepsilon_{max}(CH_2Cl_2)$] = 21.7 × 10^4 M^{-1} cm^{-1}. As expected, the ε_{max} value is nearly nine times that of *trans*-stilbene. Dendrimers prepared from such planar dendrons invariably led to strong intermolecular associations or excimer formation via π-stacking interactions, especially at a low dendrimer generation, as was evident by the extended red tailings reported in their emission spectra (up to ~650 nm). In contrast, they have shown that by using a highly branched caltrop-shaped dendron, association free emission can be obtained even in a first generation stilbene dendrimer. Therefore, caltrop-shaped tri-chromophoric dendrons can be effectively used as light harvesting antennae.

1.5 Hexasubstituted benzene

Hexasubstituted benzene has attracted much recent attention as efficient building blocks for the development of functional molecules such as molecular receptors and metal ligands in the fields of molecular recognition chemistry and supramolecular chemistry. It adopts a fully alternated “up-down” arrangement of the arms with all substituents oriented perpendicularly to aryl ring plane. In this arrangement, the substituents attached at the 1, 3 and 5 positions of the central ring all pointing to the same face while the rest of substituents point in the opposite direction. In 1976, MacNicol and coworker were among the first group to design the preorganization of the functional groups in hexasubstituted benzene derivatives and determined the molecular structures by X-ray analysis [23-25]. In these systems, six identical substituents are adopt a fully alternated “up-down” arrangement of the arms with all substituents oriented perpendicularly to aryl ring plane (**Figure 1.8**). In this arrangement, the substituents attached at the 1,3 and 5 positions of the central ring all point to the same face while the rest of substituents are pointed toward the opposite direction, so as to impart approximate D_{3d} or S_6 symmetry. The unique steric features of hexasubstituted benzenes are the design principle for host molecules and supramolecular system. Due to the unavoidable steric repulsion between 2 adjacent substituents, the 1,3,5-trisubstituted benzene spacer play an important role in controlling the steric configuration of the functional groups introduced into its 2,4,6-positions. The functional groups attached at the 2,4,6-positions are forced to lie at the opposite side of aryl ring of the spacer, so the “*ababab*” configuration (*a* denotes “above” and *b* denotes “below”) as the most thermodynamically stable configuration.

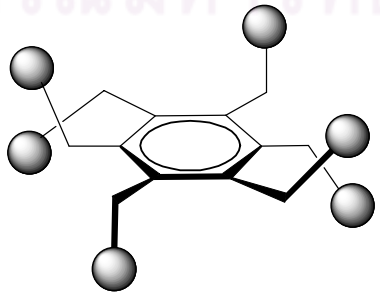
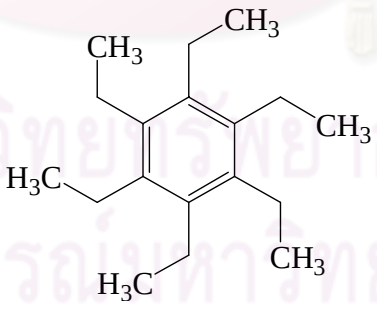


Figure 1.8 The *ababab*-configuration of the hexasubstituted benzene scaffold

1.6 Stereochemistry of hexasubstituted benzene

1.6.1 The ethyl group

The ethyl substituent is the simplest alkyl group of non-conical symmetry. An ethyl group attached to a central ring can be depicted schematically as an “arm” consisting of a CH_3 group protruding from the axis connecting the ethyl group to the central ring (**Figure 1.9**). Polyethylated aromatic compounds can be viewed as multiarmed hydrocarbon in which several arms (the ethyl groups) radiated from a central polyatomic core. Multiarmed compounds (sometimes referred as “octopus molecules”) [26] are of interest as molecular hosts and as the cores of novel polymeric systems (e.g. dendrimers). They are interest as sterically crowded compounds. The analysis of their preferred conformations is particularly challenging because of the inherent stereochemical complexity of these conformationally flexible systems. The polyethylated derivatives are capable of existing in a large number of conformations, the relative energies of which are dictated by numerous nonbonded interactions (repulsive and attractive van der Waals interactions) between the ethyl groups. Usually the lowest energy conformation results from the need to avoid repulsive steric interactions between the groups [27].



16

Figure 1.9 Hexaethylbenzene **16**

1.6.2 Conformation of hexaethylbenzene

The static and dynamic stereochemistry of hexaethylbenzene **16** were analyzed in great details by Iverson and coworkers [28]. Molecular mechanics calculation had indicated that the fully alternated conformation indeed corresponded to the lowest form in energy. The arrangement of two ethyl groups oriented towards the same face of aromatic ring is usually designated as *syn* arrangement, and its associated steric interaction (a *syn* interaction) is repulsive. All ethyl groups situate perpendicular to the central ring, giving eight possible different diastereomeric forms. Calculation has shown that relative steric energies of the form increased roughly with the number of *syn* interactions present (**Figure 1.10**).

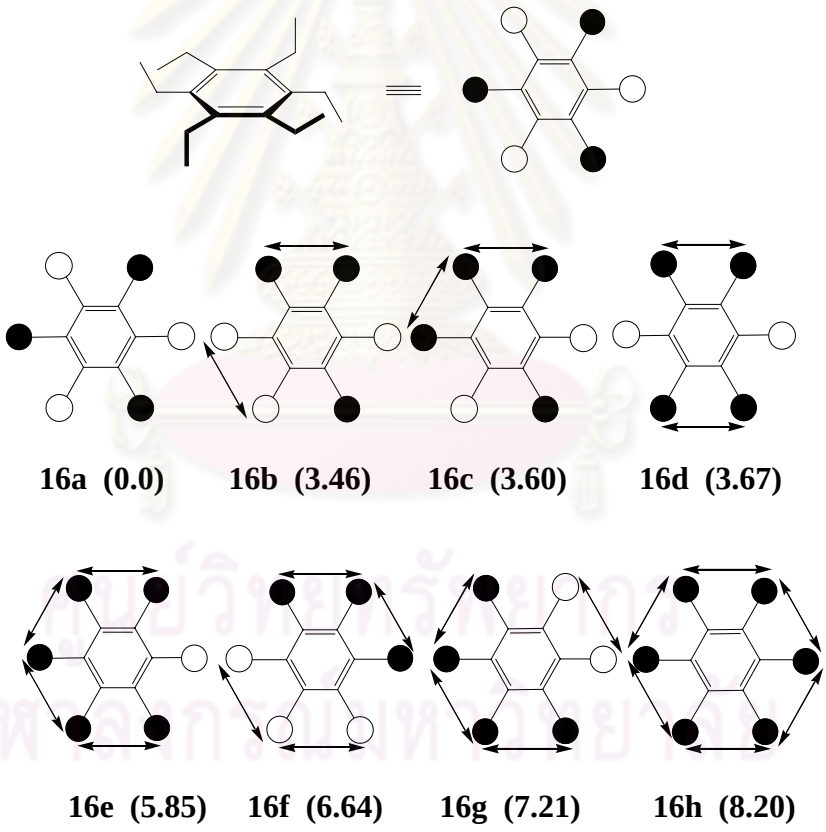


Figure 1.10 The eight ideal up-down forms of hexaethylbenzene and their calculated EFF (BIGSTRN-2) relative steric energies (filled and empty circles represent ethyl groups pointing to or away from the observer; a double arrow denotes a *syn* arrangement of two *ortho* ethyl groups)

As a further test of stereochemistry of **16**, relative energy levels for the eight structures were computed by the extended Hückel method: such hybrid EFF (BIGSTRN-2)[29] and EFF-EHMO[31] calculations showed the fully alternated form remains the ground state conformer (**Figure 1.11**). Both methods of calculations therefore predicted the same ground state conformation as found from the X-ray structure[28] and indicated that the solution of **16** contain more than 99% of this conformer at equilibrium under normal conditions. Higher energy conformers could be implicated as intermediates in the degenerate conformational rearrangement (topomerization) of the fully alternated conformer.

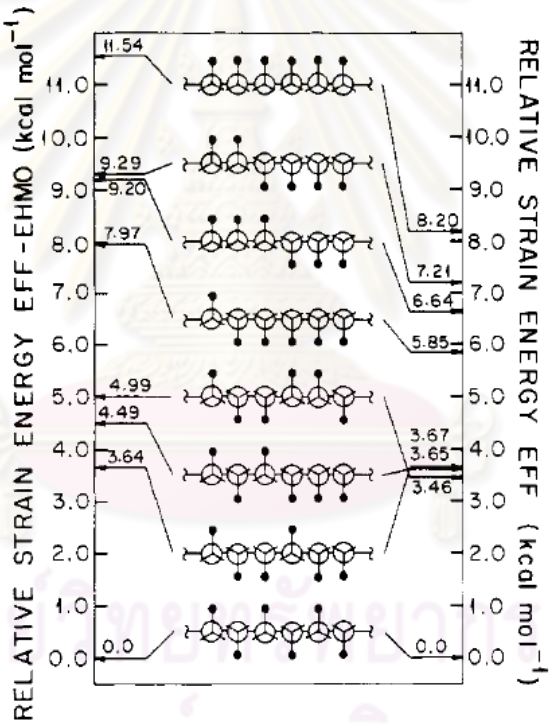
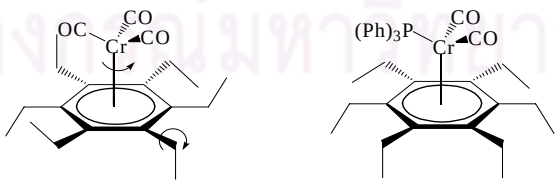


Figure 1.11 The eight up-down isomers of **16**. Each schematic projection represents a view around the perimeter of the benzene ring. The heavy dots stand for methyl groups. The scales on the right and left of the diagram indicate relative energies calculated by the EFF (BIGSTRN-2) and EFF-EHMO methods, respectively.

Transition metal complexation was used for the study the stereodynamics of alkylbenzene. The center of symmetry in D_{3d} and S_6, as well as the C_2 axes in D_{3h}, may be removed upon complexation of the aromatic ring with transition metals. As a result, the two faces of the benzene ring become nonequivalent and differentiable and site-exchange phenomena resulted from rotations of the side chains could be monitored by dynamic NMR (DNMR) techniques. Iverson and co-workers [28] were investigated the stereochemical features of such system in which hexaethylbenzene functioned as the η^6-arene in tricarbonylchromium, tricarbonyl-molybdenum and dicarbonyl(triphenylphosphine)chromium complexes (**Figure 1.12**). They provided information about the steric complimentarity between the metal fragment and the arene. The methyl groups in tricarbonylchromium **17** and tricarbonylmolybdenum complexes project alternately above and below the benzene plane. Three of ethyl groups are eclipsed by the carbonyl groups and their corresponding methyl groups project toward the uncomplexes side of the ring. But the structure of dicarbonyl(triphenylphosphine)chromium complex **18** differs markedly, in that all six methyl groups project toward the uncomplexed side of the ring, and the molecules assume a staggered rather than eclipsed conformation. This information in turn applied to the design of transition complexes where control of the steric environment around the metal modifies the reactivity of the complex. The utility of the method is limited by the degree to which the presence of the metal disturbs the stereodynamics of the parent compound. These limits can be probed through systems where the symmetry allows one to observe the stereodynamics of both free and metal-complexed arenes [30].



17 **18**

Figure 1.12 The tricarbonylchromium arene complex **17**, and the dicarbonyl (triphenylphosphine)chromium arene complex **18**

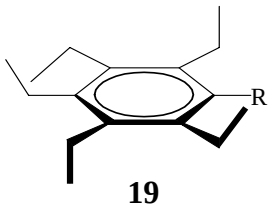
1.6.3 Rotational barriers

The rotational barrier of polyethylated arene does not usually refer to the rotation of a single ethyl group but rather to the overall topomerization barrier determined by NMR spectroscopic methods. This observation is due to the fact that if a single conformation is detected, usually the energy of barrier is determined by monitoring the line sharpness changes of diastereotopic groups that are rendered equivalent in the dynamic process. This topomerization process may involve one or several consecutive ethyl group rotations and/or several intermediate conformers along the pathway but undetected in the NMR spectrum because of their low populations.

Molecular mechanics calculations indicated that the site exchange of the methylene proton of **16** proceeded through a stepwise process. The favored rearrangement pathway was found to have calculated barrier of 11.8 kcal mol^{-1} [28]. This result was supported by an analysis of ^{13}C-NMR lineshapes of the tricarbonylchromium and tricabonylmolybdenum complexes in CD_2Cl_2 at below -30 ºC. The barriers of site exchange were 11.5 and 11.6 kcal mol^{-1} for tricarbonyl-chromium and tricarbonylmolybdenum complexes, respectively.

1.6.4 Polyethylated benzene

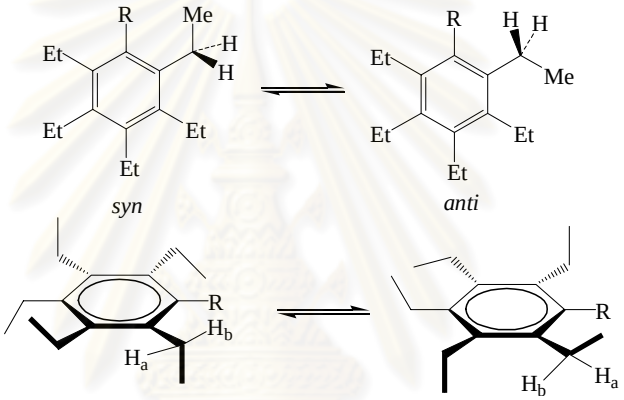
In contrast to compound **16**, in the polysubstituted derivatives **19** (**Figure 1.13**) pair of the methylene protons on ethyl groups located *ortho* or *para* to the substituent (R) are diastereotopic under the conditions of slow side chain rotation on the NMR spectroscopic timescale, and their topomerization barrier can be determined readily by DNMR spectroscopy [31-34]. As showed in **Figure 1.13**, the rotational barrier of pentaethylbenzene **19a** is lower than the calculated barrier of **16**. During the 180º rotation of an ethyl group, a conformation is reached in which the CH_2-CH_3 bond is coplanar with the benzene ring. If the two *ortho*-substituents flanking the rotating ethyl group are different, two diastereoisomeric transition states are possible (**Scheme 1.3**). In the case when R = H, the *syn* transition state should be favored on steric grounds.



19

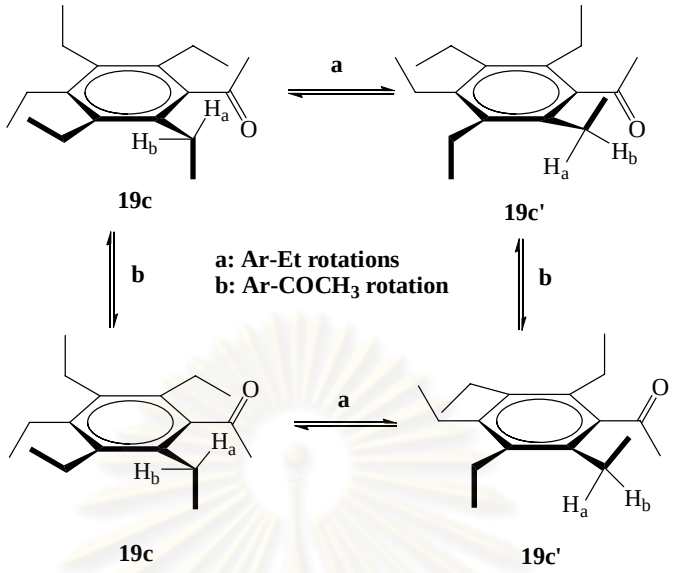
	topomerization barrier (kcal mol^{-1})
19a R = H	9.2
19b R = Br	10.2
19c R = $COCH_3$	13.7
19d R = $OCOCH_3$	14.6

Figure 1.13 Experimentally measured topomerization barriers of pentaethylphenyl derivatives **19**



Scheme 1.3 Diastereoisomeric transition states and diastereotopic protons in penta-ethylphenyl derivatives

Ketone **19c** and esters **19d,e** displayed topomerization barriers substantially higher (13.7-16.7 kcal mol^{-1}) than the barrier calculated for **16** [31]. In **19c** the carbonyl group is nearly perpendicular to the aryl plane and two diastereomeric conformations are possible (**19c** and **19c′**, **Scheme 1.4**). These two conformers may interconvert either by 180° rotation of the five ethyl groups, or by single 180° rotation along the Ar-COR bond. To achieve topomerization of a given form, however, not only must the five ethyl groups rotate, but also the COR group must rotate by 180° and the high barrier of the latter process is the one that determines the overall topomerization barrier. Low-temperature NMR spectroscopic data were in agreement with this analysis and, for example, two sets of signals were observed in ^{13}C-NMR spectra of **19d** and **19e**.



Scheme 1.4 Diastereotopic protons in pentaethylphenyl acetone **19c** and **19c´**

Kilway and Siegel presented the experimental evidence to quantify the effect of tricarbonylchromium complexation on the stereodynamic of compounds related to **16** [32-33]. The molecular models are 1,4-dimethoxy-2,3,5,6-tetraethylbenzene **20**, 1,4-bis(methoxymethyl)-2,3,5,6-tetraethylbenzene **21**, and 1,4-dineohexyl-2,3,5,6-tetraethyl benzene **22** (**Figure 1.14**). The ground states of **20**, **21** and **22** are calculated by EFF methods to be the alternating up-down conformer analogous to **16**. In all three systems, they found only a minor perturbation of the barrier to ethyl group rotation when the metal tripod was introduced onto the arene. These results would indicate that for these systems the use of transition metals as desymmetrizing units for the study of such stereodynamics provides data that is a relatively accurate assessment of the parent-ligand dynamics. This lock-and-key fit is also of importance to the design of arene ligands which modify the steric environment around a transition metal; 1,3,5-substituted hexaalkylbenzenes should be capable of enshrouding the metal without strongly altering the strength of the metal-arene bond.

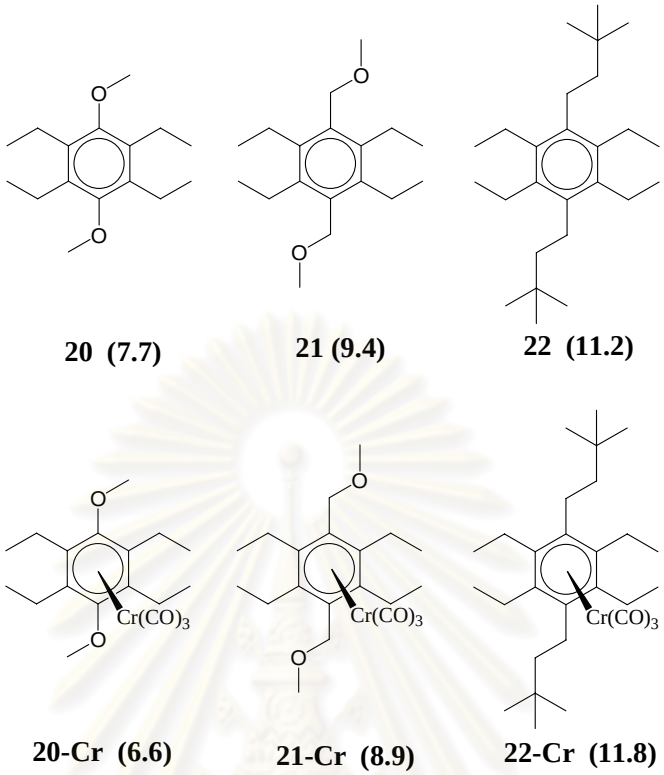
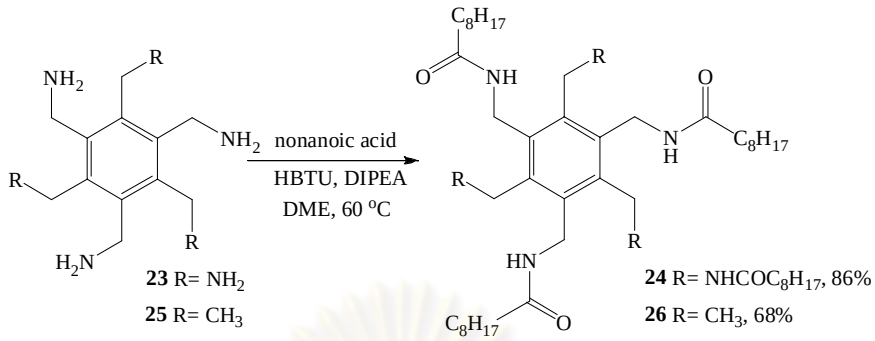


Figure 1.14 The barriers to rotation (kcal mol^{-1}) about the sp^2-sp^3 bond for 1,4-dimethoxy-2,3,5,6-tetraethylbenzene **20**, 1,4-bis(methoxymethyl)-2,3,5,6-tetraethyl-benzene **21**, and 1,4-dineohexyl-2,3,5,6-tetraethylbenzene **22** and their tricarbonyl-chromium complexes, **20-Cr**, **21-Cr** and **22-Cr**

1.6.5 Hydrogen bonding vs steric gearing in hexasubstituted benzene

Gavett and coworkers [34] synthesized and characterized compound **24** and **26** from **23** and **25**, respectively (**Scheme 1.5**). DFT calculations [35-36] were performed to shed light on the anomalous solution behavior of **23**. In the most stable conformation to be identified, all six nonanamide substitutents lie on one side of the benzene plane, forming a bowl (**Figure 1.15**). Averaging the distances between the C=O atoms of *para* disposed arms gives a calculated diameter of 9.1 Å. An uninterrupted seam of hydrogen-bonds (average NH···O=C separation= 1.88 Å) circles the molecule. In the gas phase, the bowl is favored by 15.2 kcal/mol over an alternating up-down conformation that benefits from steric gearing [37]. (**Figure 1.15**) This value narrows to 3.1 kcal/mol when a solvent with dielectric constant corresponding to chloroform is applied using COSMO.



Scheme 1.5 Synthesis of compound **24** and **26**

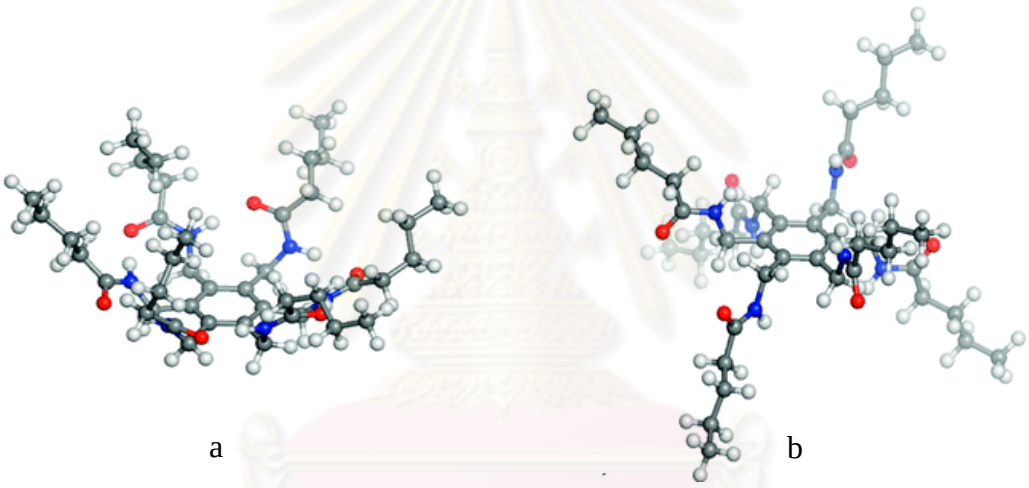


Figure 1.15 DFT-optimized views of truncated **24** in the (a) bowl and (b) up-down conformations

Hexasubstituted benzene has attracted much recent attention as efficient building blocks for the development of functional molecules such as molecular receptors and metal ligands in the field of molecular recognition chemistry and supramolecular chemistry. It adopts a fully alternated “up-down” arrangement of the arms with the substituents oriented perpendicularly to aryl ring plane. In this arrangement, all substituents attached at the 1, 3, and 5 positions of the central ring all point to the same face while the rest of the substituents point in the opposite direction. Traditionally, 1,3,5-trisubstituted core dendrimer can not control the growth direction, and the first and second generations possessed more open structures as compared to

higher generation dendrimers. Consequently, low generation dendrimers were less efficient to be used as receptors or to encapsulate a guest. Modification of the core structure to become the hexasubstituted benzene is expected to better control the dendrimer growth toward certain directions either above or below the benzene ring. The first and second generation dendrimers of this new core structure should become more densely packed than those from the 1,3,5-trisubstituted benzene core and may be ready for the desired applications with less synthetic effort. Moreover, since the substituents are divided into two groups that point toward different directions, one group of the substituents can be engineered to augment the desired property of the other or even carry its own property, making the whole molecule become a ditopic, difunctionalized macromolecular host.

1.7 Objective

The goal of this research is to synthesize the first generation of poly(alkyl aryl ether) dendrimer based on the hexasubstituted benzene derived from phloroglucinol as the core structure.

CHAPTER II

EXPERIMENTS

2.1 Instruments and equipments

Melting points were determined with a Stuart Scientific Melting Point SMP1 (Bibby Sterlin Ltd., Staffordshire, UK). The FT-IR spectra were recorded on a Perkin-Elmer FT-IR spectroscopy, spectrum RXI spectrometer (Perkin Elmer Instruments LLC., Shelton., U.S.A.). Samples were dissolved in dichloromethane or ethylacetate and then droped on potassium bromide crystal cell. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$), hexadeuterated dimethylsulfoxide (DMSO-d_6) or hexadeuterated acetone ($(CD_3)_2CO$) using Varian Mercury NMR spectrometer which operated at 400.00 MHz for ^{1}H and 100.00 MHz for ^{13}C nuclei (Varian Company, CA, USA). The mass spectra were recorded on Mass Spectrometer: Waters Micromass Quatto micro API ESCi (Waters, MA, USA.). Samples were dissolved in solvent and directly injected 100 µL in to the Mass Specrometer. Alternatively, mass spectrum of a high molecular weight sample was Matrix Assisted Laser Desorption Ionization-Time of Flight technique (MALDI-TOF): Microflex mass spectrometer (Bruker Daltonik GmbH, Germany). The instrument was equipped with nitrogen laser to desorb and ionize the samples, deposited on a stainless steel target. The sample was mixed with dithranol matrix 10 mg mL^{-1} solution in tetrahydrofuran.

2.2 Chemicals

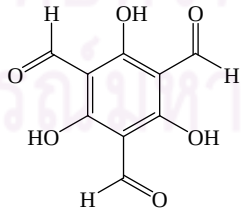
Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck Kieselgel 60 F_{254}) (Merck KgaA, Darmstadt, Germany). Column chromatography was performed in silica gel (0.06-0.2 mm, 70-230 mesh ASTM), Merck Kieselgel 60 G (Merck KgaA, Darmstadt, Germany) or Scharlau Chemie S. A. (Barcelona, Spain). Solvents used in synthesis were reagent or analytical grades. Solvents used in column chromatography were distilled from

commercial grade prior to use. The reagents used for synthesis were purchased from the following vendors:

- Labscan (Bangkok, Thailand): chloroform, concentrated hydrochloric acid, 1,4-dioxane
- Acros Organic (New Jersey, USA): phloroglucinol dihydrate, acetyl chloride, *N*-bromosuccinimide, bromoacetaldehyde diethylacetal, 1,5-dibromopentane, *N*-(2-bromoethyl)phthalimide, chlorotrimethylsilane
- Aldrich Chemical Company (Steinheim, Germany): benzyl bromide
- Carlo Erba Reagent (Milan, Italy): anhydrous calcium chloride, anhydrous potassium carbonate
- Fluka Chemical Company (Buchs, Switzerland): 1,3,5-trimethoxybenzene
- Merck Co. Ltd. (Darmstadt, Germany): ethanol, anhydrous sodium hydrogen carbonate, sodium hydroxide, sodium iodide, anhydrous sodium carbonate, anhydrous sodium sulfate, potassium cyanide, acetone, acetonitrile
- Riedel-de Haën: anhydrous aluminum (III) chloride,
- BDH Chemicals (Poole, England): potassium iodide
- Wilmad (New Jersey, USA): deuterated chloroform, hexadeuterated dimethylsulfoxide, hexadeuterated acetone

2.3 Synthesis of hexasubstituted benzene derivatives

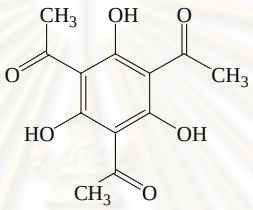
2.3.1 1,3,5-Triformyl-2,4,6-trihydroxybenzene 28



Phloroglucinol dihydrate (0.32 g, 2 mmol) was suspended and refluxed in chloroform, sodium hydroxide (4.15 g, 36 mmol) was added to the suspension and then water (0.14 mL, 8 mmol) was added. Additional sodium hydroxide (0.72 g, 18 mmol) was added after 1.5 hour. The mixture was further refluxed for 24 hours. The

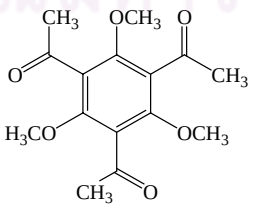
solvent was removed then the resulting residue was dissolved in water and acidified to pH 1 with 1 M HCl. The product was precipitated and filtered .The desired product was collected as red powder (0.25 g, 59% yield). m.p. 198-200 ºC; IR (KBr, cm^{-1}): 3343 (O-H st), 1633 (C=O st), 1584 (C=C st) (**Figure A.3**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 10.15 (s, 3H), 14.11 (s, 3H) (**Figure A.1**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 102.9, 173.6, 192.1 (**Figure A.2.**); MS-H^+ (CH_2Cl_2): m/z = 209.07 (**Figure A.4**)

2.3.2 1,3,5-Triacetyl-2,4,6-trihydroxybenzene 29



Phloroglucinol dihydrate (0.32 g, 2 mmol) was dissolved in excess acetyl chloride 5 mL and then added anh. $AlCl_3$ (1.30 g, 10 mmol). The reaction mixture was refluxed for 1 hour and then quenched with water (15 mL). The mixture was filtered, rinsed with water (20 mL) and the precipitate was collected. The crude product was recrystalized in EtOH to give colorless needle crystals product (0.43 g, 85% yield). m.p. 149-151 ºC; IR (KBr, cm^{-1}): 3433 (O-H st), 1622 (C=O st), 1576 (C=C st) (**Figure A.7**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.72 (s, 9H), 17.16 (s, 3H) (**Figure A.5**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.9, 103.1, 175.8, 205.0 (**Figure A.6**); MS-H^+ (CH_2Cl_2): m/z = 252.98 (**Figure A.8**)

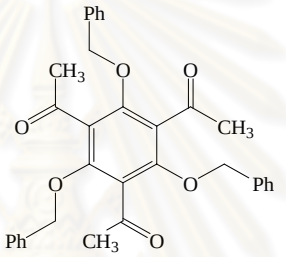
2.3.3 1,3,5-Triacetyl-2,4,6-trimethoxybenzene 30



1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** (0.25 g, 1 mmol) was dissolved in 20 mL MeCN, K_2CO_3 (2.07 g, 15 mmol) was added and refluxed for 1 hour. Then dimethyl sulfate (0.57 mL, 6 mmol) was added. After 2 hours and the reaction had

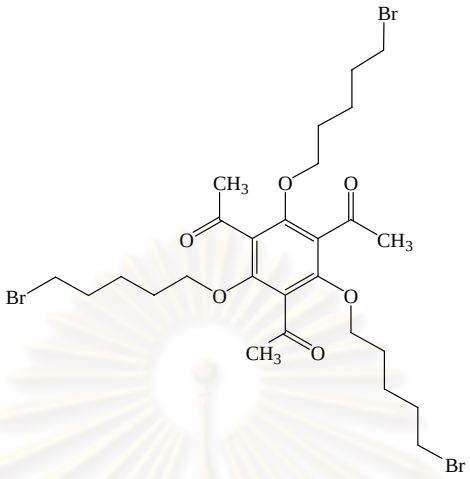
been cooled down, 15 mL of water was added and the reaction mixture was neutralized with 10% HCl. The product was precipitated and collected in white powder (0.23 g, 75% yields). m.p. 124-126 ºC; IR (KBr, cm^{-1}): 2947 (C-H st), 1704 (C=O st), 1570 (C=C st), 1453 and 1358 (C-H bend), 1205 and 1089 (C-O st) (**Figure A.11**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.54 (s, 9H), 3.74 (s, 9H) (**Figure A.9**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.5, 64.5, 127.1, 155.3, 200.7 (**Figure A.10**); MS-H^+ (CH_2Cl_2): m/z = 295.16 (**Figure A.12**)

2.3.4 1,3,5-Triacetyl-2,4,6-tribenzyloxybenzene 31



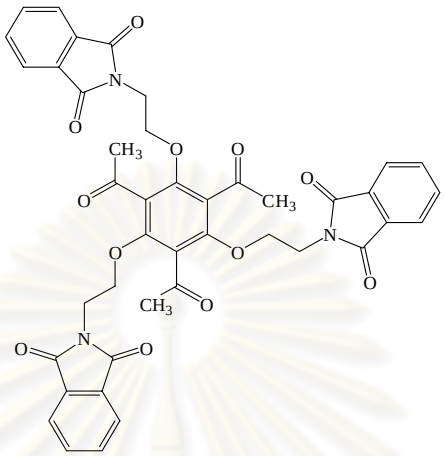
1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** (0.25 g, 1 mmol) was dissolved in 20 mL MeCN and K_2CO_3 (2.07 g, 15 mmol) was added. The reaction mixture was stirred at reflux temperature for 1 hour and benzyl bromide (0.7 mL, 6 mmol) was added. Stirring at reflux was continued until no more substrate was found by TLC monitoring (about 8 hours). The reaction was then cooled down, added 15 mL of water and neutralized with 10% HCl. The solution was extracted with CH_2Cl_2 (20 mL, 3 times). The organic layers was separated, combined, dried with Na_2SO_4 anhydrous and removed the solvent. The concentrated crude product was recrystalized by 3:7 CH_2Cl_2/EtOH to give colorless needle crystals product (0.52 g, 65% yield). m.p. 189-191 ºC; IR (KBr, cm^{-1}): 3027 (=C-H st), 2920 (C-H st), 1706 (C=O st), 1578 (C=C st), 1417 and 1361 (C-H bend), 1204 and 1085 (C-O st) (**Figure A.15**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.46 (s, 9H), 4.91 (s, 6H), 7.35 (m, 15H) (**Figure A.13**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 32.7, 79.9, 128.6, 128.7, 128.9, 135.7, 153.8, 200.9 (**Figure A.14**); MS-H^+ (CH_2Cl_2): m/z = 523.20 (**Figure A.16**)

2.3.5 1,3,5-Triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene 32



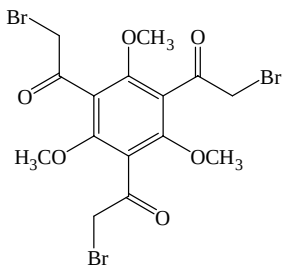
1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** (0.51 g, 2 mmol) was dissolved in 20 mL MeCN and stirred with K_2CO_3 (4.15 g, 30 mmol) at reflux temperature for 1 hour and then added 1,5-dibromopentane (2.76 g, 6 mmol). After 5 days, the reaction was then cooled down, added 15 mL of water and neutralized with 10% HCl. The solution was extracted with EtOAc (20 mL, 3 times). The organic layers were separated, combined, dried with anh. Na_2SO_4, and removed solvent. The concentrated crude product was purified by column chromatography (90:10 hexane/EtOAc) to give the colorless oil product (0.37 g 56% yield). IR (KBr, cm^{-1}): 2940 (C-H st), 1704 (C=O st), 1570 (C=C st), 1420 and 1355 (C-H bend), 1198 and 1085 (C-O st), 560 (C-Br st) (**Figure A.19**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.48 (m, 6H), 1.62 (m, 6H), 1.86 (m, 6H), 2.52 (s, 9H), 3.40 (t, 6H), 3.82 (t, 6H) (**Figure A.17**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 24.4, 29.0, 32.3, 32.8, 33.6, 77.4, 127.7, 154.0, 201.0 (**Figure A.18**); MS-H^+ (EtOAc): m/z = 699.26 (**Figure A.20**)

2.3.6 1,3,5-Triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy)benzene 33



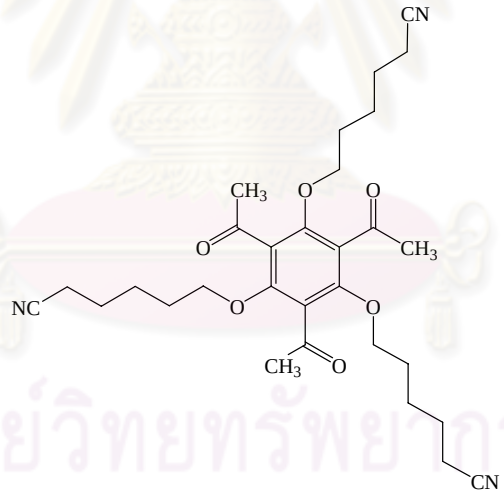
1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** (0.51 g, 2 mmol) was dissolved in 20 mL MeCN and stirred with *t*-BuOK (0.74 g, 6.6 mmol) at reflux temperature for 1 hour and then added *N*-(2-bromoethyl)phthalimide (2.29 g, 6 mmol). After 2 days, the reaction was then cooled down, added 15 mL of water and neutralized with 10% HCl. The solution was extracted with EtOAc (20 mL, 3 times). The organic layers were separated, combined, dried with anh. Na_2SO_4, and removed solvent. The concentrated crude product was purified by column chromatography (90:10 hexane/EtOAc) to give the colorless needle crystals product (0.44 g, 44% yield). m.p. 87-89 ºC; IR (KBr, cm^{-1}): 2947 (C-H st), 1723 (C=O st), 1424 and 1391 (C-H bend), 1065 (C-O st) (**Figure A.23**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.95 (s, 9H), 3.88 (t, 6H), 4.24 (t, 6H), 7.66 (m, 6H), 7.78 (m, 6H) (**Figure A.21**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 20.8, 36.9, 61.5, 123.3, 131.9, 134.0, 168.0, 170.8 (**Figure A.22**)

2.3.7 1,3,5-Tris(α-bromoacetyl)-2,4,6-trimethoxybenzene 35



1,3,5-Triacetyl-2,4,6-trimethoxybenzene **30** (0.23 g, 0.76 mmol) was dissolved in 5 mL CH_2Cl_2, NBS (0.45 g, 2.5 mmol) and $AlCl_3$ (0.003 g, 0.02 mmol) was added and stirred the mixture at room temperature under N_2. After 5 days the reaction mixture was filtered to remove excess NBS and $AlCl_3$ from the reaction and then removed the solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/EtOAc) to give the yellow oil product (0.05 g, 17 % yield). IR (KBr, cm^{-1}): 2955 (C-H st), 1708 (C=O st), 1562 (C=C st), 1457 and 1391 (C-H bend), 1198 and 1118 (C-O st), 590 (C-Br st) (**Figure A.26**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.75 (s, 9H), 4.31 (s, 6H) (**Figure A.24**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 35.3, 63.9, 121.8, 156.8, 191.7 (**Figure A.25**) MS-H^+ (CH_2Cl_2): m/z = 531.13 (**Figure A.27**)

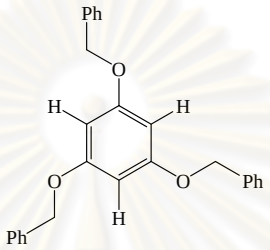
2.3.8 1,3,5-Triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene 37



1,3,5-Triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32** (0.70 g, 1 mmol) was dissolved in MeCN (5 mL) and stirred with KCN (0.39 g, 6 mmol) added. The reaction was refluxed until no substrate, monosubstituted and disubstituted intermediates was found by TLC monitoring (about 10 days). The reaction was cooled down, added 15 mL of water then extracted with EtOAc (10 mL, 3 times). The organic layers were separated, combined, dried with anh. Na_2SO_4 and removed the solvent to give the yellow oil product (0.53 g, 99% yield). IR (KBr, cm^{-1}): 2947 (C-H st), 2244 (C≡N st), 1708 (C=O st), 1570 (C=C st), 1424 and 1358 (C-H bend), 1187

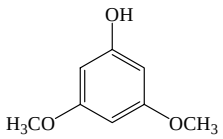
and 1085 (C-O st) (**Figure A.30**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.48 (m, 6H), 1.64 (m, 12H), 2.35 (t, 6H), 2.51 (s, 9H), 3.82 (t, 6H) (**Figure A.28**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 17.1, 24.8, 24.9, 29.0, 32.8, 76.7, 119.5, 127.9, 153.9, 201.0 (**Figure A.29**); MS-Na^+ (MeOH): m/z = 560.29 (**Figure A.31**)

2.3.9 1,3,5-Tribenzyloxybenzene 40



Phloroglucinol dihydrate (0.32 g, 2 mmol) was dissolved in MeCN 15 mL and stirred with K_2CO_3 (4.14 g, 30 mmol) for 1 hour at reflux temperature and then added benzyl bromide (0.23 mL, 2 mmol). After 1 hour and the reaction was cooled down, 15 mL of water was added and the reaction mixture was neutralized with 10% HCl. The solution was extracted with CH_2Cl_2 (20 mL, 3 times). The organic layers were separated, combinded, dried with anh. Na_2SO_4 and removed solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/EtOAc) to give colorless needle crystals product (0.06 g, 13% yield). m.p. 80-83 ºC; IR (KBr, cm^{-1}): 3030 (=C-H st), 2863 (C-H st), 1601 (C=C st), 1451 and 1378 (C-H bend), 1159 (C-O st) (**Figure A.38**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 5.00 (s, 6H), 6.27 (s, 3H), 7.40 (m, 15H) (**Figure A.36**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 70.1, 94.8, 127.6, 127.9, 128.6, 136.8, 160.6 (**Figure A.37**); MS-H^+ (EtOAc): m/z = 397.32 (**Figure A.39**)

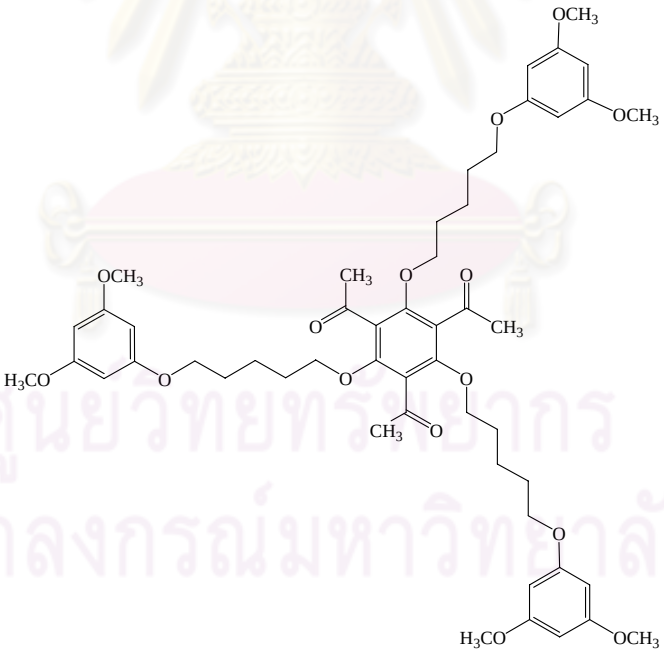
2.3.10 3,5-Dimethoxyphenol 43



1,3,5-Trimethoxybenzene (0.25 g, 1.5 mmol) was dissolved in 10 mL MeCN then NaI (0.33 g, 2.3 mmol) and TMSCl (0.29 mL, 2.3 mmol) were added. The

reaction was stirred at room temperature. After 5 days, the solvent was removed . The residue was dissolved in water and extracted with CH_2Cl_2 (20 mL, 3 times). The organic layers were separated, dried with anh. Na_2SO_4 and removed the solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/EtOAc) to give the yellow oil product (0.14g, 43%). The yield was excluding the recovered starting material (0.045 g, 55%). IR (KBr, cm^{-1}): 3387 (O-H st), 2944 (C-H st), 1602 (C=C st), 1464 and 1336 (C-H bend), 1154 (C-O st) (**Figure A.42**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.68 (s, 6H), 5.95 (s, 2H), 6.00 (s, 1H) (**Figure A.40**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 55.3, 93.0, 94.2, 157.4, 161.6 (**Figure A.41**); MS-H^+ (EtOAc): m/z = 155.05 (**Figure A.43**)

2.3.11 1,3,5-Triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy) benzene 44



3,5-Dimethoxyphenol **43** (0.19 g , 1.2 mmol) was dissolved in MeCN (10 mL) and stirred with K_2CO_3 (0.42 g, 3 mmol) for 1 hour. Then 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32** (0.14 g, 0.2 mmol) was added. The reaction was refluxed until no substrate was found by TLC monitoring (about 6 hours). The reaction was

cooled down, 15 mL of water was added and the reaction mixture was neutralized with 10% HCl. The solution was extracted with EtOAc (20 mL, 3 times). The organic layers were separated, combined dried with anh. Na_2SO_4 and removed the solvent. The concentrated crude product was purified by column chromatography (80:20 hexane/EtOAc) to give colorless oil product (0.13 g, 73 % yield). IR (KBr, cm^{-1}): 2943 (C-H st), 1705 (C=O st), 1602 (C=C st), 1468 and 1355 (C-H bend), 1198 and 1154 (C-O st) (**Figure A.46**); ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.50 (m, 6H), 1.69 (m, 6H), 1.77 (m, 6H), 2.52 (s, 9H), 3.76 (s, 18H), 3.84 (t, 6H) 3.91 (t, 6H), 6.07 (s, 9H) (**Figure A.44**); ^{13}C-NMR ($CDCl_3$): δ (ppm) = 22.3, 28.9, 29.7, 32.7, 55.3, 67.7, 77.6, 92.9, 93.3, 127.6, 154.2, 160.9, 161.5, 201.0 (**Figure A.45**); MS-H^+ (EtOAc): m/z = 920.67 (**Figure A.47**)

2.3.12 Demethylation of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxy phenoxy)pentyloxy)benzene 44

1,3,5-Triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy)benzene **44** (0.34 g, 0.3 mmol) was dissolved in 5 mL MeCN and stirred with $AlCl_3$ (0.38 g, 2.4 mmol). After 2 days, the reaction was then cooled down and the solvent was removed. The residue was dissolved in water, extracted with EtOAc (10 mL, 3 times). The organic layers were separated, combined, dried with anh. Na_2SO_4 and removed the solvent. The concentrated crude product was purified by column chromatography (30:70 MeOH/EtOAc) to give a yellow oil product (0.18 g).

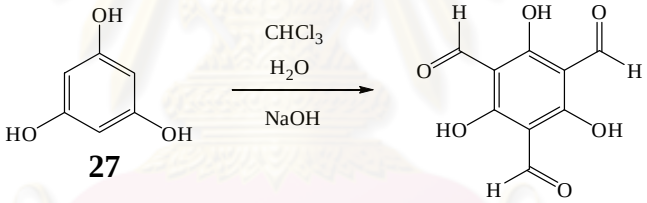
CHAPTER III

RESULTS AND DISCUSSION

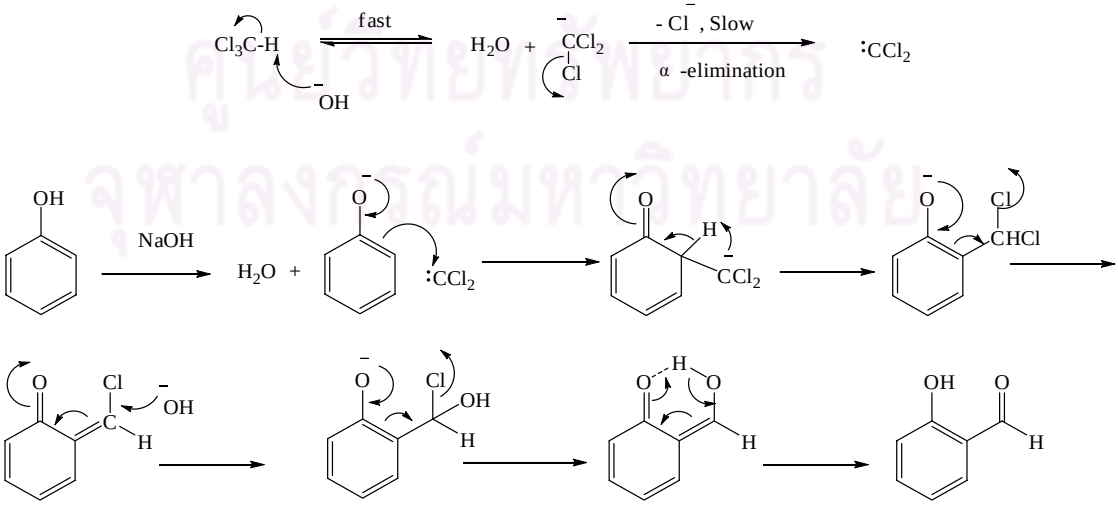
3.1 Synthesis of 1,3,5-trisubstituted-2,4,6-trihydroxybenzene

3.1.1 Synthesis of 1,3,5-triformyl-2,4,6-trihydroxybenzene 28

1,3,5-Triformyl-2,4,6-trihydroxybenzene **28** was synthesized through the Reimer-Tiemann reaction, the *ortho* formylation of phenols (**Scheme 3.1**) [38]. Sodium hydroxide was reacted with chloroform generating dichlorocarbene which then reacted at the *ortho*-position of phenolate anion. After basic hydrolysis, the desired product was formed (**Scheme 3.2**).



Scheme 3.1 Synthesis of 1,3,5-triformyl-2,4,6-trihydroxybenzene

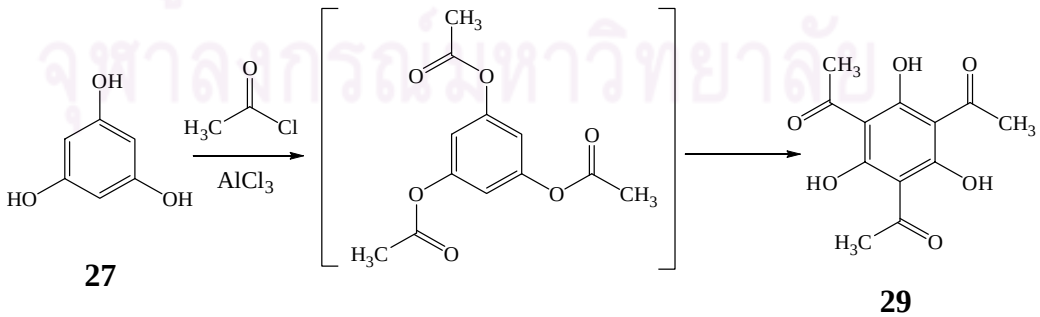


Scheme 3.2 The mechanism of Reimer-Tiemann reaction

In this work, the process was repeated three times. After a workup, the desired product **28** was obtained in 59% yield. ^{1}H NMR spectrum showed only two singlet peaks at δ 10.15 and 14.11 ppm in $CDCl_3$, assigned to aldehyde and phenolic protons, respectively (**Figure A.1** in Appendix). ^{13}C-NMR spectrum of compound **28** correctly revealed the 3 different types of carbon that substantiated the compound **28** (**Figure A.2** in Appendix). The IR spectrum showed O-H stretching of compound **28** at 3343 cm^{-1} (**Figure A.3** in Appendix). The molecular weight was confirmed by mass spectrometry showing the molecular ion peak at 209.07 m/z (**Figure A.4** in Appendix). However, compound **28** was found to be relatively unstable. Oxidation of compound **28** could have readily happened yielding an unidentified solid that could not be solubilized in any solvents but aqueous hydroxide. This solid was assumed to be the tricarboxylic acid. Since compound **28** was not stable enough to be used further and the oxidized by-product could not be confirmed and made soluble, this potential core structure **28** was not further pursued in the later steps of synthesis.

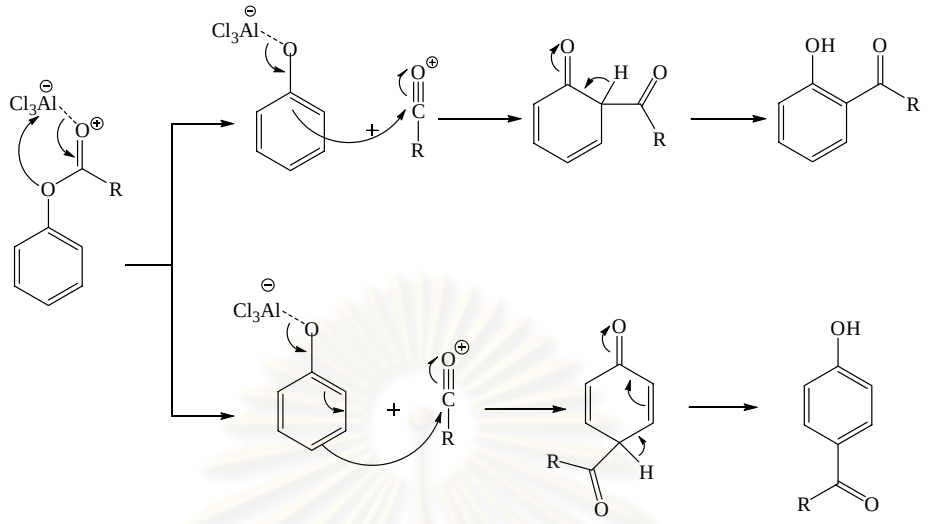
3.1.2 Synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene 29

The synthesis of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29** was done through triple *O*-acylations between phloroglucinol **27** and excess of acetyl chloride at its reflux temperature (**Scheme 3.3**). The triester intermediate underwent Fries rearrangement in situ to the tris-*ortho* or *para*-positins upon treatment of about five equivalents of anhydrous $AlCl_3$. The desired product **29** could be synthesized in 85% yield. The mechanism of this rearrangement is shown in **Scheme 3.4**.



27 **29**

Scheme 3.3 Synthesis of hexasubstituted benzene from phloroglucinol



Scheme 3.4 Mechanism of the Fries rearrangement of acyloxybenzene to hydroxy alkanophenone derivatives

From ^{1}H-NMR spectrum analysis, the signal of phenolic protons of compound **29** appeared as a singlet at δ 17.16 ppm (lit. 17.09 ppm [39], **Figure A.5** in Appendix) indicating that the molecule was not arranged in an *ababab* geometric pattern. It was perhaps assumed to be relatively flat platform with strong three intramolecular hydrogen bonds of all the three *ortho*-hydroxy groups to the adjacent carbonyl groups of the acyl aromatics (**Figure 3.1**). Similarly compound **28** showed their proton signals of the phenolic groups at relatively downfield chemical shift due to the analogous intramolecular hydrogen bonds, although at perhaps weaker strength at δ 14.11 ppm (lit. 14.1 ppm [40]). ^{13}C-NMR spectrum of compound **29** correctly revealed the 4 different types of carbon that substantiated the compound **29** (**Figure A.6** in Appendix). The IR spectrum showed O-H stretching of compound **28** at 3433 cm^{-1} (**Figure A.7** in Appendix). Mass spectrum of compound **29** confirmed the expected molecular weight showing the molecular ion peak at 252.98 m/z (**Figure A.8** in Appendix).

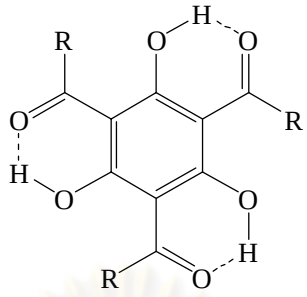
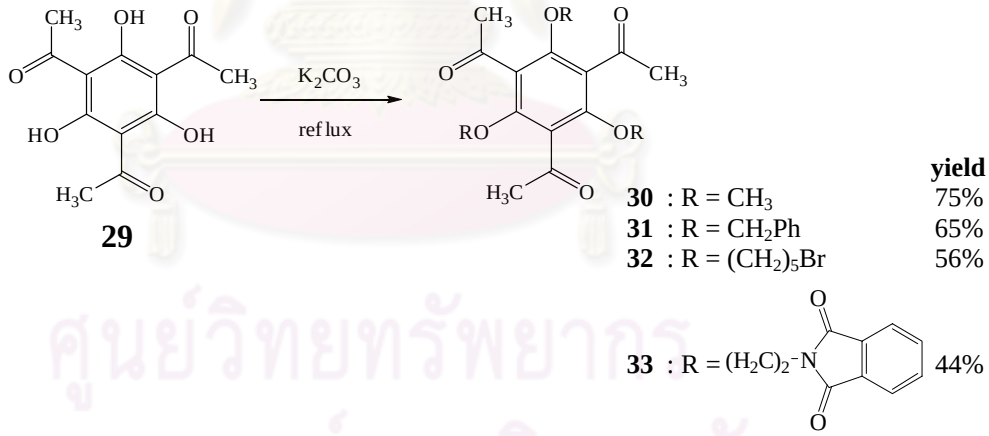


Figure 3.1 Intramolecular hydrogen bonds of the *ortho*-hydroxy acyl aromatics

3.2 Functionalization of 1,3,5-triacetyl-2,4,6-trihydroxybenzene

1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** was functionalized on the phenolic hydroxyl groups by alkylation reactions in order to be modified into the *ababab* geometry. Four syntheses of this type of derivatives were accomplished using dimethyl sulfate, benzyl bromide, 1,5-dibromopentane or *N*-(2-bromoethyl) phthalimide as the alkylating agent in basic condition (**Scheme 3.5**).



Scheme 3.5 Functionalization of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29** at phenolic hydroxyl groups

3.2.1 Synthesis of 1,3,5-triacetyl-2,4,6-trimethoxybenzene 30

Compound **29** was trimethylated using dimethyl sulfate in basic condition to provide 1,3,5-triacetyl-2,4,6-trimethoxybenzene **30**. The desired product was obtained as white powder in 75% yield. ^{1}H NMR spectrum of compound **30** showed singlet protons of methyl and methoxy protons at δ 2.54 and 3.74 ppm, respectively (**Figure**

A.9 in Appendix). ^{13}C-NMR spectrum of compound **30** correctly revealed the 5 different types of carbon that substantiated the compound **30** (**Figure A.10** in Appendix). Mass spectrum showed the corresponding molecular ion peak at 295.16 m/z (**Figure A.12** in Appendix), which confirmed the molecular weight of compound **30**.

3.2.2 Synthesis of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene 31

1,3,5-Triacetyl-2,4,6-tribenzyloxybenzene **31** was generated from the reaction of compound **29** and benzyl bromide in basic condition. After a workup, the mixture of compound **31**, benzyl alcohol and remaining benzyl bromide could be separated easily by rinsing off the benzyl alcohol by-product and remaining benzyl bromide by hexane. However, small part of compound **31** might be lost by the rinse. Compound **31** was recrystalized by 3:7 CH_2Cl_2/EtOH in 65% yield. ^{1}H-NMR spectrum showed singlet signals of methyl, benzyl protons and multiplet signals of aromatic protons at δ 2.46, 4.91 and 7.35 ppm (**Figure A.13** in Appendix), respectively. ^{13}C-NMR spectrum of compound **31** correctly revealed the 9 different types of carbon that substantiated the compound **31** (**Figure A.14** in Appendix). Mass spectrum of compound **31** confirmed the molecular weight showing molecular ion peak at 523.20 m/z (**Figure A.16** in Appendix).

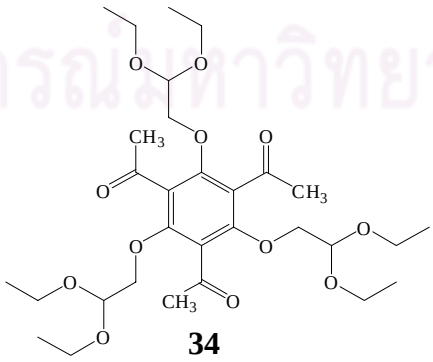
3.2.3 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene 32

O-alkylations of compound **29** with 1,5-dibromopentane in basic condition obtained 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32** in 56% yield after purification by column chromatography [16]. From ^{1}H-NMR spectrum, the signal of methyl protons appeared at δ 2.52 ppm while those of the five methylene groups in the alkyl chain appeared at δ 1.48, 1.62, 1.86, 3.40 and 3.82 ppm (**Figure A.17** in Appendix). ^{13}C-NMR spectrum of compound **32** correctly revealed the 9 different types of carbon that substantiated the compound **32** (**Figure A.18** in Appendix). Mass spectrum of compound **32** confirmed the molecular weight showing molecular ion peak at 699.26 m/z (**Figure A.20** in Appendix).

3.2.4 Synthesis of 1,3,5-triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy) benzene 33

Compound **29** was reacted with *N*-(2-bromoethyl)phthalimide in basic condition to provide 1,3,5-triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy) benzene **33**. The desired product was obtained as colorless needle crystals in 44% yield. From ^{1}H-NMR spectrum, the signal of methyl protons appeared at δ 1.95 ppm while those of the two methylene groups in the alkyl chain appeared at δ 3.88, 4.24 ppm and multiplet signals of aromatic protons at δ 7.66 and 7.78 ppm (**Figure A.21** in Appendix). ^{13}C-NMR spectrum of compound **33** showed 8 different types of carbon that mostly corresponded to compound **33**, however, the signals of the acetyl carbonyl carbons and one type of quaternary carbons were missing from the spectrum. It was possible that the first missing signal might coincidently overlap with the signal of the carbonyl carbons of the phthalimide groups at δ 170.8 ppm which the other one might be under the $CDCl_3$ solvent signals at δ 77.0 ppm (**Figure A.22** in Appendix). ^{1}H-NMR characterizations of compounds **30**, **31**, **32** and **33** all confirmed the symmetric structures of these products.

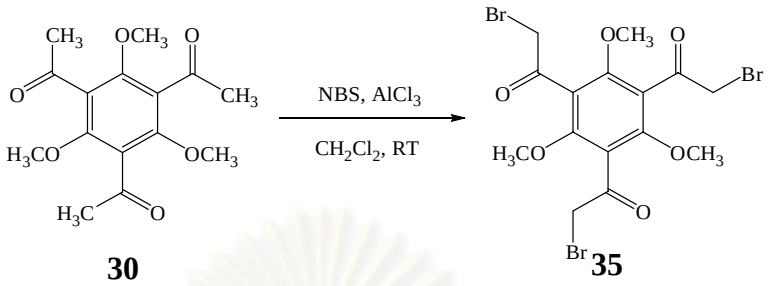
Preparation of compound **34** has been attempted using similar condition from the synthesis of compound **33** with α-bromoacetaldehyde diethylacetal as the reagent. Unfortunately, the reaction was not successful. Only starting material was recovered. Various conditions were tried including performing the reactions with other bases such as K_2CO_3 and NaH; or using other solvents such as THF and DMF. Nevertheless, no recation was yet observed in all cases.



34

Figure 3.2 The expected structure of compound **34**

3.3 α-Bromination of 1,3,5-triacetyl-2,4,6-trimethoxybenzene



30 **35**

Scheme 3.6 Synthesis of 1,3,5-tris(bromoacetyl)-2,4,6-trimethoxybenzene **35**

Compound **30** was brominated using *N*-bromosuccinimide (NBS) catalysed by $AlCl_3$ under N_2 at room **(Scheme 3.6)**. 1,3,5-Tris(α-bromoacetyl)-2,4,6-trimethoxy benzene **35** was obtained in 17% yield which 30% recovered starting material. ^{1}H NMR showed singlet protons of methoxy and methylene protons at 3.75 and 4.31, respectively (**Figure A.24** in Appendix). ^{13}C-NMR spectrum of compound **35** correctly revealed the 5 different types of carbon that substantiated the compound **35** (**Figure A.25** in Appendix). Mass spectrum of compound **35** confirmed the molecular weight showing molecular ion peak at 531.13 m/z (**Figure A.27** in Appendix). However, The major product of reaction was brominated three times at the same α-carbon obtained 1,3-diacetyl-5-(tribromoacetyl)-2,4,6-trimethoxybenzene **36** as product in 40% yield (**Figure 3.3**).

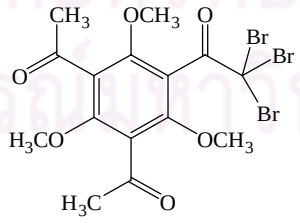
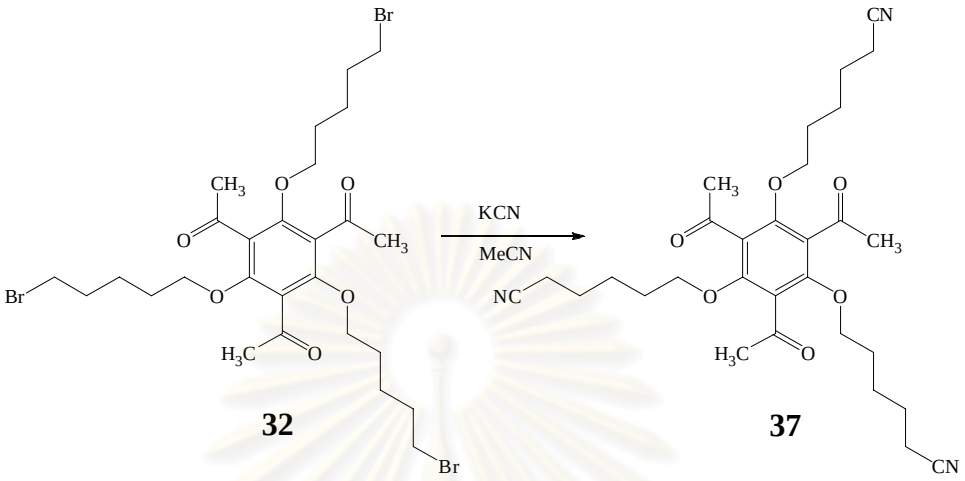


Figure 3.3 Structure of 1,3-diacetyl-5-(tribromoacetyl)-2,4,6-trimethoxybenzene **36**

3.4 Functionalization of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene

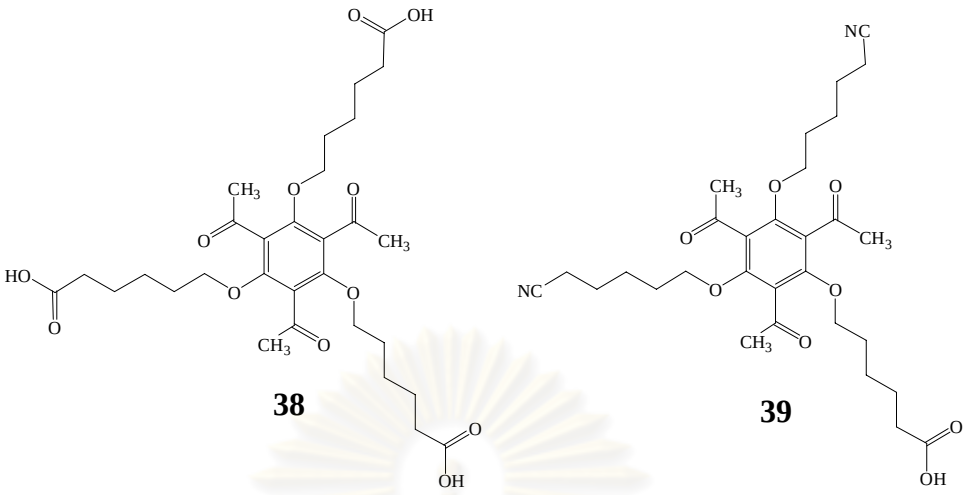


32 **37**

Scheme 3.7 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37**

1,3,5-Triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37** was generated from compound **32** and KCN at reflux temperature. The assumed intermediates with mono-substitution and disubstitution with cyano groups could be detected by TLC monitoring during the reaction time (about 10 days). After a workup, compound **37** was obtained in 99% yield. From ^{1}H-NMR spectrum, the signal of the methyl protons appeared at δ 2.51 ppm and the signals of the five methylene protons of the of alkyl chain of compound **37** appeared at δ 1.48, 1.64, 2.35, 3.82 ppm (**Figure A.28** in Appendix). ^{13}C-NMR spectrum of compound **37** correctly revealed the 10 different types of carbon that substantiated the compound **37** (**Figure A.29** in Appendix). IR spectrum showed C≡N stretching of compound **37** at 2244 cm^{-1} (**Figure A.30** in Appendix). Mass spectrum of compound **37** confirmed the molecular weight showing molecular ion peak at 560.30 m/z (**Figure A.31** in Appendix).

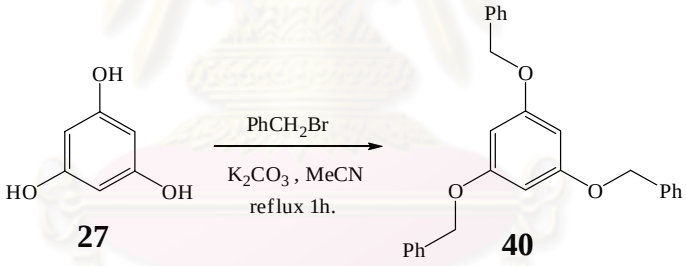
Hydrolysis of compound **37** to tricarboxylic acid **38 (Figure 3.4)** had been attempted. Using 10% HCl in 1,4-dioxane, the substrate was partially hydrolyzed at only one of the nitrile groups (**Figure 3.4**) giving the monocarboxylic acid **39** in 25% yield excluding the 67% of the recovered starting material (**Figure A.32-34** in Appendix) . Mass spectrum confirmed the molecular weight showing the molecular ion peak at 555.52 m/z (**Figure A.35** in Appendix).



38 **39**

Figure 3.4 The desired tricarboxylic acid product **38** and structure of 6-(2´,4´,6´-triacetyl-3´,5´-bis(5´´-cyanopentyloxy)phenoxy)hexanoic acid **39**

3.5 Synthesis of 1,3,5-tribenzyloxyphloroglucinol 40

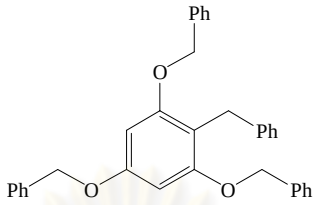


27 **40**

Scheme 3.8 Synthesis of 1,3,5-tribenzyloxyphloroglucinol **40**

In an attempt to partially protect the phenolic groups, phloroglucinol **27** was benzylated with benzyl bromide in basic condition at reflux temperature for 1 h. (**Scheme 3.8**). 1,3,5-Tribenzyloxyphloroglucinol **40** was obtained in only 13% yield. ^{1}H-NMR spectrum showed the singlet protons of benzyl, the central benzene and mutiplet signals of the remaining aromatic protons at δ 5.00, 6.27 and 7.40 ppm, respectively (**Figure A.36** in Appendix). ^{13}C-NMR spectrum of compound **40** correctly revealed the 7 different types of carbon that substantiated the compound **40** (**Figure A.37** in Appendix). Mass spectrum confirmed the molecular weight showing the molecular ion peak at 397.32 m/z (**Figure A.39** in Appendix). The major by-

product from the reaction was compound **41** derived from the overbenzylation on the central benzene ring of compound **40** (**Figure 3.5**).

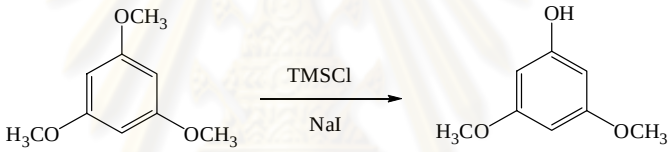


41

Figure 3.5 Structure of the tetrabenzylated compound **41**

3.6 The first generation of poly(alkyl aryl ether) dendrimer

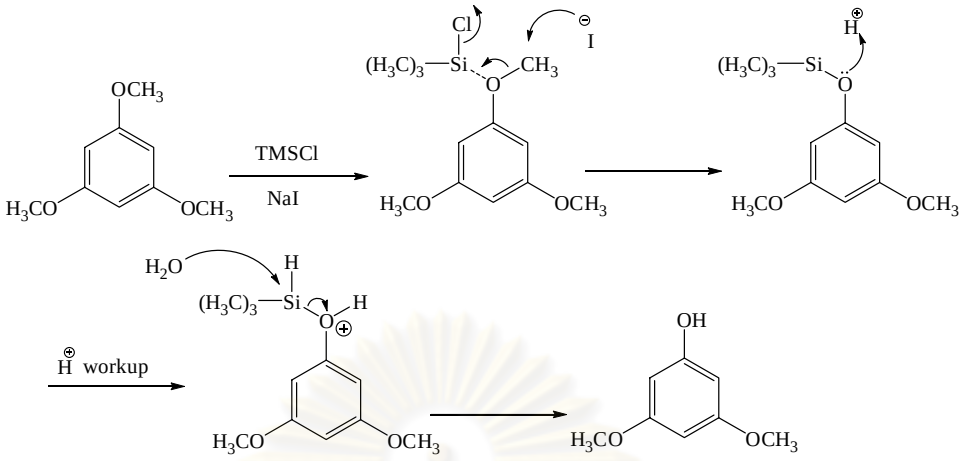
3.6.1 Synthesis of 3,5-dimethoxyphenol 43



42 **43**

Scheme 3.9 Synthesis of 3,5-dimethoxyphenol **43**

1,3,5-Trimethoxybenzene **42** was monodemethylated by trimethylsilyl chloride (TMSCl) and NaI at room temperature (**Scheme 3.9**). The desired product was obtained in 43% yield excluding 55% of the recovered starting material. ^{1}H-NMR spectrum showed the signals at δ 3.68, 5.95 and 6.00 ppm, which were assigned to the methoxy, *ortho*- and *para*- protons of the phenol ring, respectively (**Figure A.40** in Appendix), ^{13}C-NMR spectrum of compound **43** correctly revealed the 5 different types of carbon that substantiated the compound **43** (**Figure A.41** in Appendix). IR spectrum showed O-H stretching of compound **43** at 3387 cm^{-1} (**Figure A.42** in Appendix). Mass spectrum of compound **43** confirmed the molecular weight showing molecular ion peak at 155.06 m/z (**Figure A.43** in Appendix). The mechanism of the demethylation reaction could be depicted in **Scheme 3.10**.



Scheme 3.10 Mechanism of demethylation of 1,3,5-trimethoxybenzene

3.6.2 Synthesis of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy) pentyloxy)benzene 44

The tribromo compound **32** was reacted with 3,5-dimethoxyphenol **43** in basic condition at reflux temperature**.** The desired product was obtained after purified by column chromatography in 73% yield. ^{1}H-NMR spectrum (**Figure A.44** in Appendix) of compound **44** confirmed a symmetric structure of the desired product indicating the molecule arrangement of the expected *ababab* geometric pattern (**Figure 3.6**). ^{13}C-NMR spectrum of compound **44** correctly revealed the 14 different types of carbon that substantiated the compound **44** (**Figure A.45** in Appendix). MALDI-TOF-MS spectrum confirmed the molecular weight showing the molecular ion peak at 920.67 m/z (**Figure A.47** in Appendix).

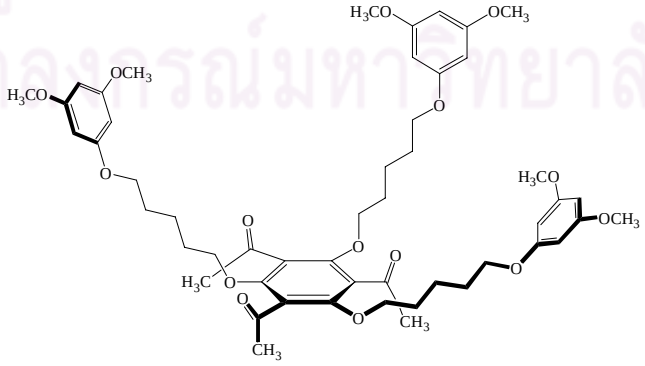


Figure 3.6 The *ababab* geometry of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxy phenoxy)pentyloxy)benzene **44**

3.6.3 Attempted demethylations of compound 44

Table 3.1 Conditions for the demethylations of compound **44**

Entry	Conditions	Results
1	7 eq. TMSCl, 7 eq. NaI, MeCN,	Lose its acetyl groups
2	7 eq. LiCl, 7 eq. NaI, 1,2-dichloroethane	Partial demethylation
3	7 eq. $FeCl_3$, 7 eq. NaI, 1,2-dichloroethane	Partial demethylation
4	10 eq. $AlCl_3$, MeCN [41]	mixed products of the monomethoxy, dimethoxy, the expected compound **45** and unidentified compounds

Demethylations of compound **44** toward the first generation of poly(alkyl aryl ether) dendrimer have been attempted. In entry 1 **Table 3.1**, TMSCl and NaI were used to remove the methyl of methoxy groups. However, only the product from compound **44** losing three of its acetyl groups was observed. From ^{1}H-NMR spectrum of product obtained from this condition, the signal of acetyl groups at δ 2.6 ppm disappeared (**Figure A.48** in Appendix). In entry 2, LiCl was used as the Lewis acid catalyst. ^{1}H-NMR spectrum of the product obtained from this condition showed a singlet signal of methoxy protons at δ 3.7 ppm and the splitted terminal aromatic protons at δ 6.00, 6.05 and 6.06 ppm indicated the partial demethylation of compound **44** (**Figure A.49** in Appendix). Similarly in the case of $FeCl_3$ and NaI in entry 3, ^{1}H-NMR spectrum of the resulted product showed a singlet signal of methoxy protons at δ 3.8 ppm and of the splitted terminal aromatic protons at δ 6.00, 6.06, 6.08, 6.10 and 6.11 ppm indicated the partial demethylation of compound **44 (Figure A.50** in Appendix). In entry 4, the condition was modified to use the $AlCl_3$ and MeCN following the procedure by Moher [41]. The obtained crude liquid could only be dissolved in highly polar solvents such as MeOH. The product was highly polar and could not be purified by column chromatography. ^{1}H-NMR spectrum of this product (**Figure A.51** in Appendix) showed complicated signals of the protons of the still remaining methoxy and two methylene groups at δ 3.5-4.2 ppm, complicated signals

of the protons of the periphery aromatic rings at δ 5.9-6.3 ppm and complicated signals of the protons of acetyl at δ 2.2-2.7 ppm. ^{13}C-NMR spectrum showed two signals of the carbon of methoxy groups at δ 56.2 ppm and complicated signals of the carbon of the periphery aromatic rings at 91 and 157-162 ppm (**Figure A.52** in Appendix). From ^{1}H-NMR and ^{13}C-NMR analysis, this product was postulated to be mixed products of monomethoxy, dimethoxy, the expected fully demethylated compound **45** and perhaps other compounds that could not yet be identified. Mass spectrum (**Figure A.54** in Appendix) of this mixture showed an ion peak at 779.85 m/z that did not match with any related compounds except the proposed structure of the fragment **46** derived from compound **45** (**Figure 3.7**). If this result held true, it's possible that longer reaction time might be able to completely demethylate the remaining methoxy groups and yield the desired product **45**.

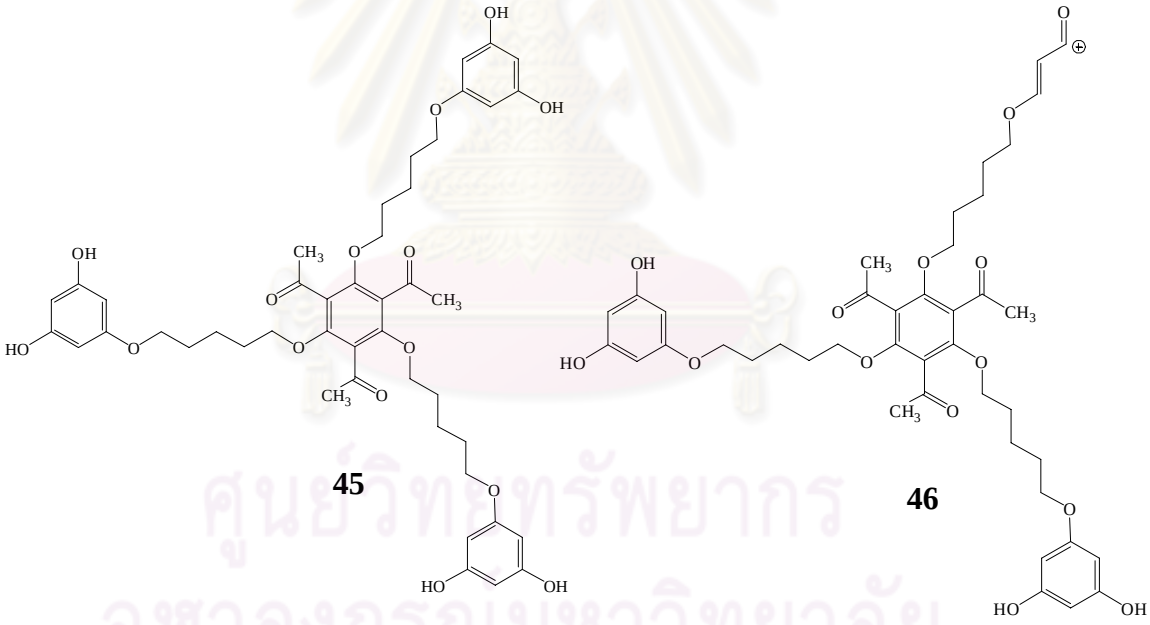


Figure 3.7 The expected product 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dihydroxy phenoxy)pentyloxy)benzene **45** and the structure of the possible major fragment **46** found in Mass spectrum

CHAPTER IV

CONCLUSION

The synthesis of 1,3,5-triformyl-2,4,6-trihydroxybenzene **28** was successfully carried out through Reimer-Tiemann reaction. Mixture of sodium hydroxide and chloroform generated dichlorocarbene to react with phloroglucinol to give the desired product after hydrolysis in 59% yield. 1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** was synthesized by using phloroglucinol reacting with acetyl chloride as the electrophilic reagent and medium. The reaction presumably went through triple *O*-acylation and then Fries rearrangement to become the targeted molecule upon treatment with $AlCl_3$. The signals of the phenolic protons of compounds **28** and **29** in ^{1}H-NMR spectra appeared as singlets at unusually downfield chemical shifts indicating that the molecules were not arranged in *ababab* geometry, but were relatively flat induced by three strong intramolecular hydrogen bonds between the hydroxy groups and the adjacent carbonyl groups.

1,3,5-Triacetyl-2,4,6-trihydroxybenzene **29** was modified into the *ababab* geometry by functionalization to various derivatives. The reactions of *O*-alkylations were found to occur yielding compounds **30, 31**, **32** and **33** under basic condition using acetonitrile as the solvent. Compound **29** was methylated by dimethyl sulfate to provide the symmetric structure compound **30** in 75% yield. Compound **30** was further brominated with NBS at α-carbon atoms providing the desired tribromo product **35** in 17% yield. However, the major product of the reaction was the compound that was brominated three times at the same α-carbon **36**. The reaction of compound **29** with benzyl bromide provided a symmetric compound **31** in 65% yield. *O*-alkylations of compound **29** with 1,5-dibromopentane obtained the tribromo product **32** in 56% yield. Compound **29** was reacted with *N*-(2-bromoethyl)phthalimide providing the desired product **33** in 44% yield. Reaction of compound **32** with KCN provided compound **37** in 99% yield. Unfortunately,

attempted hydrolysis of compound **37** by 10% HCl in 1,4-dioxane hydrolyzed only one of the nitrile groups to provide monocarboxylic acid **39** in 25% yield.

Phloroglucinol was benzylated with benzyl bromide in basic condition to provide 1,3,5-tribenzyloxyphloroglucinol **40** in 13% yield. The major by-product from the reaction was compound **41** derived from the overbenzylation on the central benzene ring of compound **40**.

Partial demethylation of 1,3,5-trimethoxybenzene with TMSCl in acetonitrile was provided 3,5-dimethoxyphenol **43** in 43% yield. The reaction of the tribromo compound **32** with compound **43** under basic condition in acetonitrile was provided the desired product **44** in 73% yield. Attempted demethylations of compound **44** using TMSCl reagent were not successful. Only the deaceylation of the substrate was observed. In the case of LiCl, and $FeCl_3$ and $AlCl_3$, the products of these incomplete reactions were only partially demethylated.

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APPENDIX

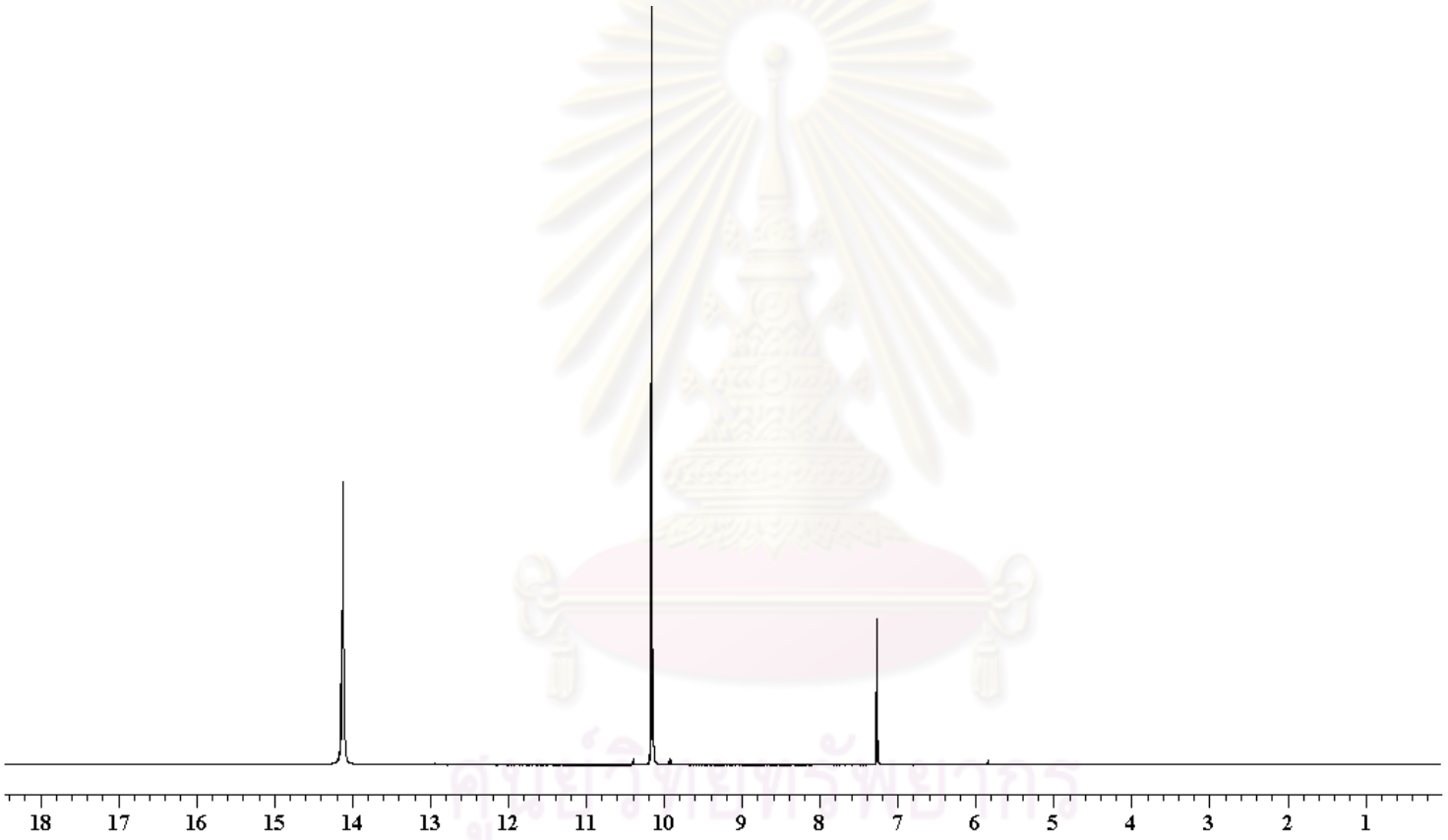

Figure A.1 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triformyl-2,4,6-trihydroxybenzene **28**

54

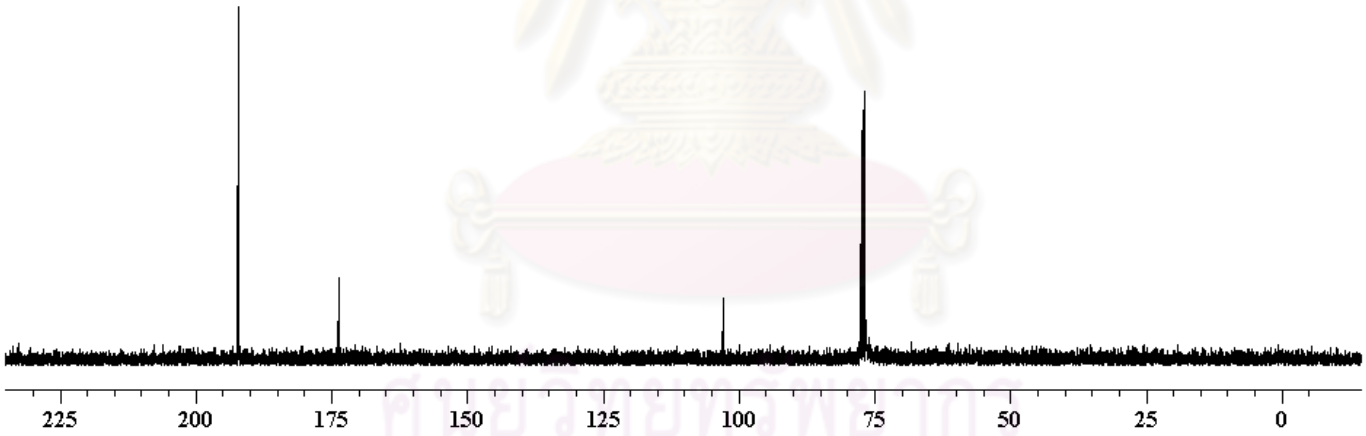

Figure A.2 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triformyl-2,4,6-trihydroxybenzene **28**

55

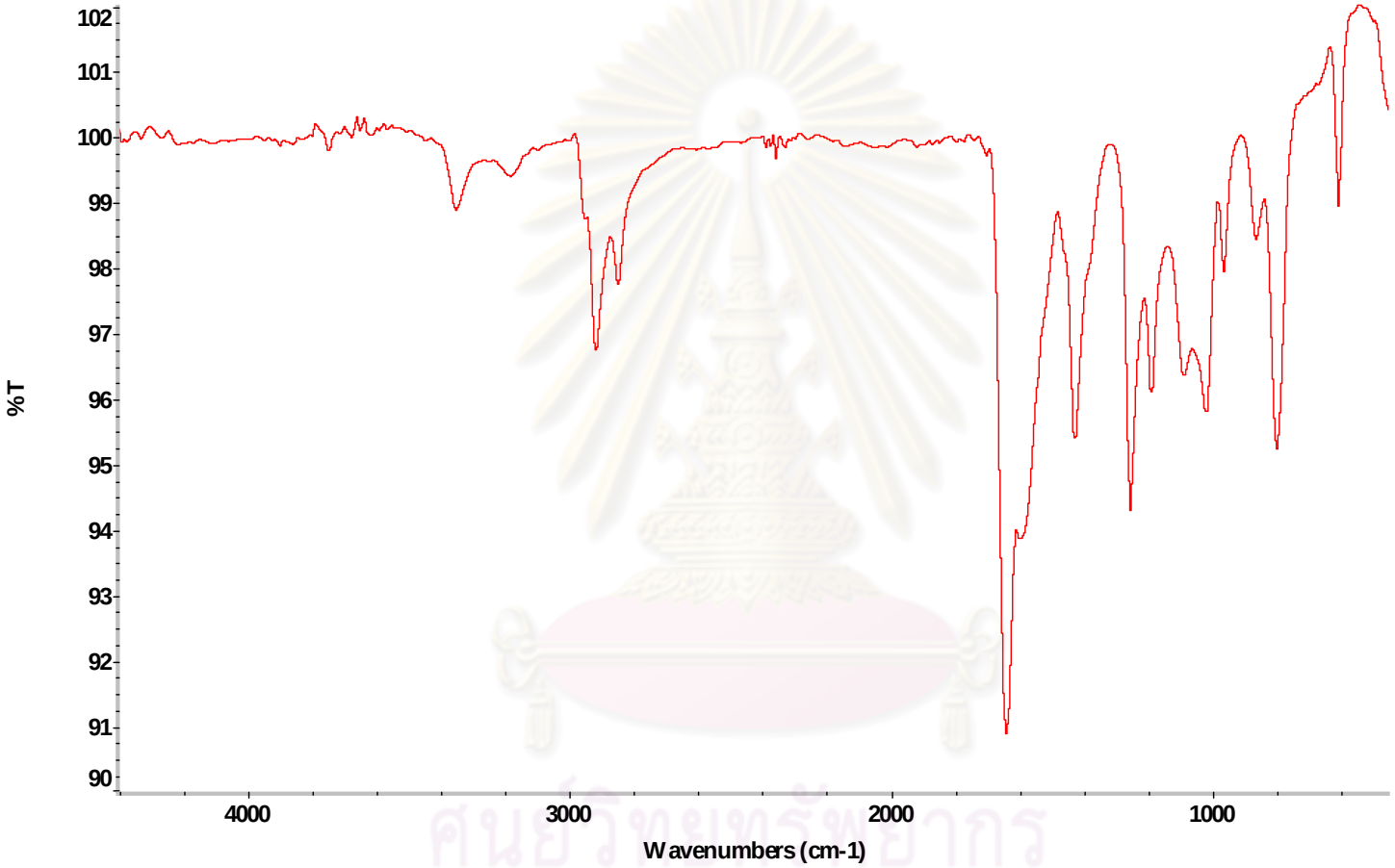

Figure A.3 IR (KBr) spectrum of 1,3,5-triformyl-2,4,6-trihydroxybenzene **28**

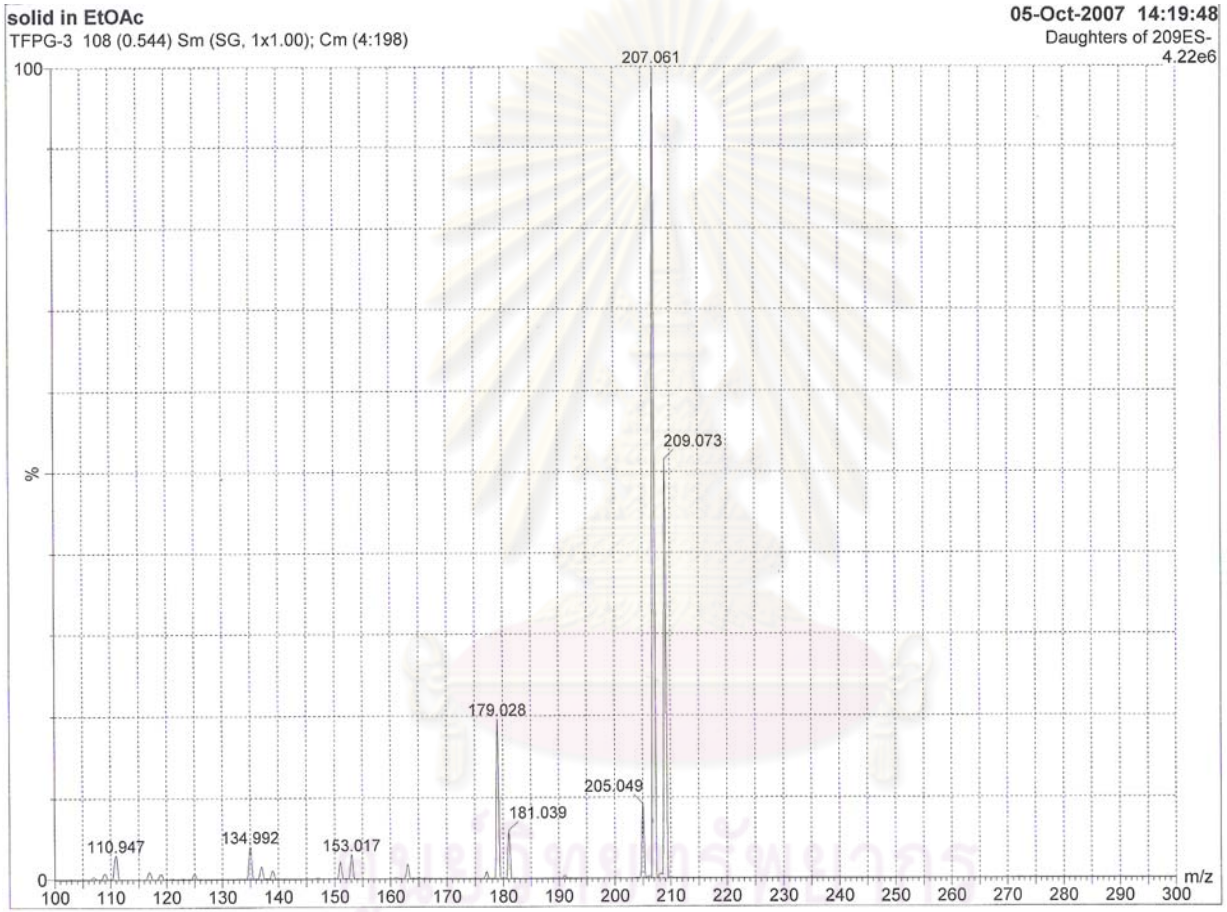

Figure A.4 Mass spectrum of 1,3,5-triformyl-2,4,6-trihydroxybenzene **28**

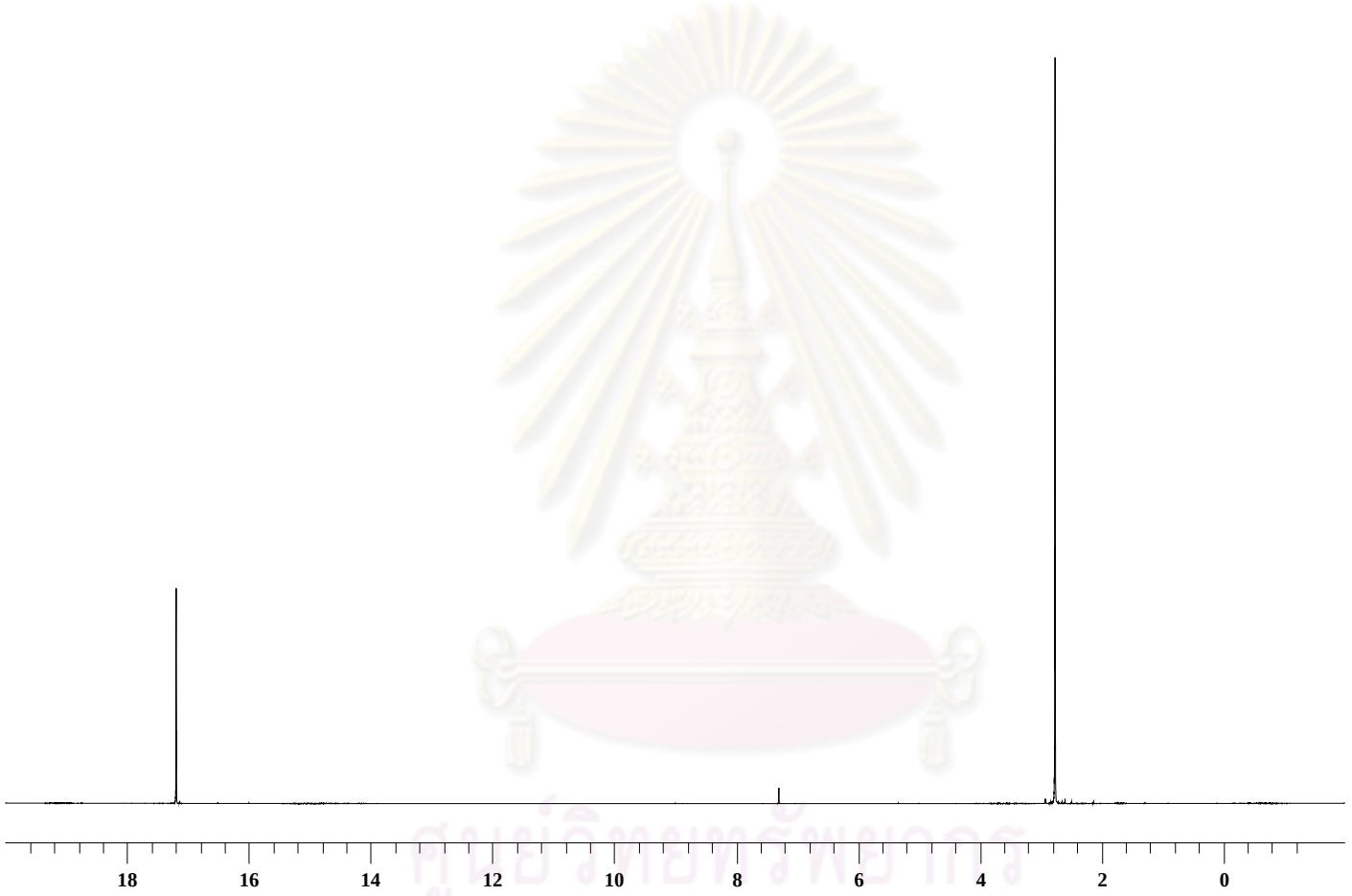

Figure A.5 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29**

58

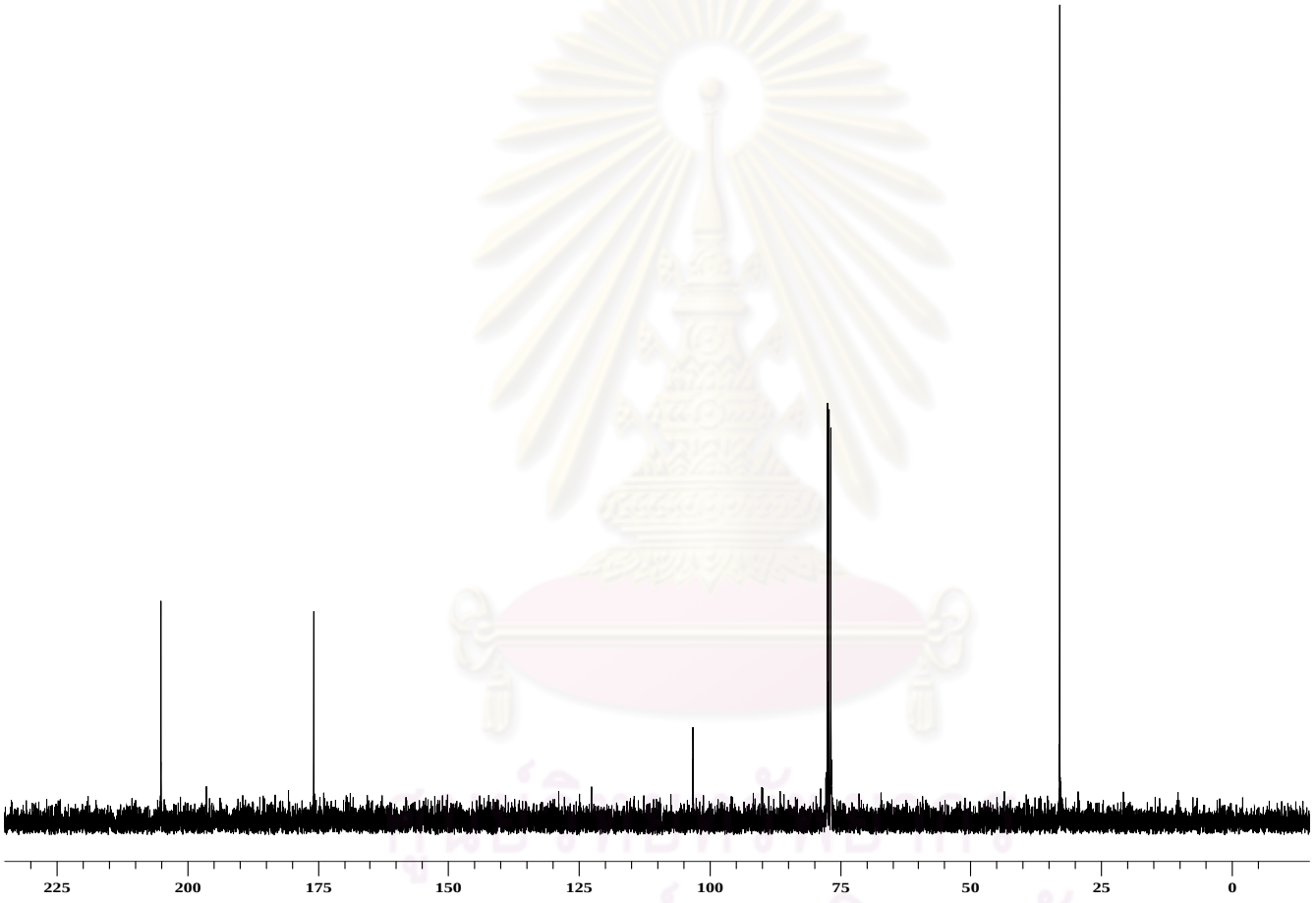

Figure A.6 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29**

59

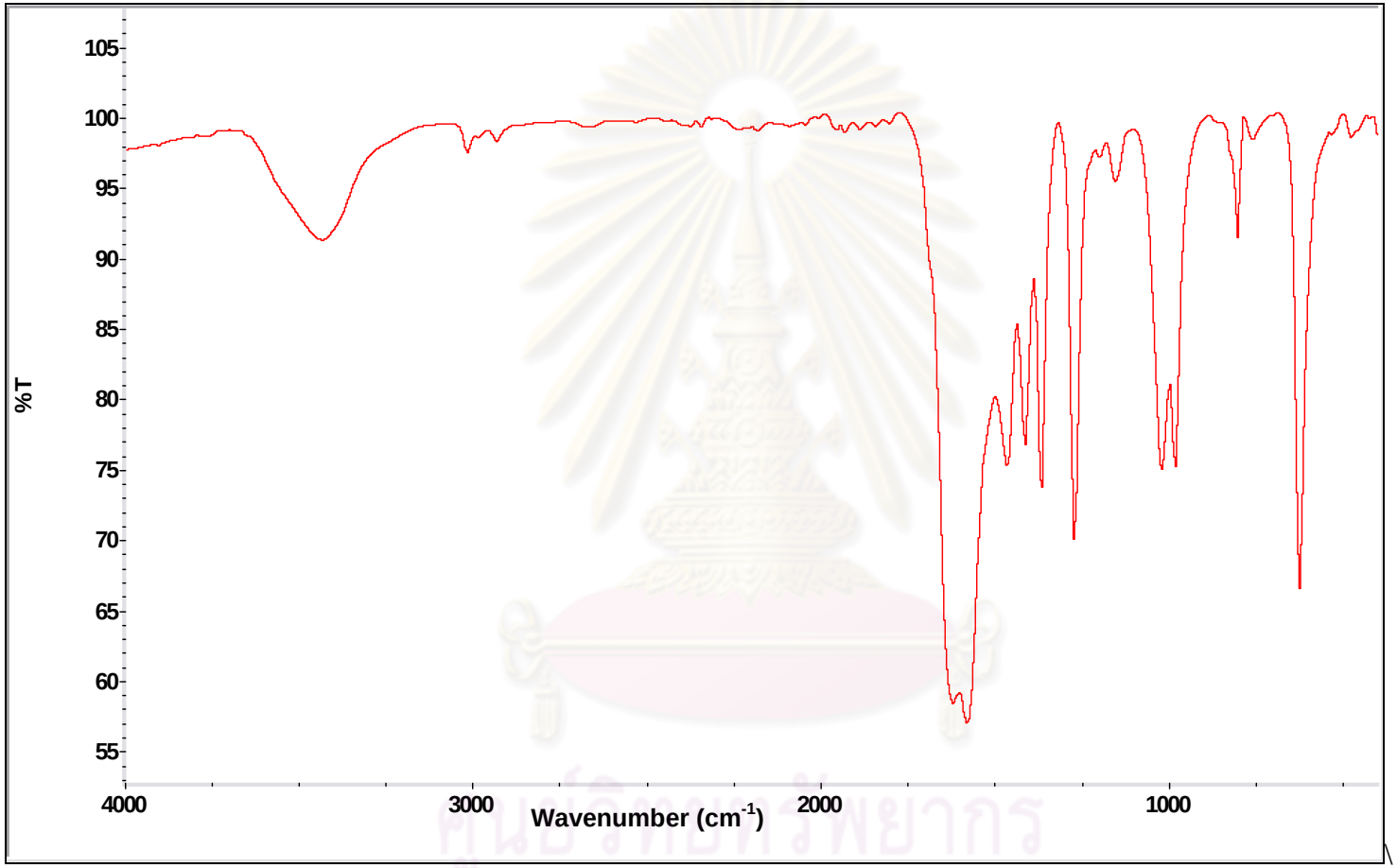

Figure A.7 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29**

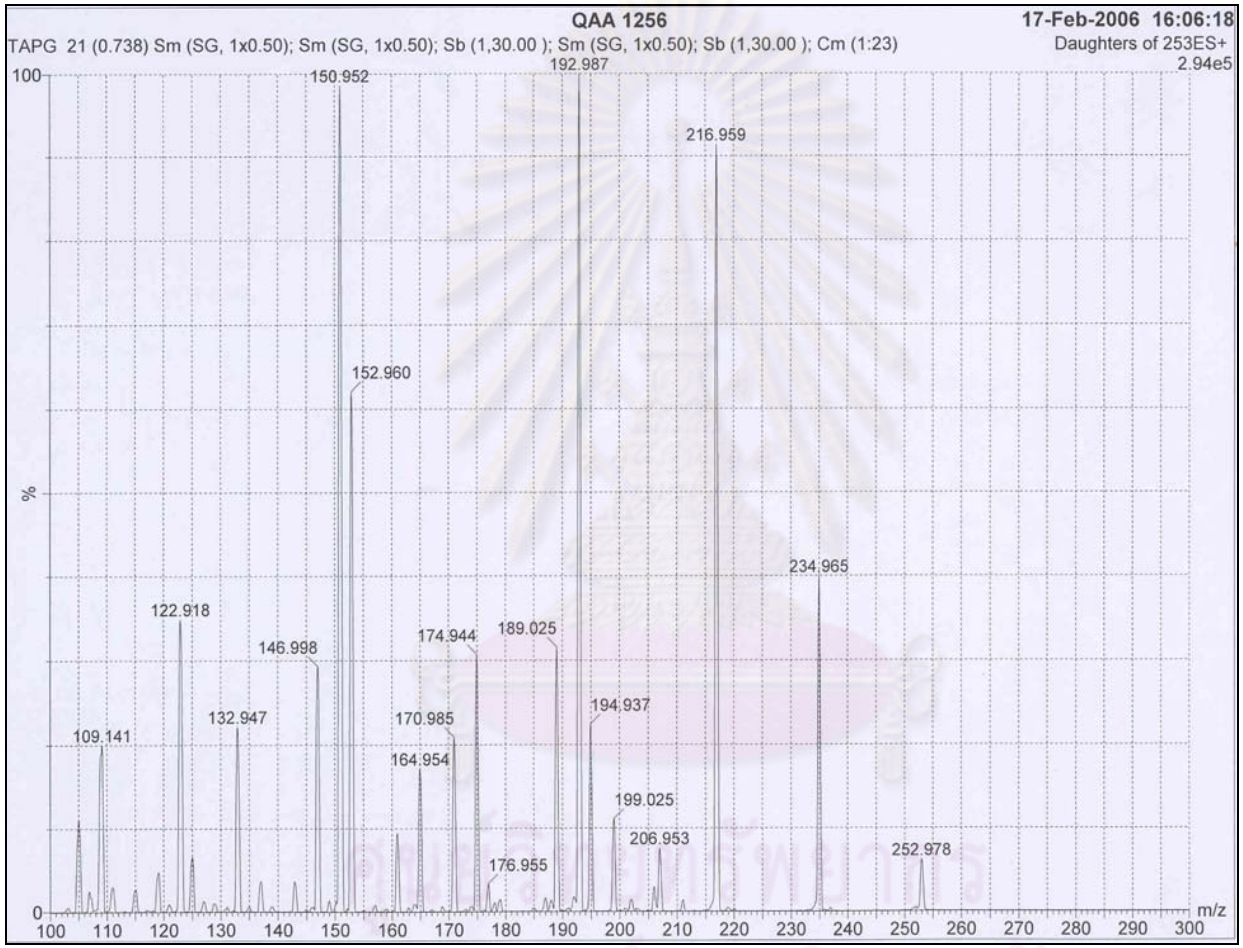

Figure A.8 Mass spectrum of 1,3,5-triacetyl-2,4,6-trihydroxybenzene **29**

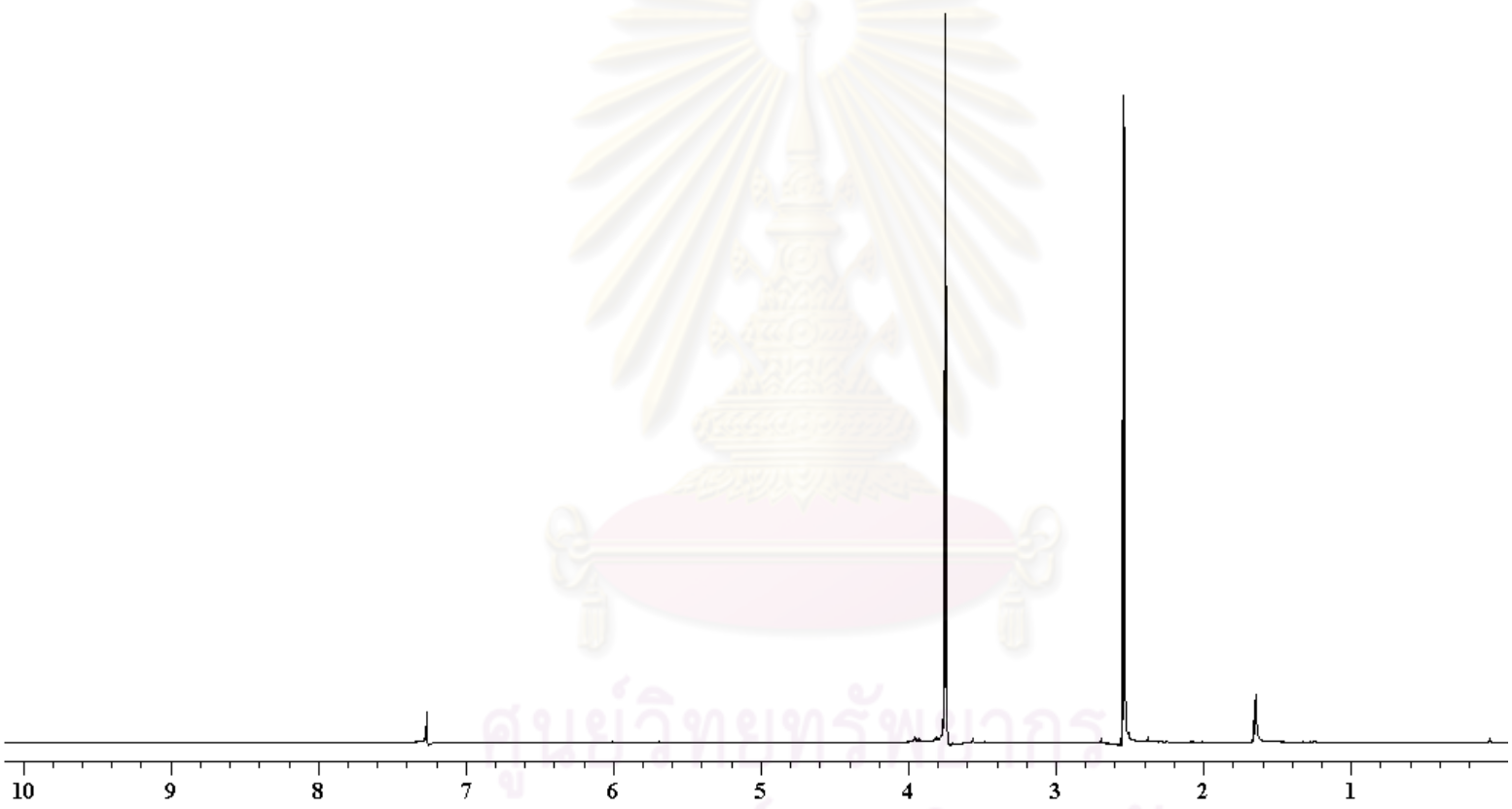

Figure A.9 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-trimethoxybenzene **30**

62

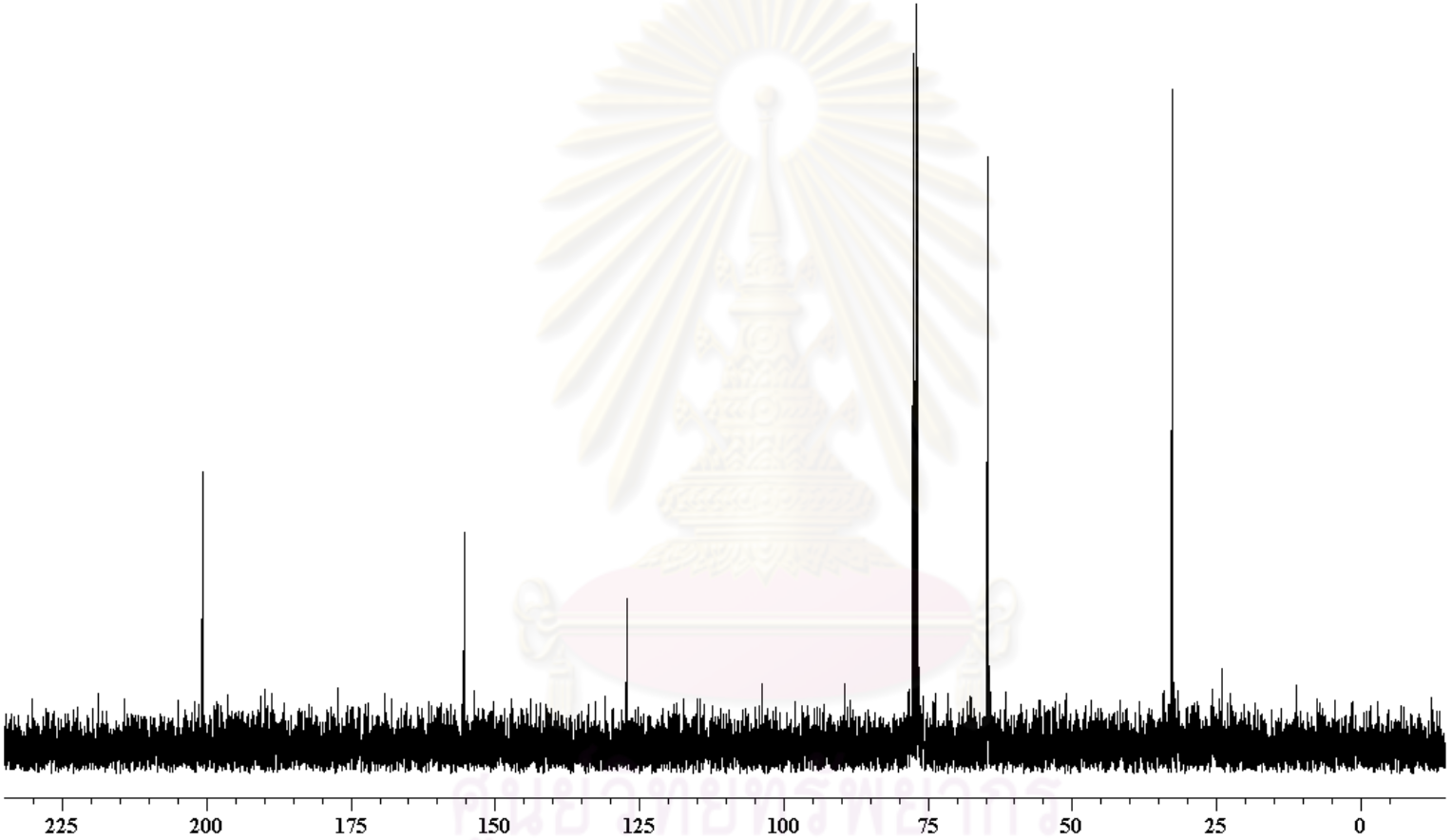

Figure A.10 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-trimethoxybenzene **30**

63

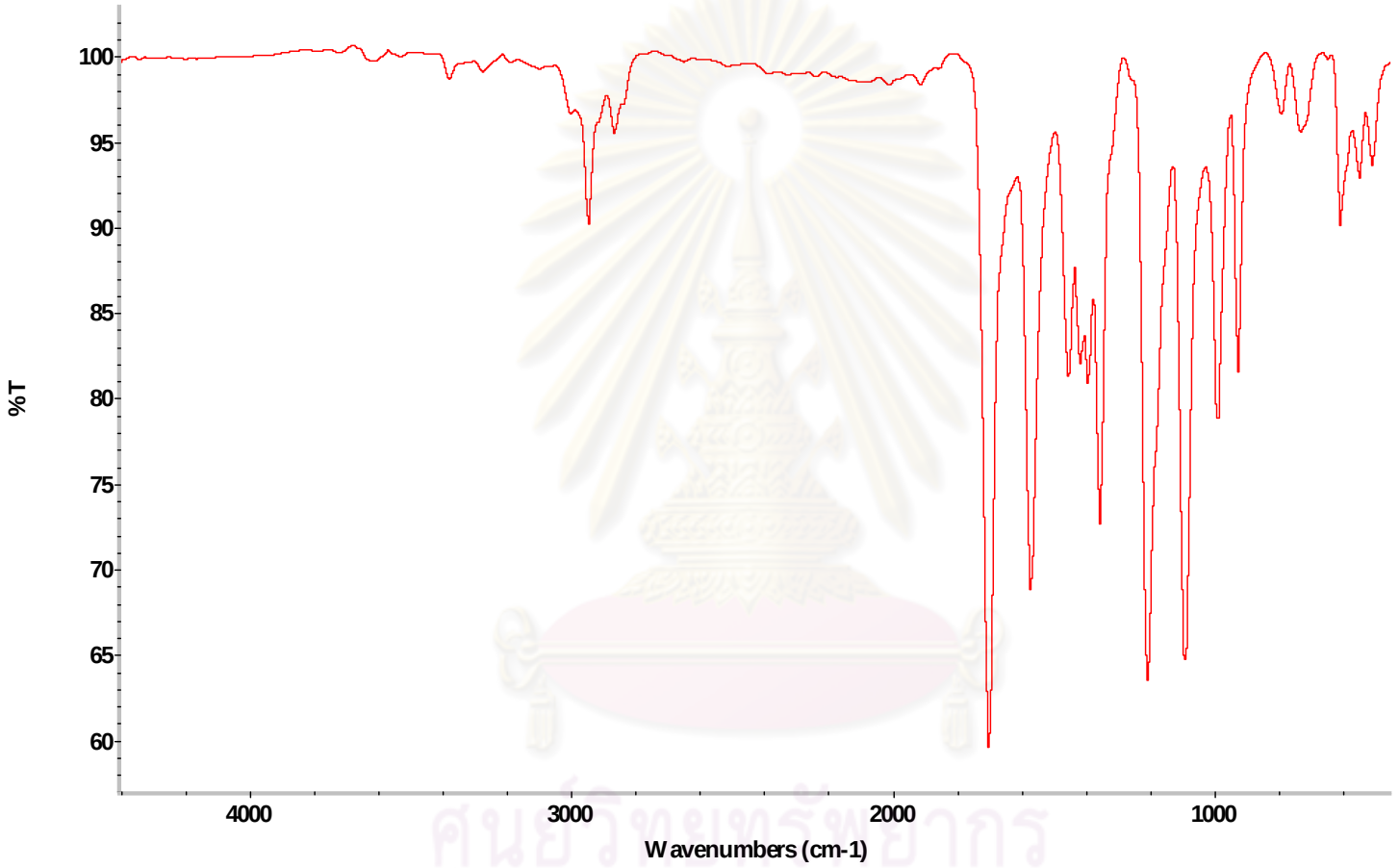

Figure A.11 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-trimethoxybenzene **30**

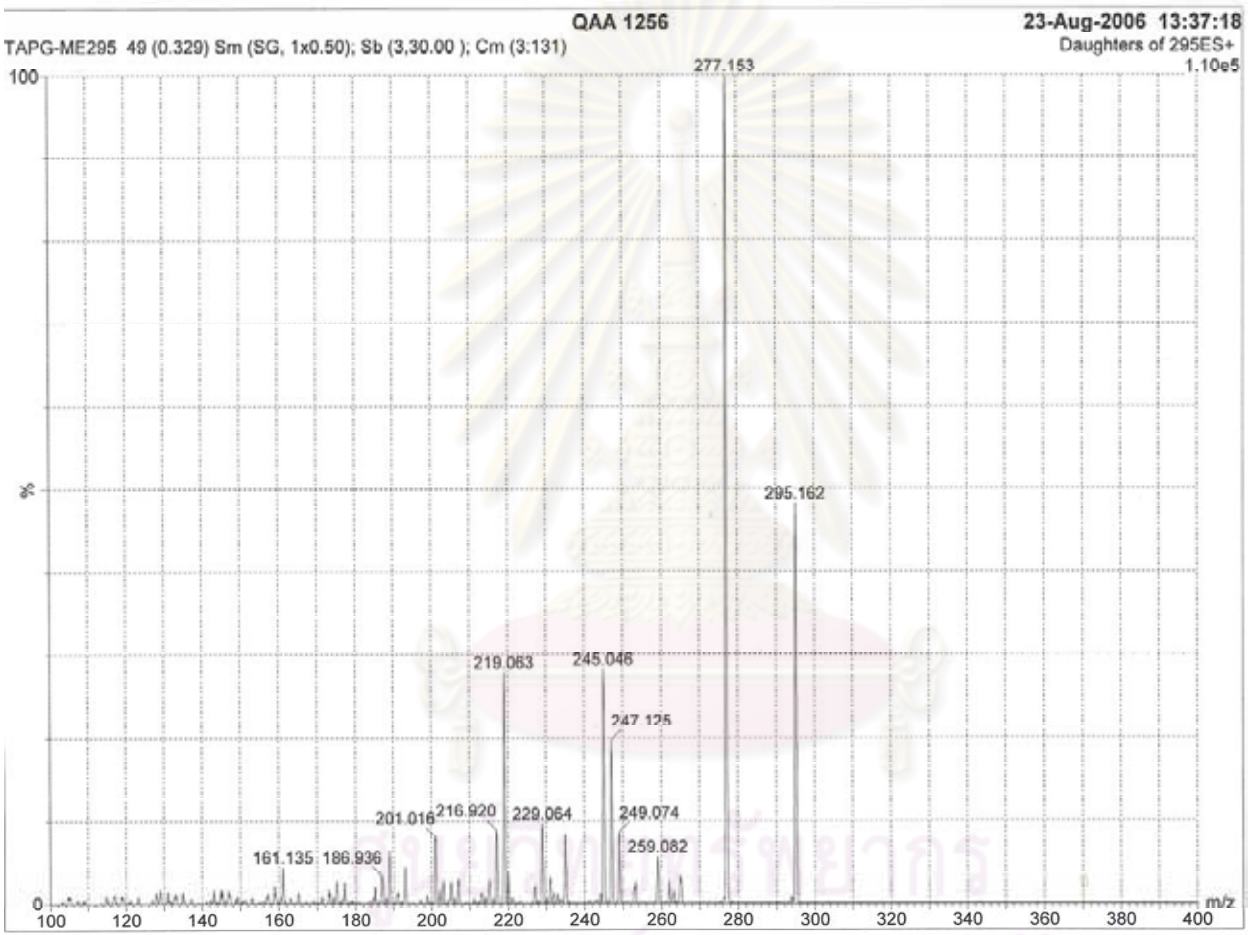

Figure A.12 Mass spectrum of 1,3,5-triacetyl-2,4,6-trimethoxybenzene **30**

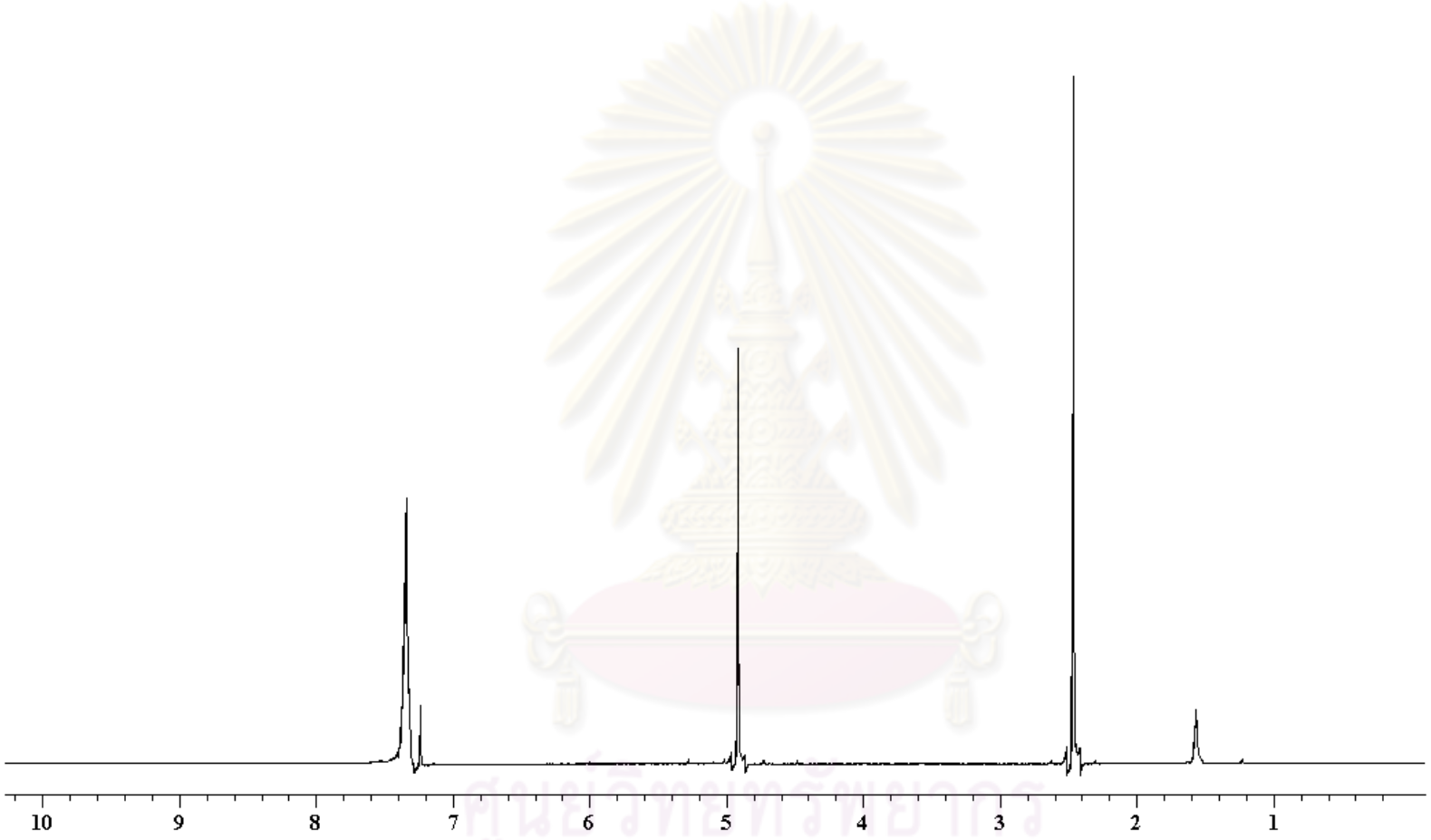

Figure A.13 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene **31**

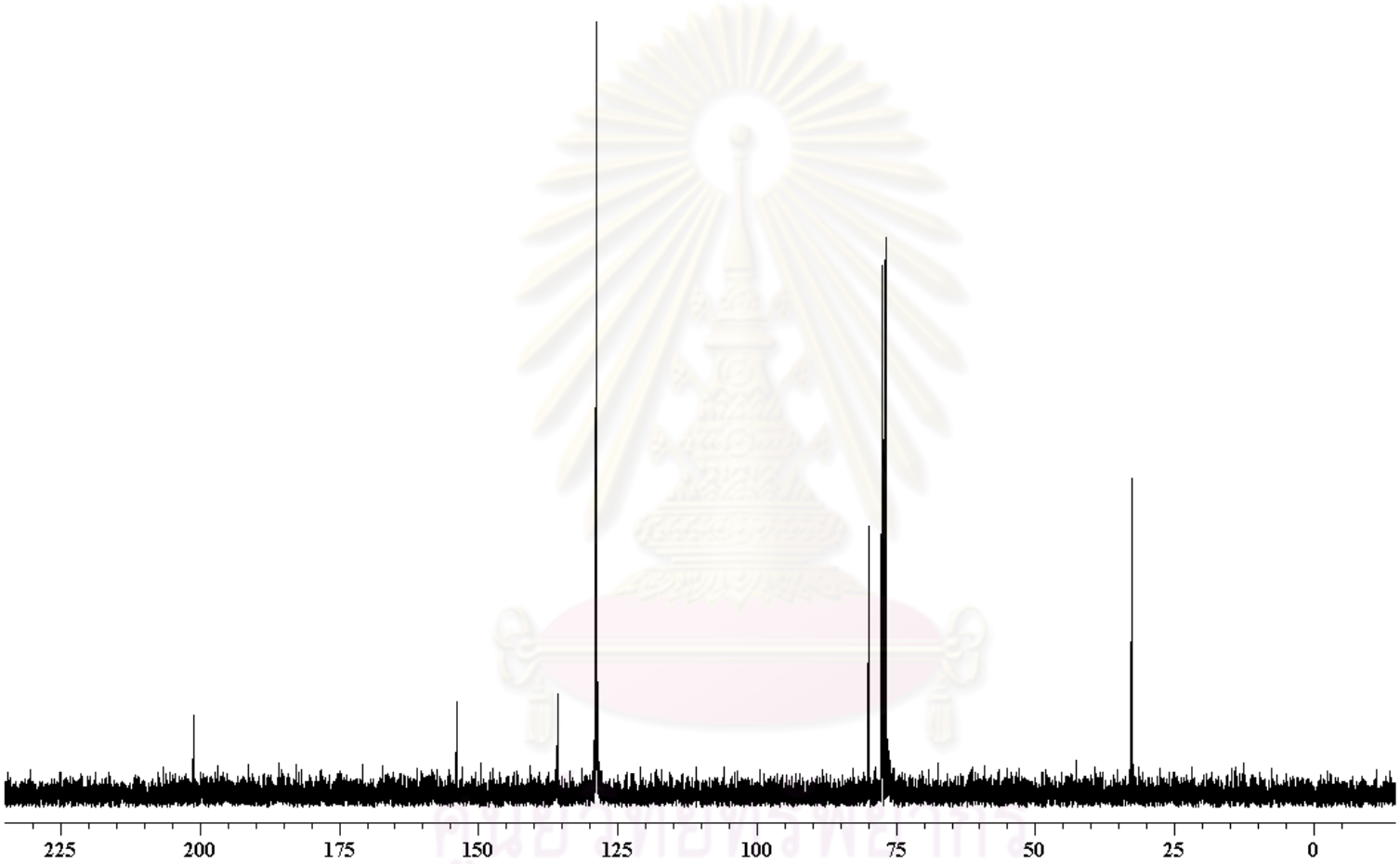

Figure A.14 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene **31**

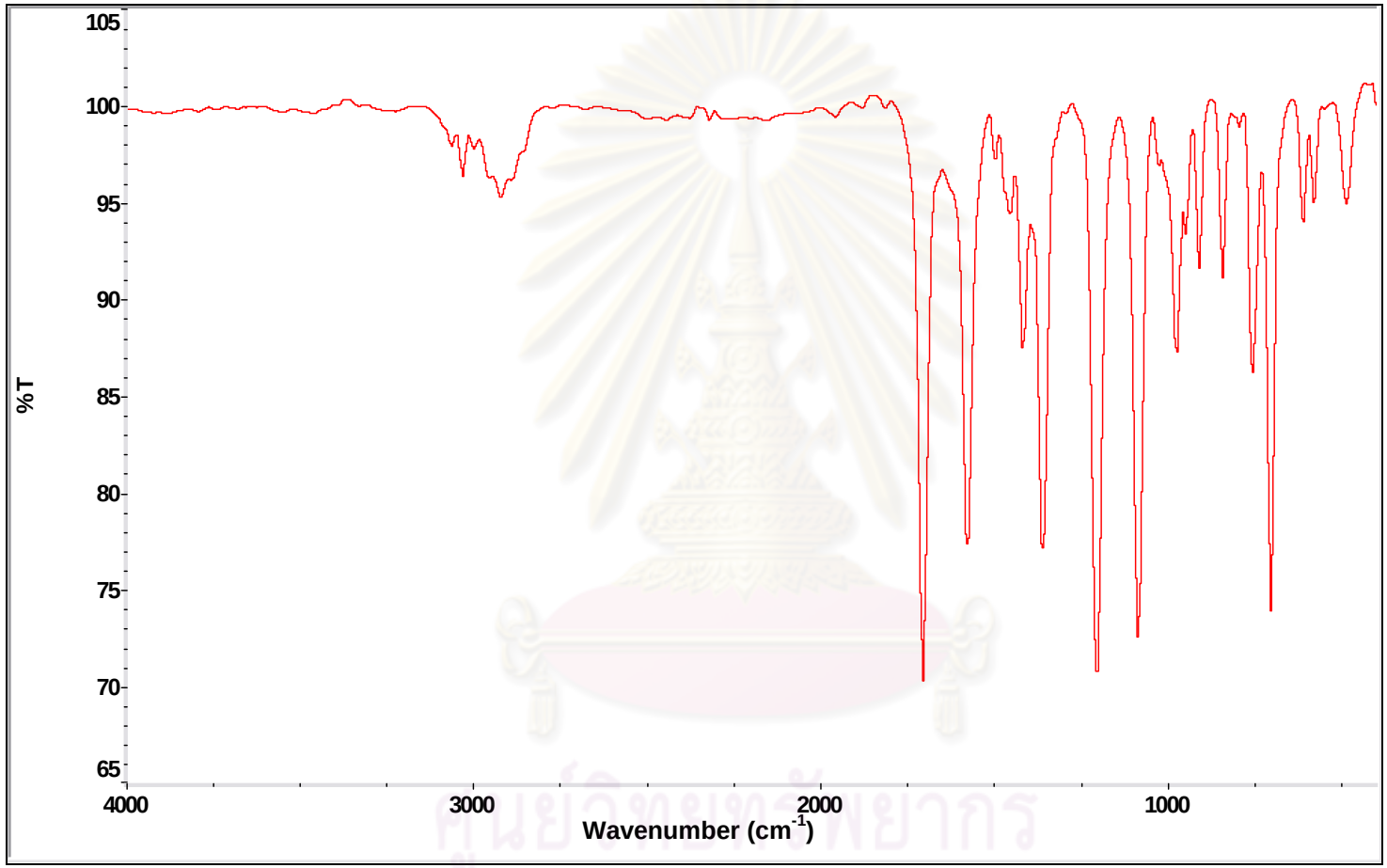

Figure A.15 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene **31**

68

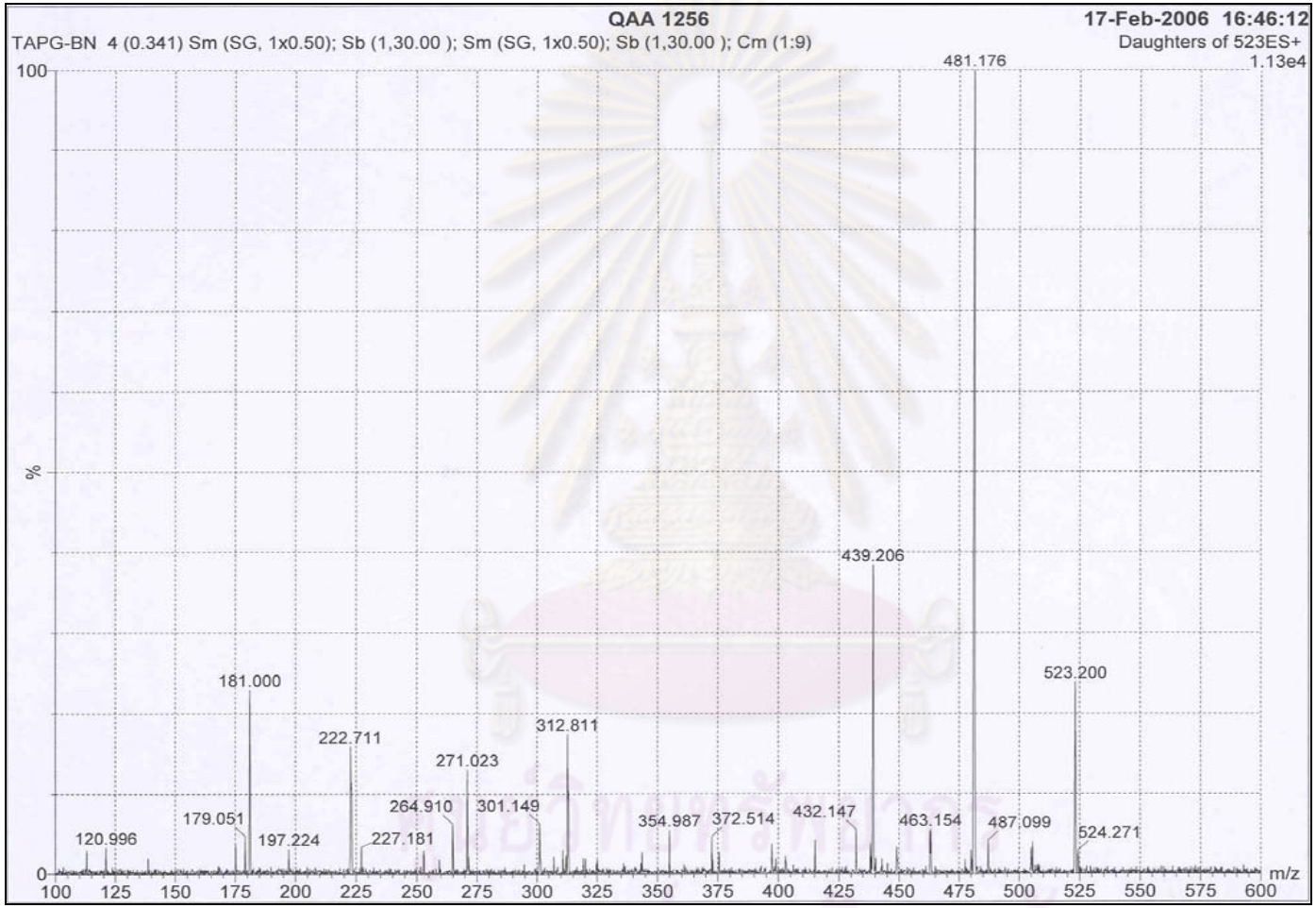

Figure A.16 Mass spectrum of 1,3,5-triacetyl-2,4,6-tribenzyloxybenzene **31**

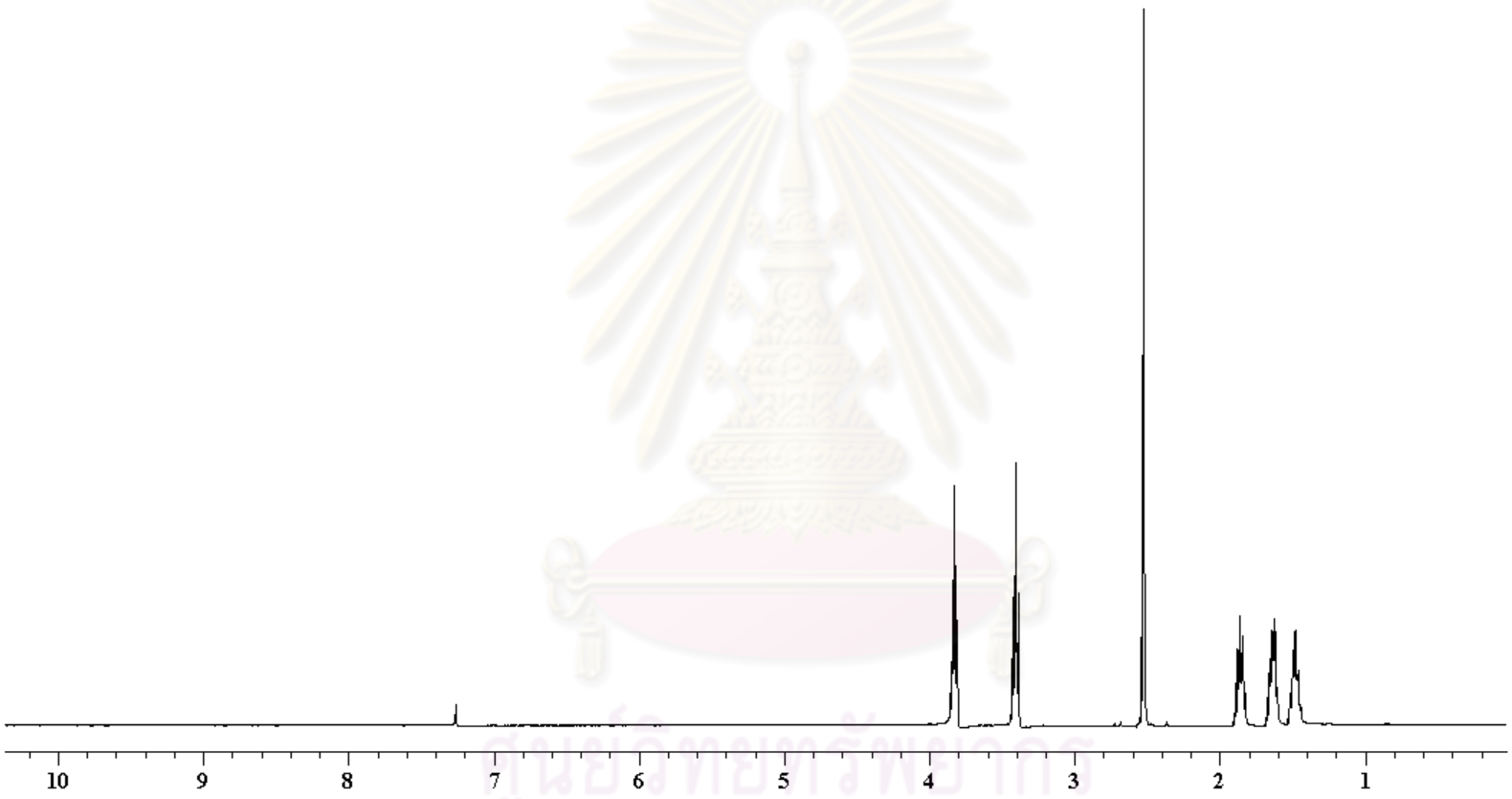

Figure A.17 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32**

70

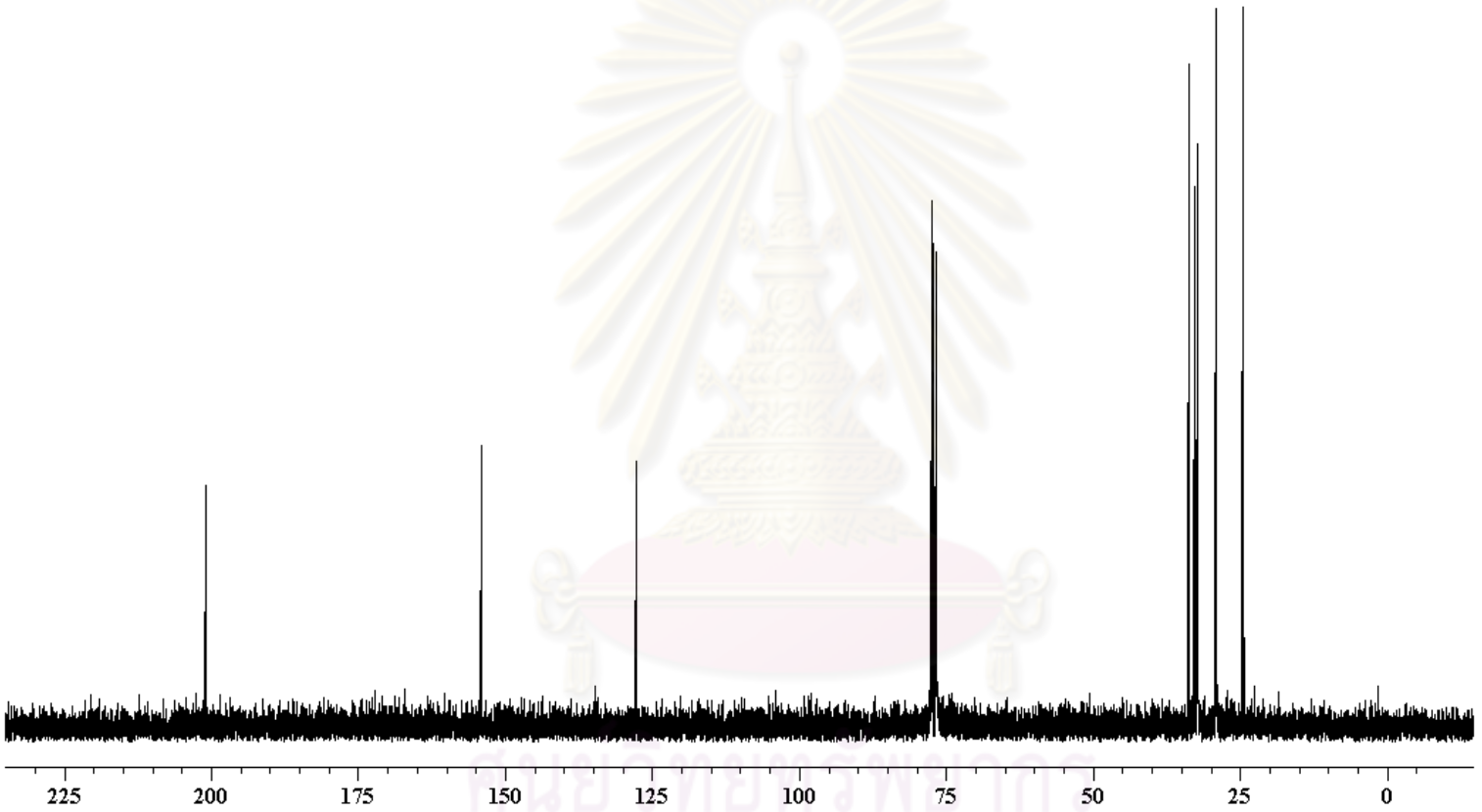

Figure A.18 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32**

71

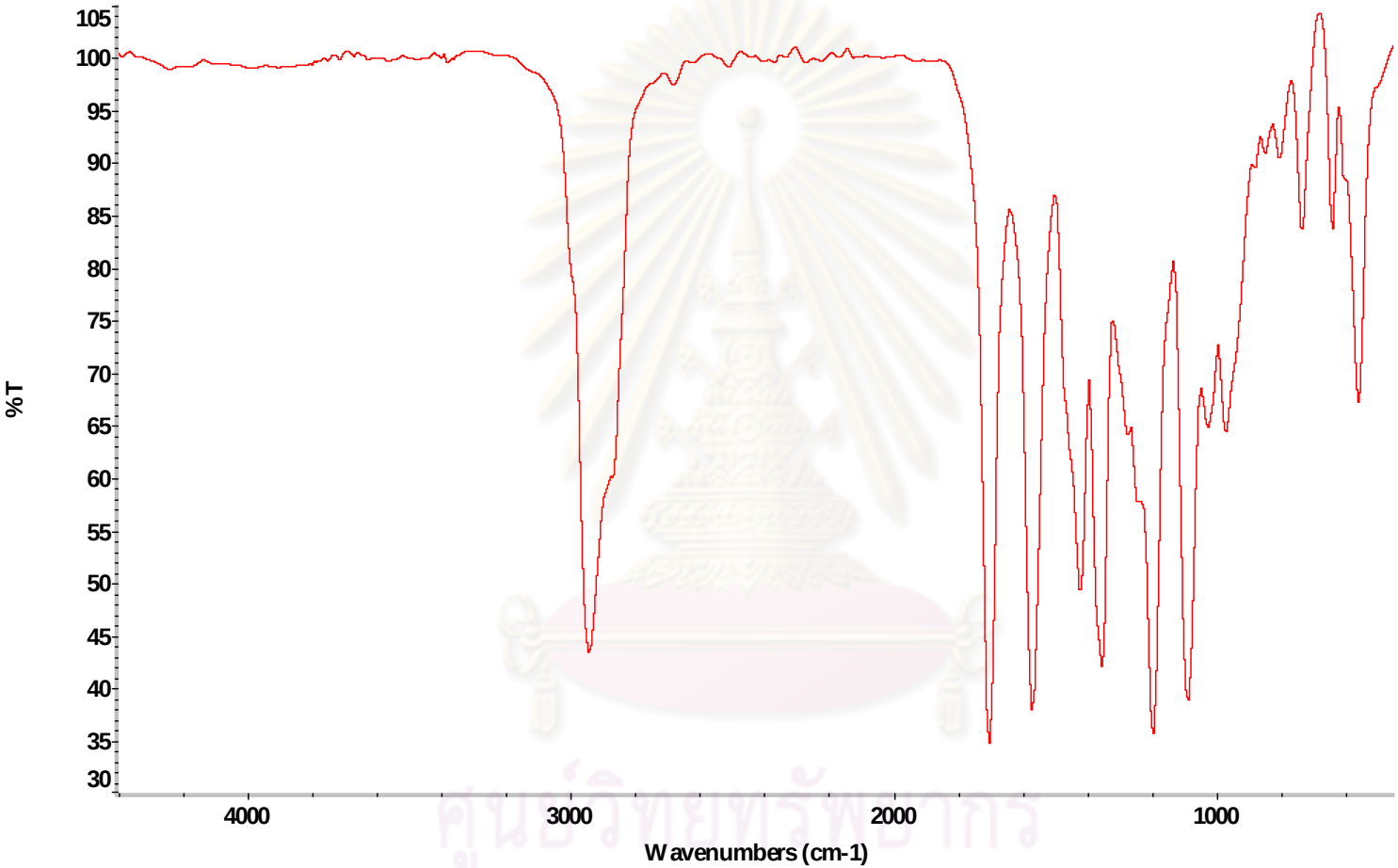

Figure A.19 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32**

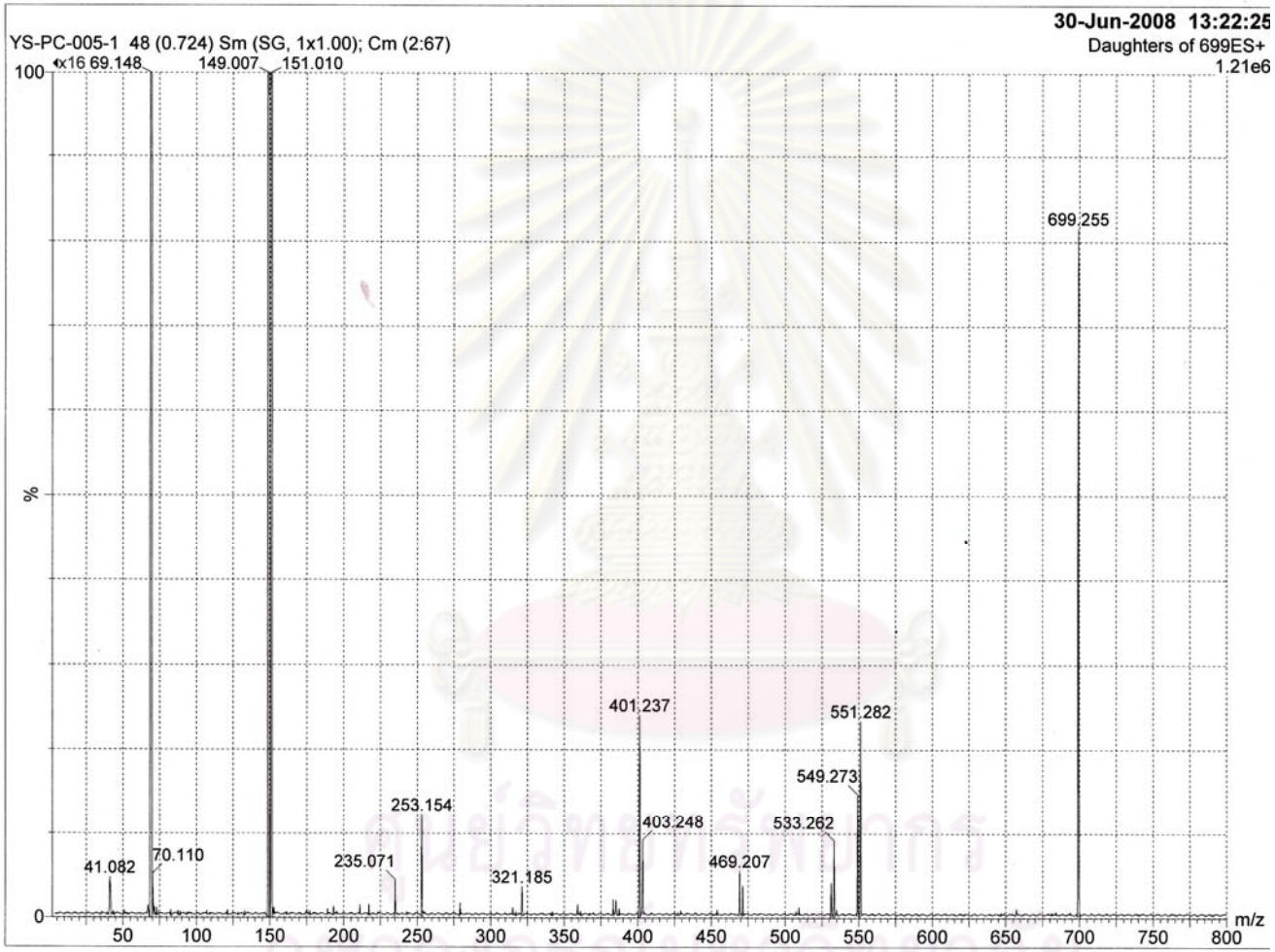

Figure A.20 Mass spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-bromopentyloxy)benzene **32**

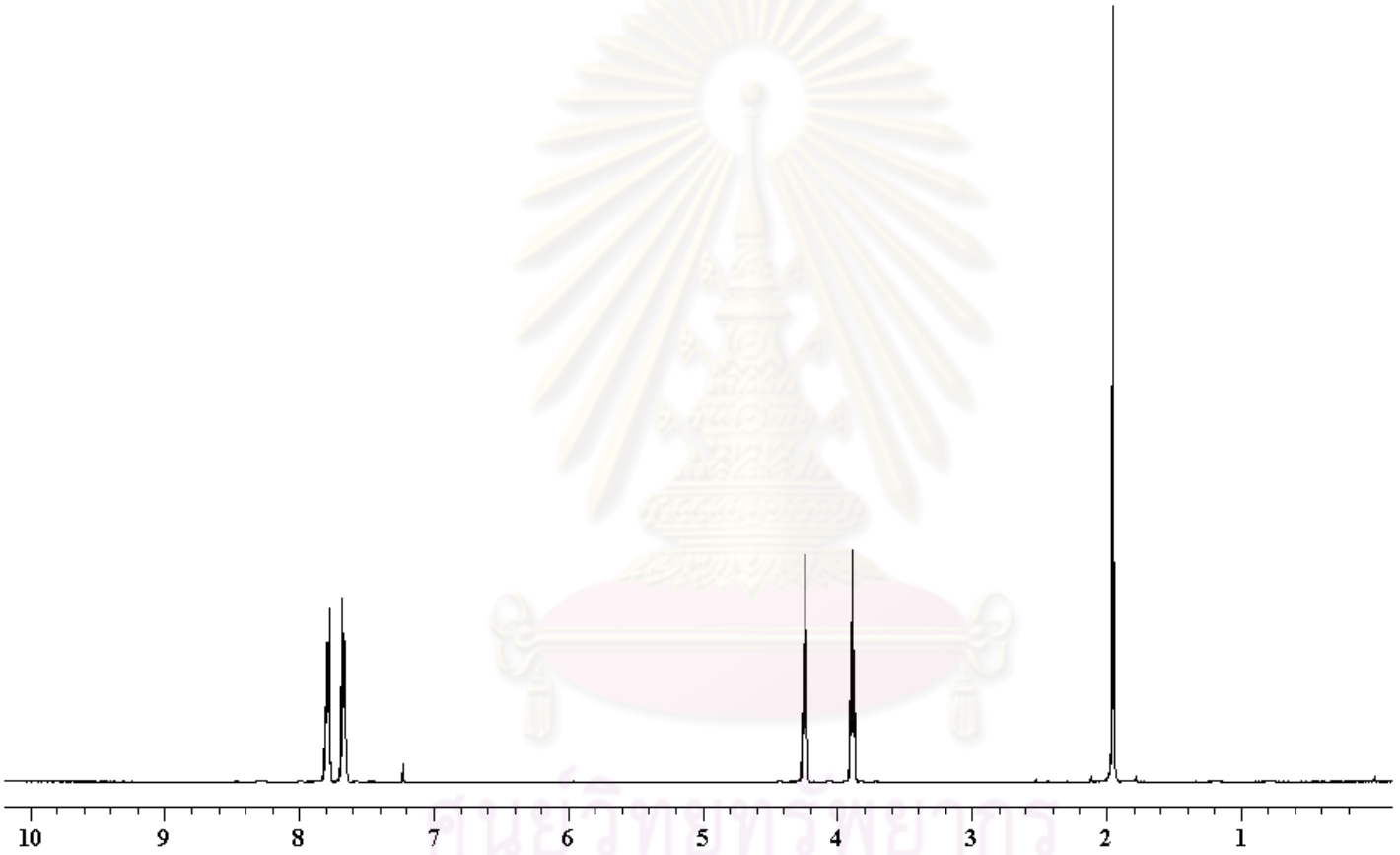

Figure A.21 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy)benzene **33**

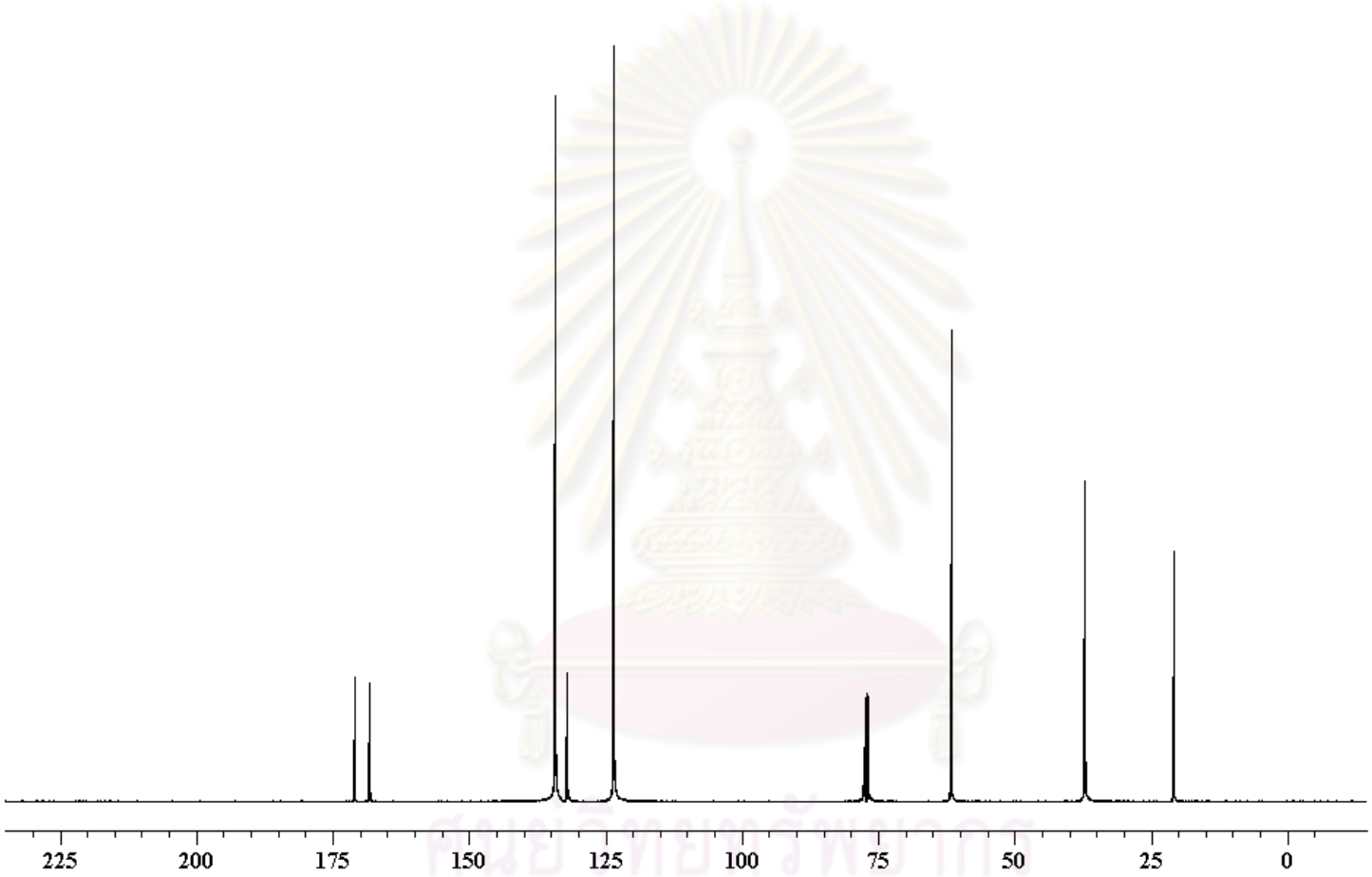

Figure A.22 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy)benzene **33**

75

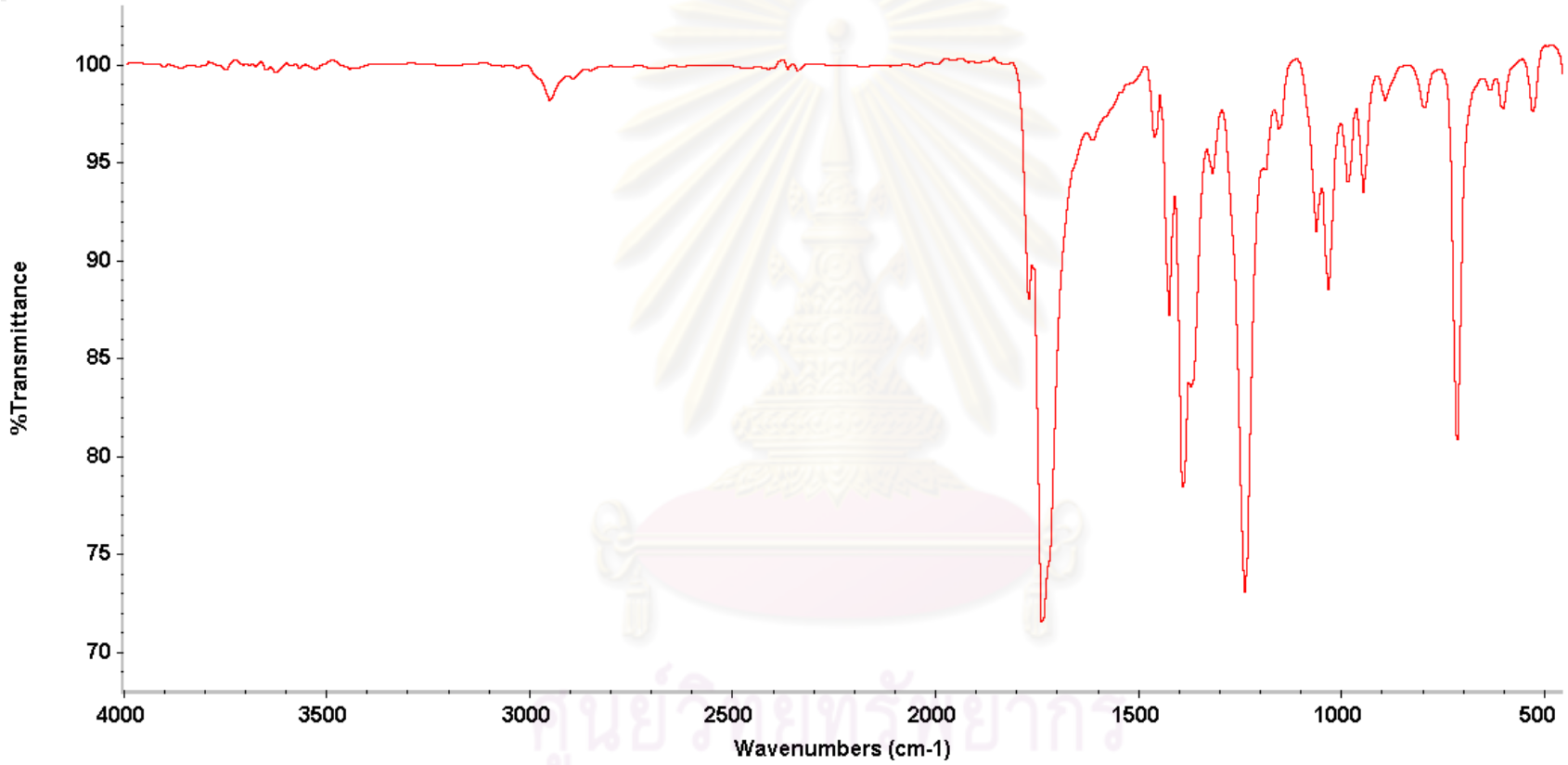

Figure A.23 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-tris(2´(*N*-phthalimido)ethoxy)benzene **33**

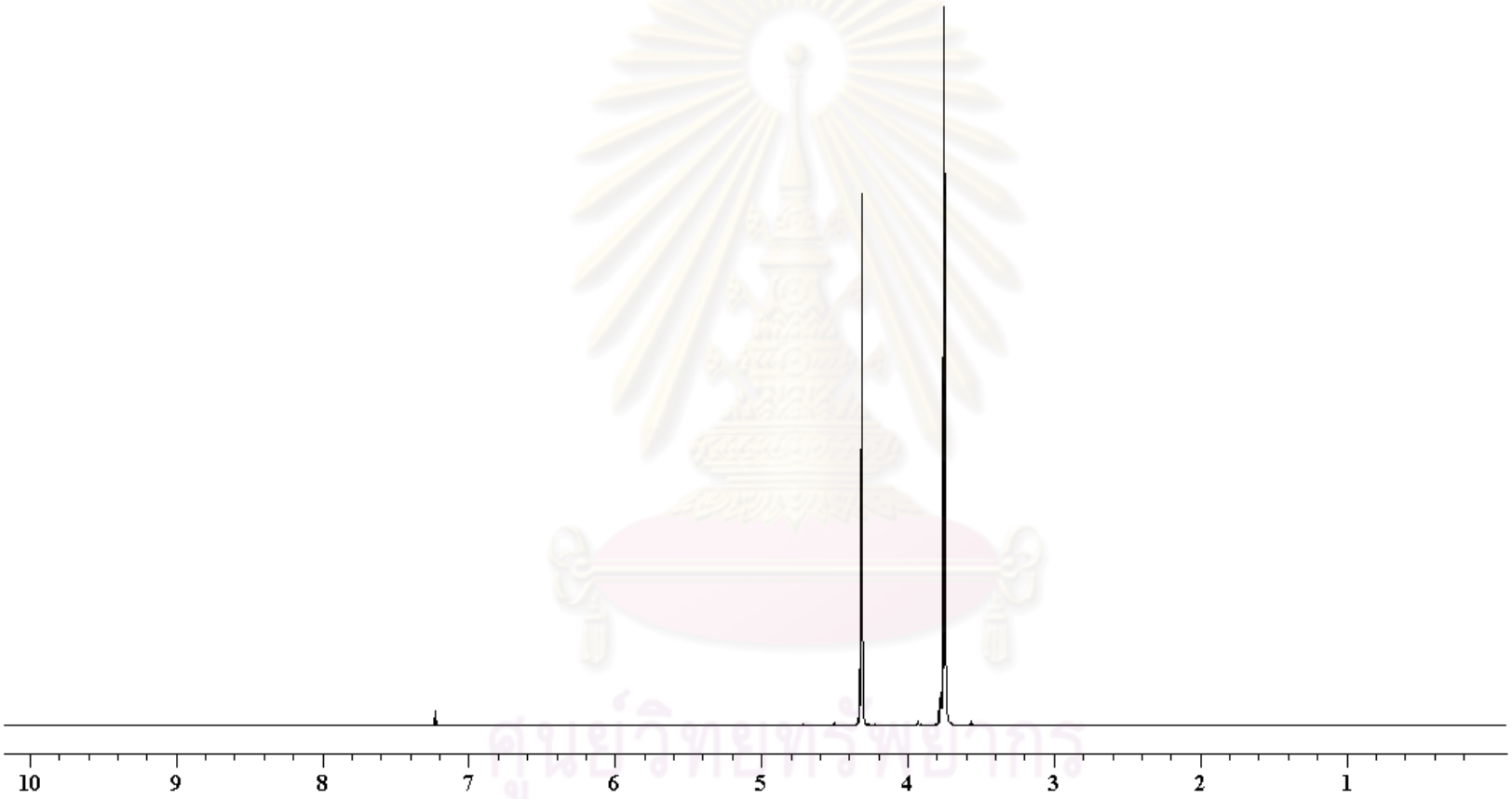

Figure A.24 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene **35**

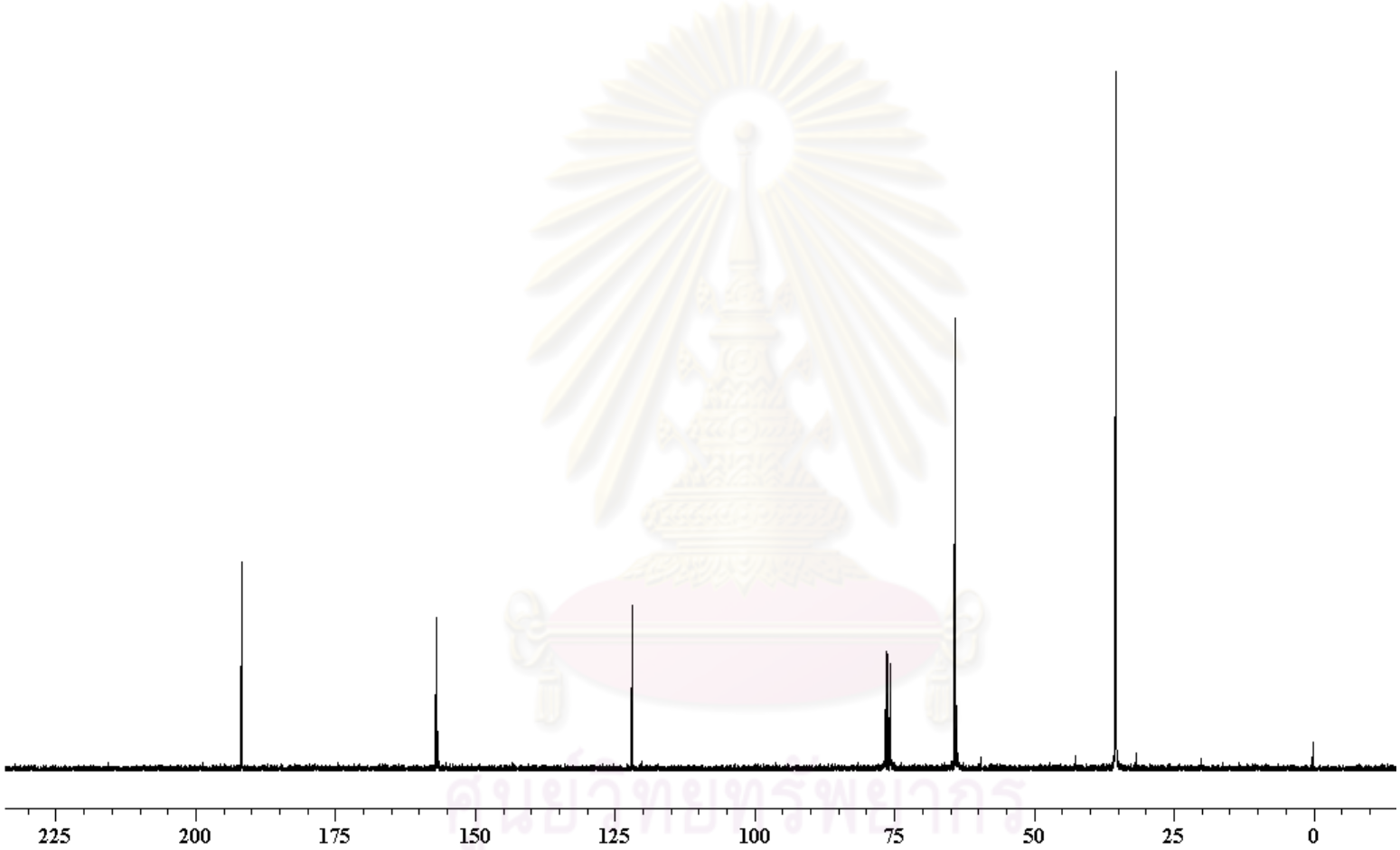

Figure A.25 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene **35**

78

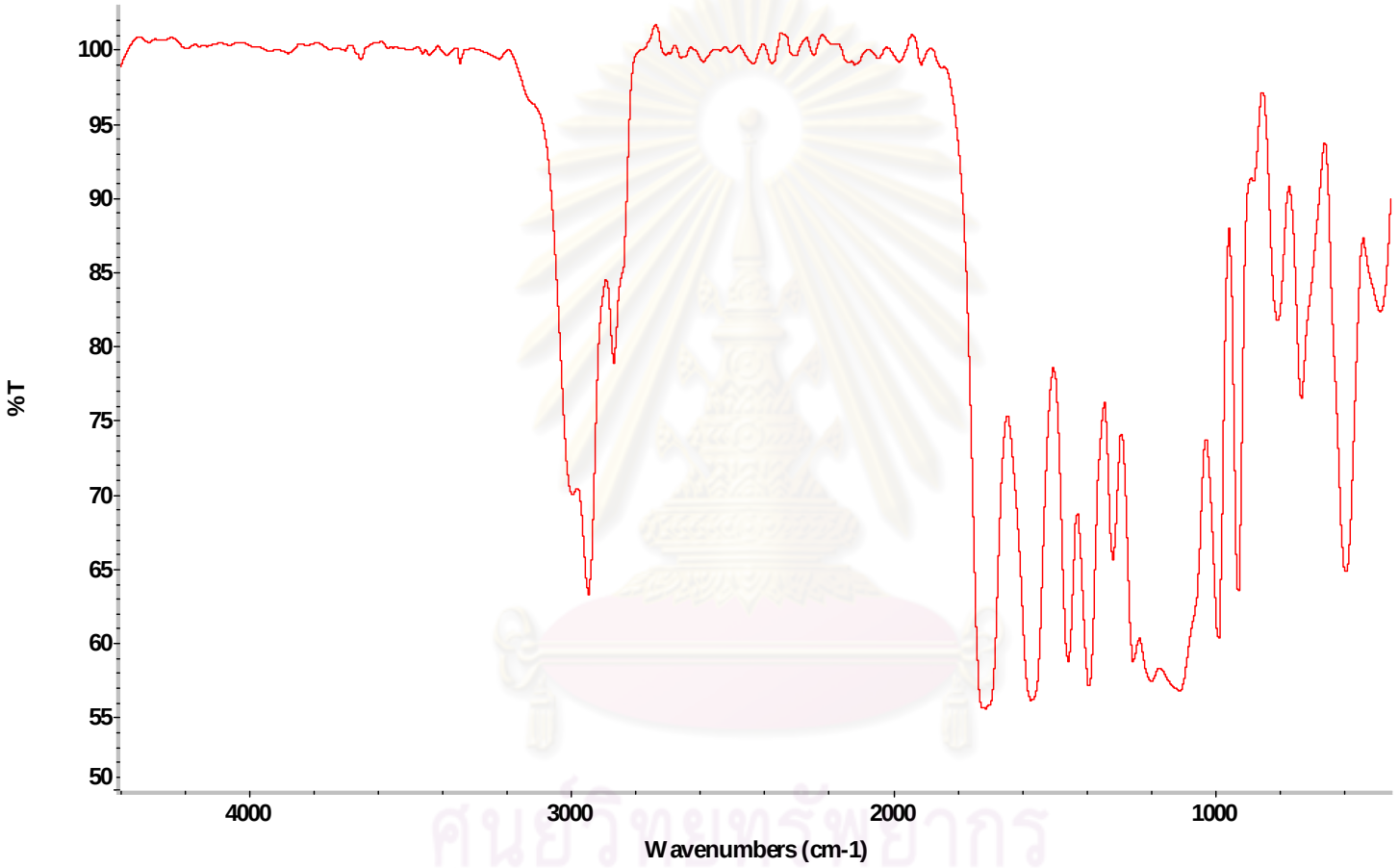

Figure A.26 IR (KBr) spectrum of 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene **35**

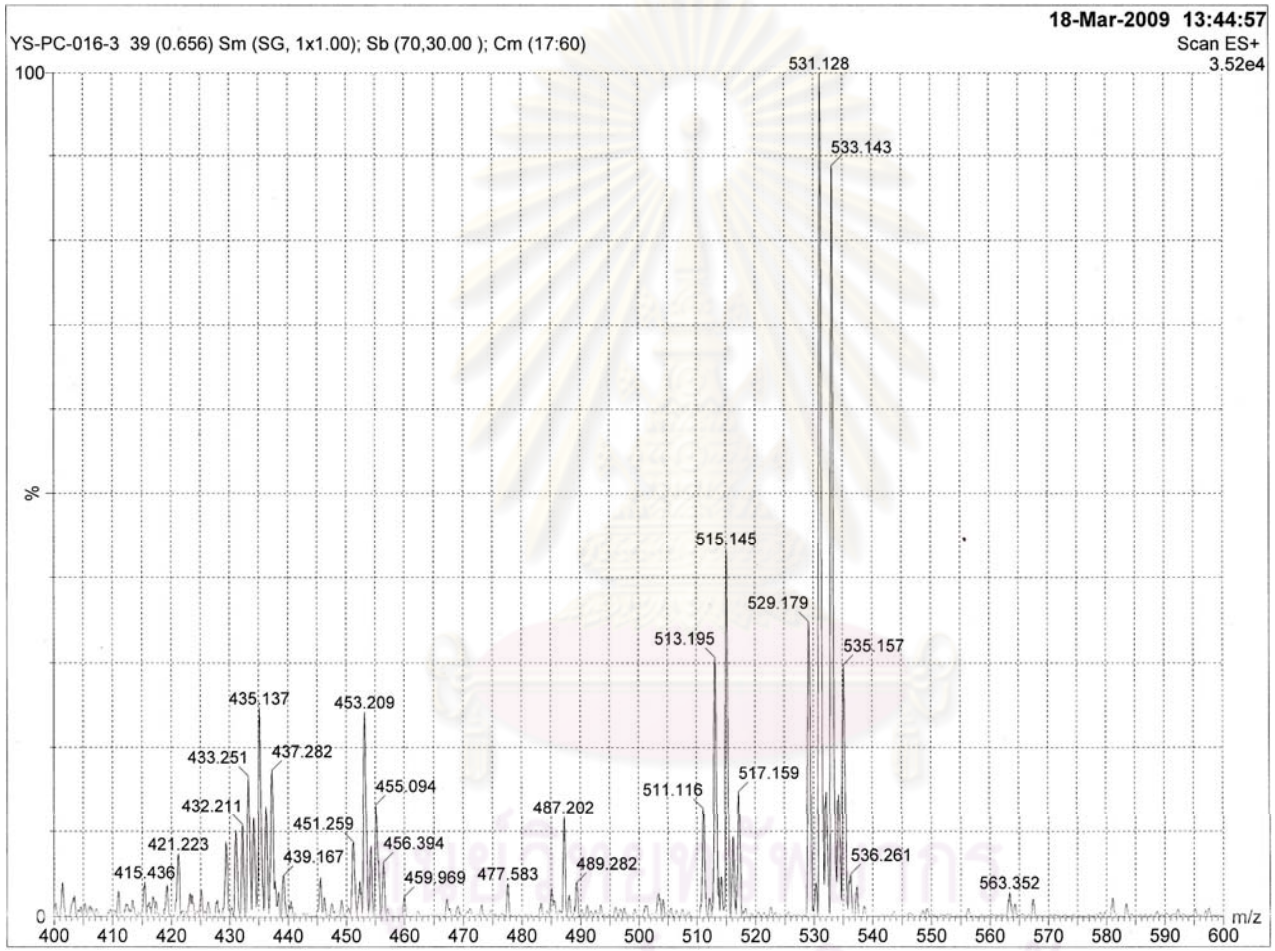

Figure A.27 Mass spectrum of 1,3,5-tris(α-bromoacetyl)-2,4,6-trimethoxybenzene **35**

80

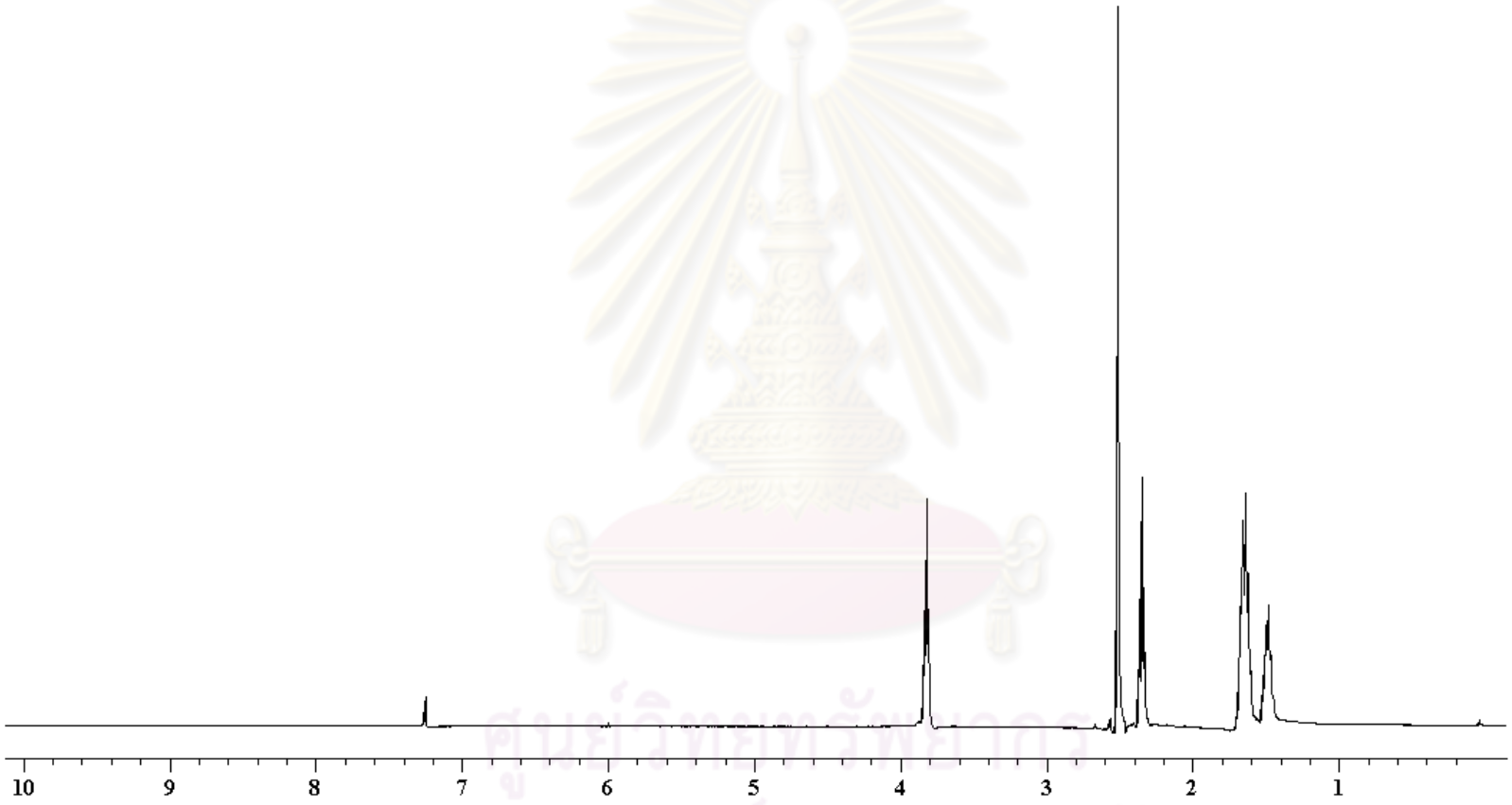

Figure A.28 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37**

81

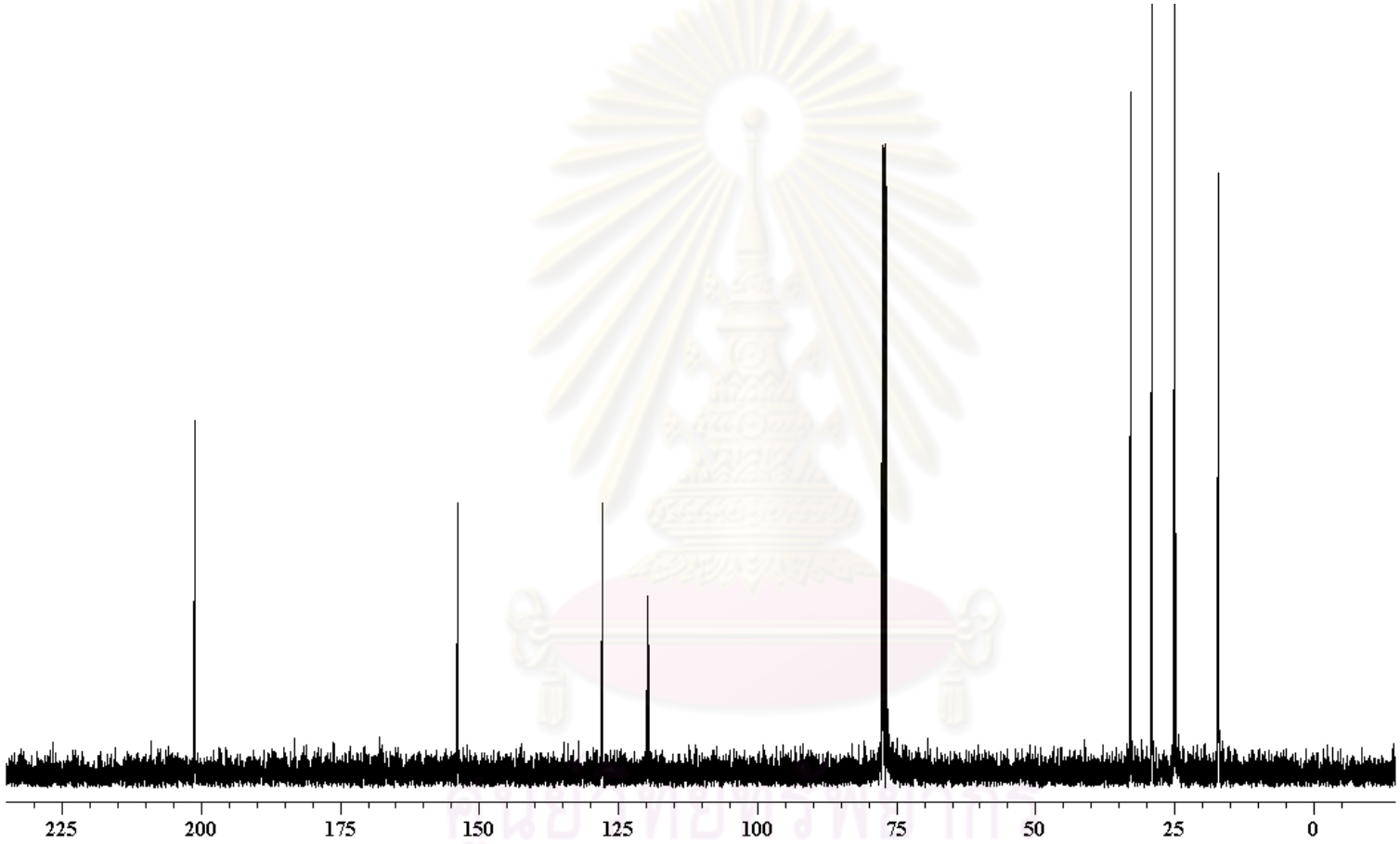

Figure A.29 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37**

82

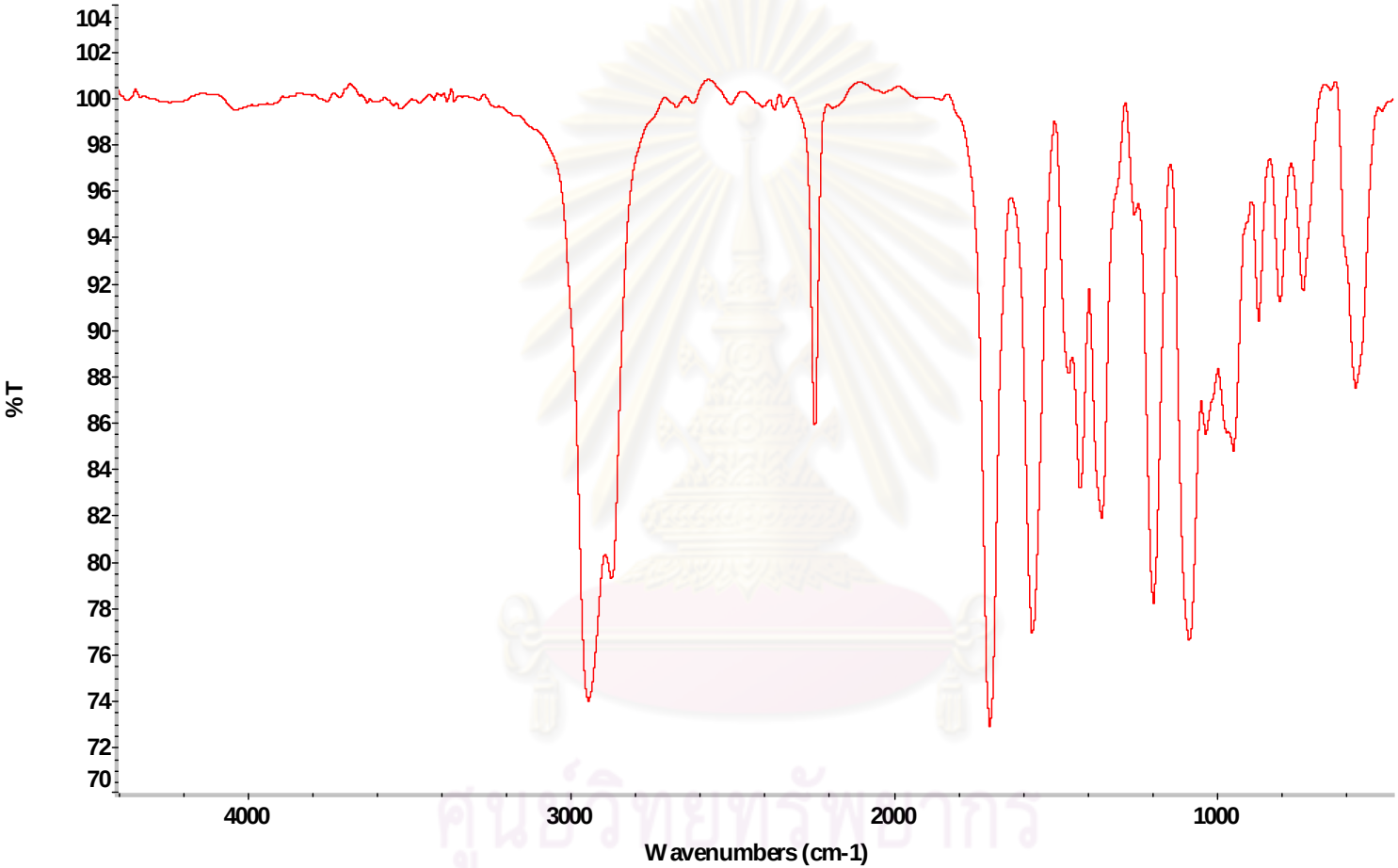

Figure A.30 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37**

83

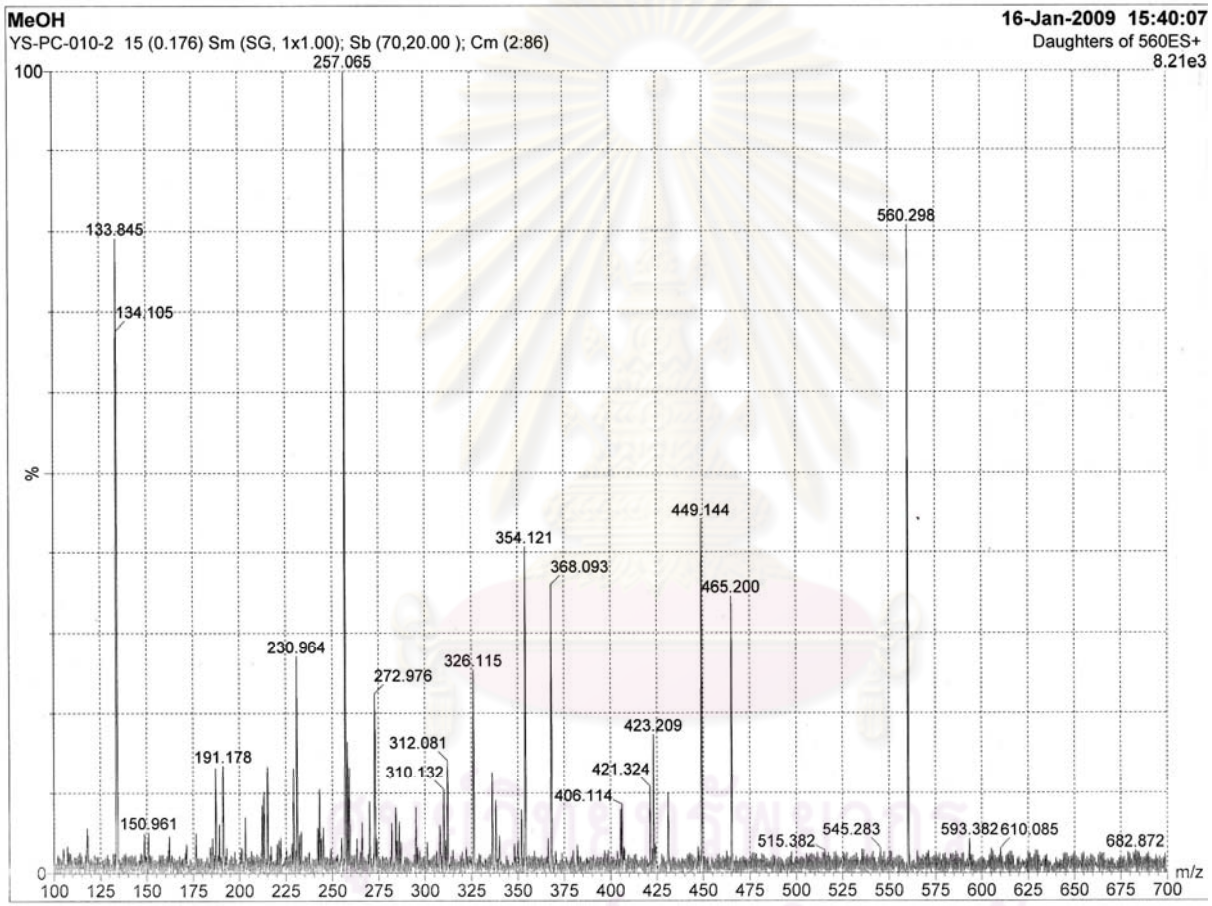

Figure A.31 Mass spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-cyanopentyloxy)benzene **37**

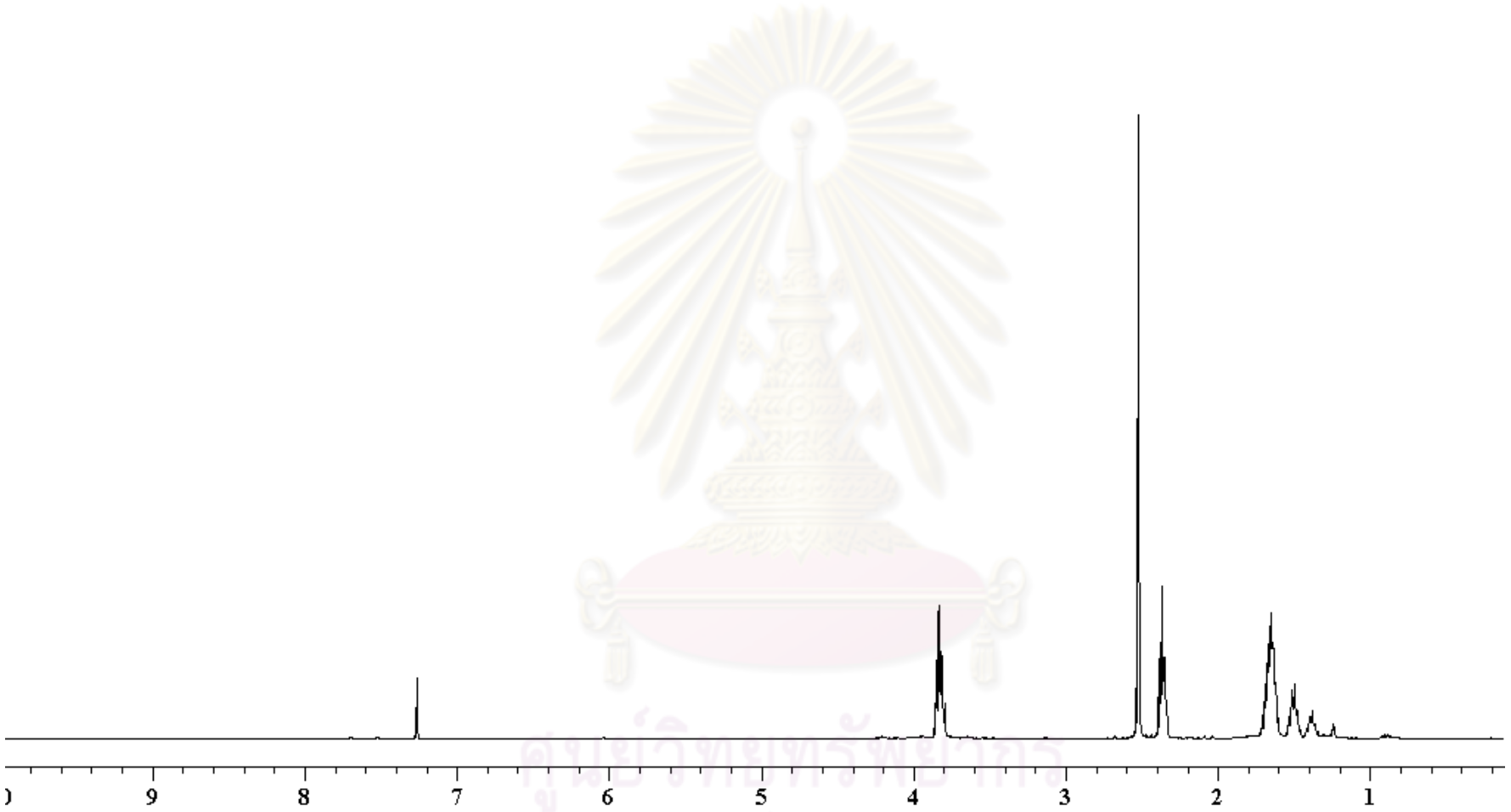

Figure A.32 ^{1}H-NMR ($CDCl_3$) spectrum of 6-(2´,4´,6´-triacetyl-3´,5´-bis(5´´-cyanopentyloxy)phenoxy)hexanoic acid **39**

85

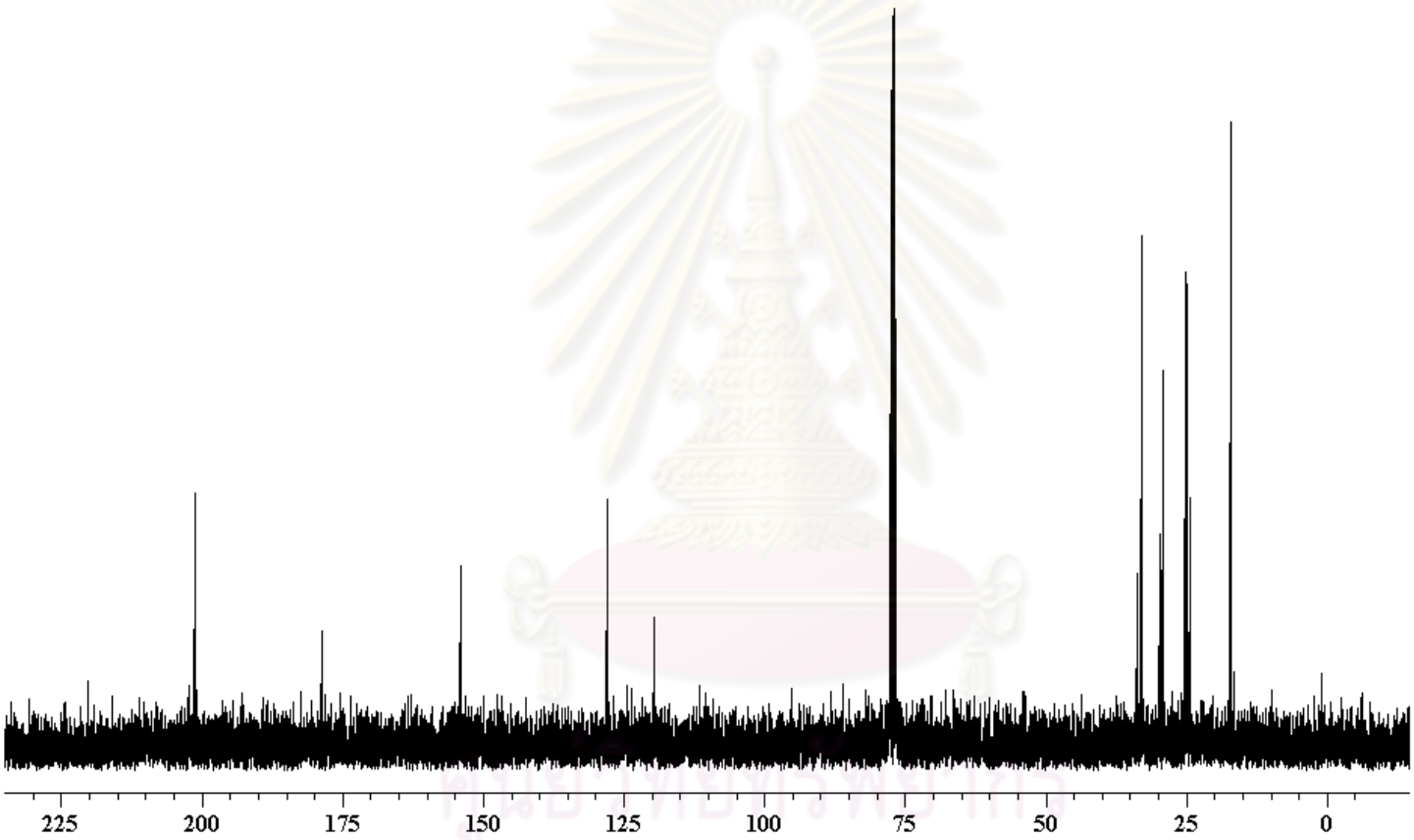

Figure A.33 ^{13}C-NMR ($CDCl_3$) spectrum of 6-(2´,4´,6´-triacetyl-3´,5´-bis(5´´-cyanopentyloxy)phenoxy)hexanoic acid **39**

86

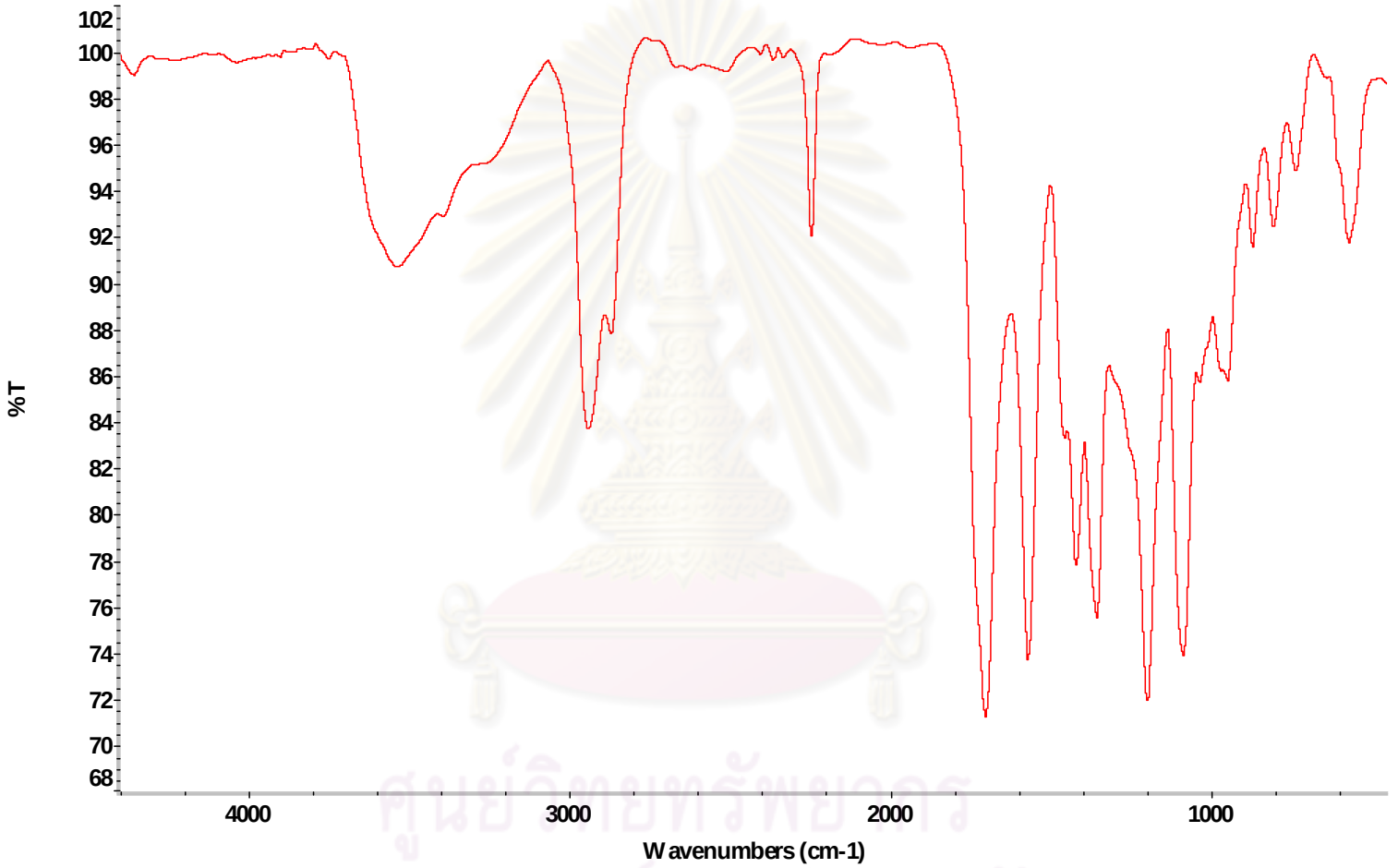

Figure A.34 IR (KBr) spectrum of 6-(2´,4´,6´-triacetyl-3´,5´-bis(5´´-cyanopentyloxy)phenoxy)hexanoic acid **39**

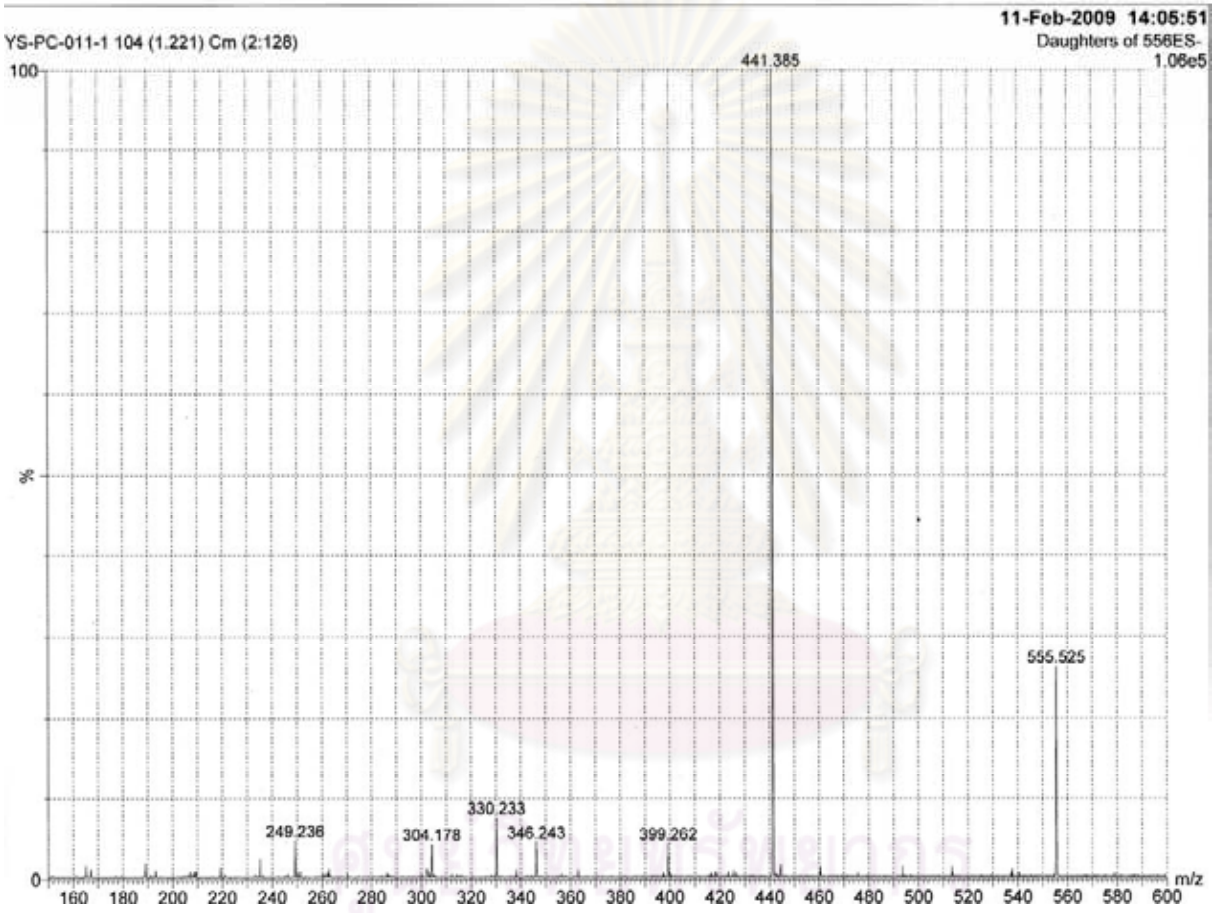

Figure A.35 Mass spectrum of 6-(2´,4´,6´-triacetyl-3´,5´-bis(5´´-cyanopentyloxy)phenoxy)hexanoic acid **39**

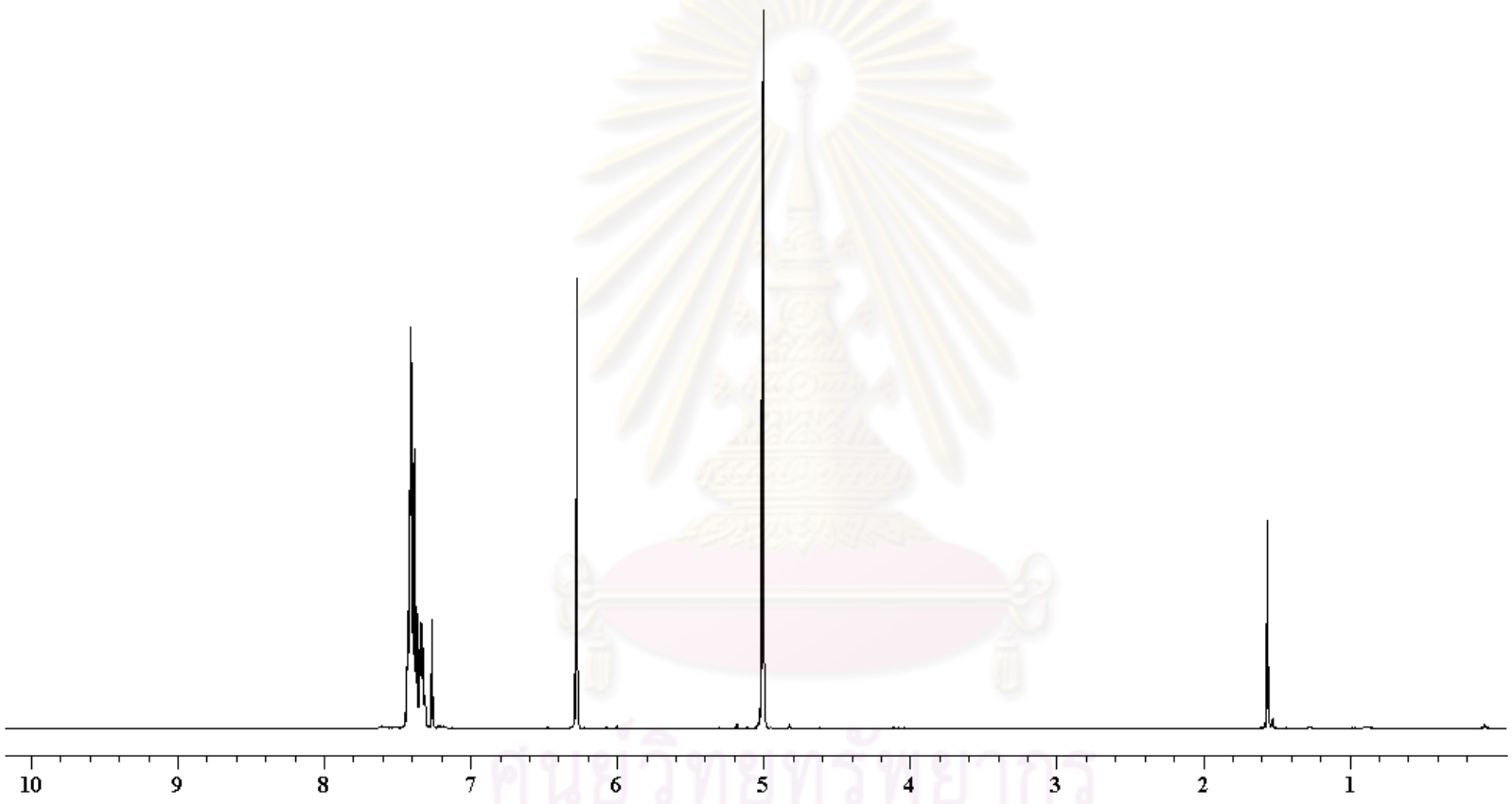

Figure A.36 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-benzyloxybenzene **40**

89

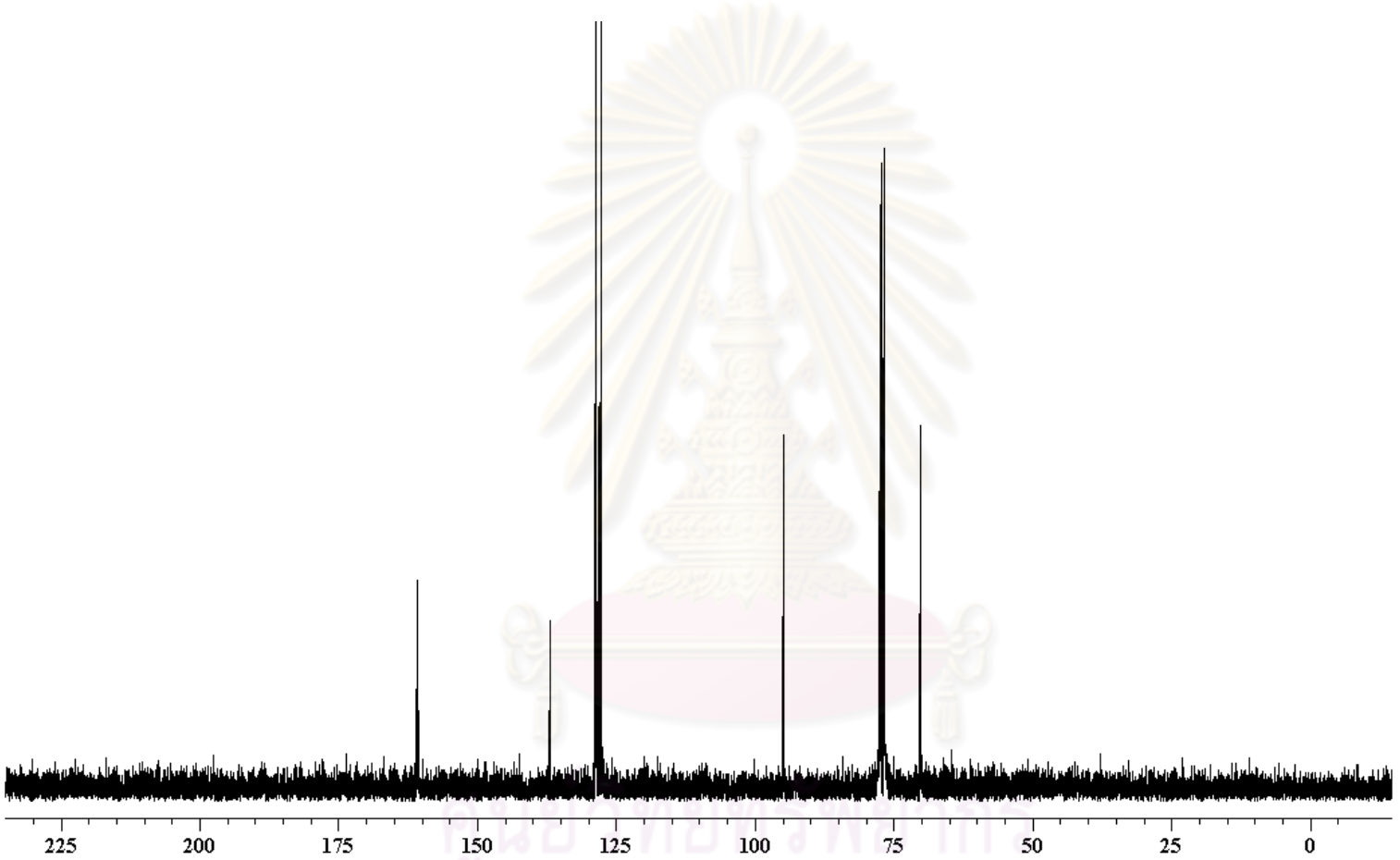

Figure A.37 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-benzyloxybenzene **40**

90

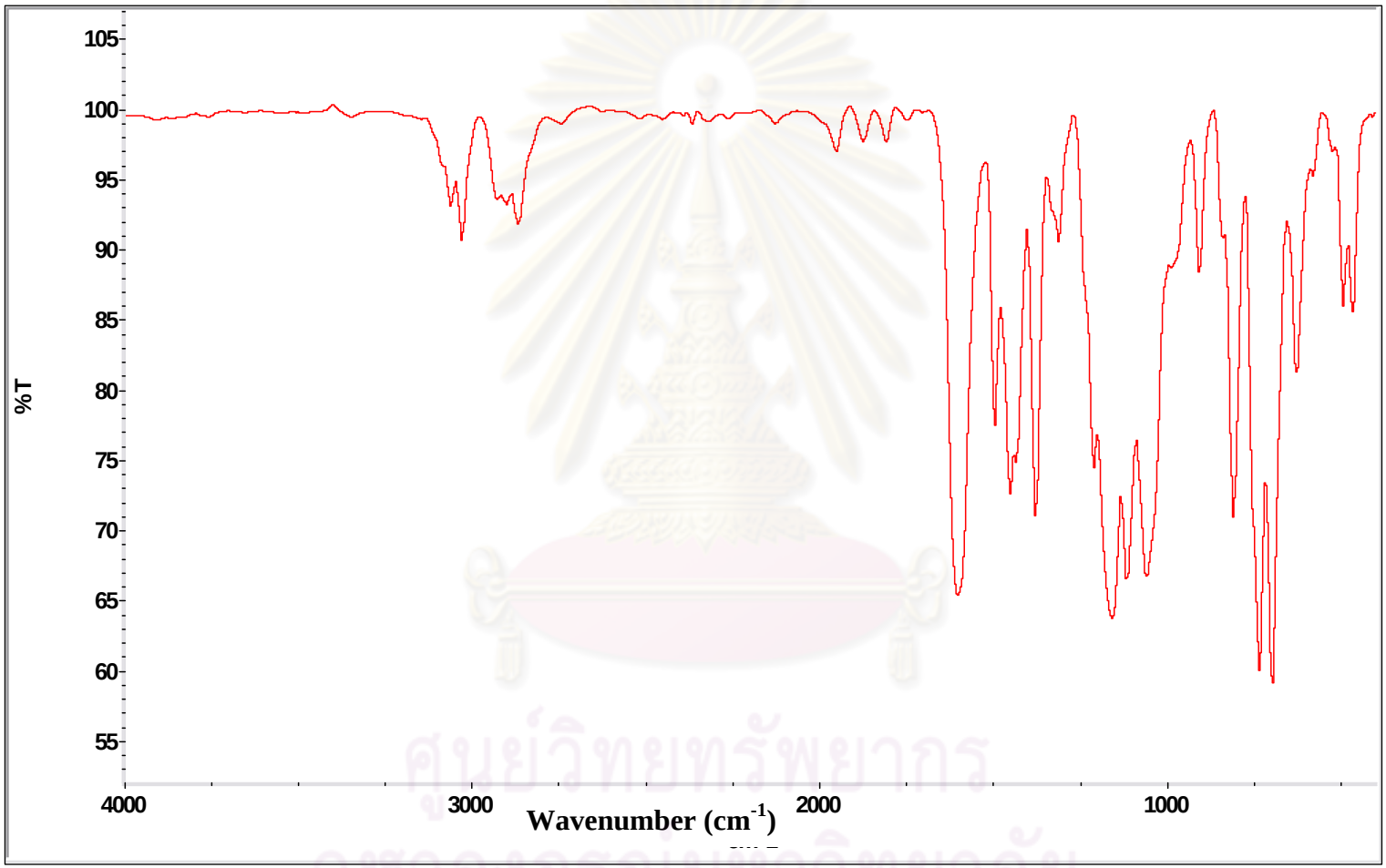

Figure A.38 IR (KBr) spectrum of 1,3,5-benzyloxybenzene **40**

91

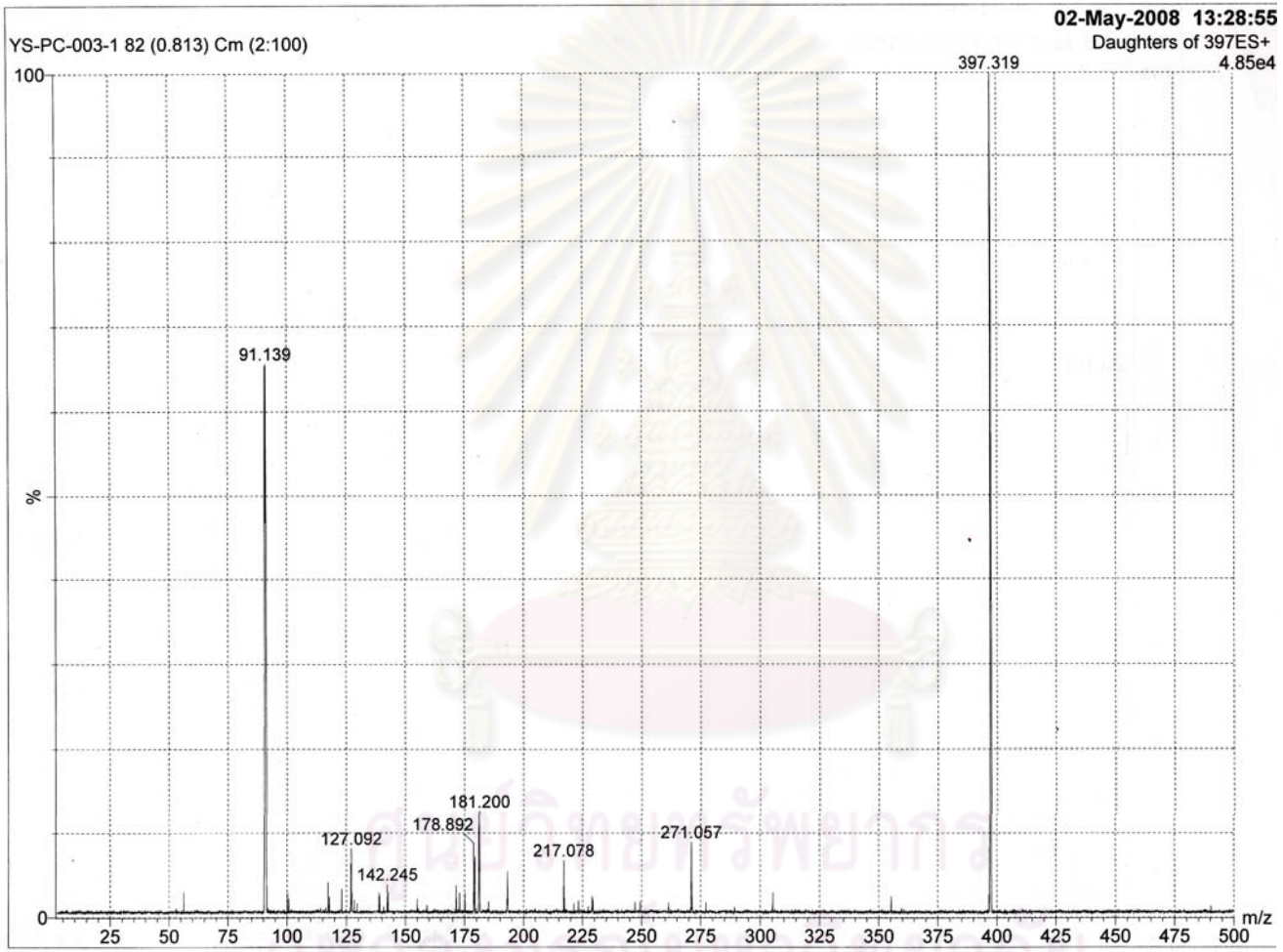

Figure A.39 Mass spectrum of 1,3,5-benzyloxybenzene **40**

92

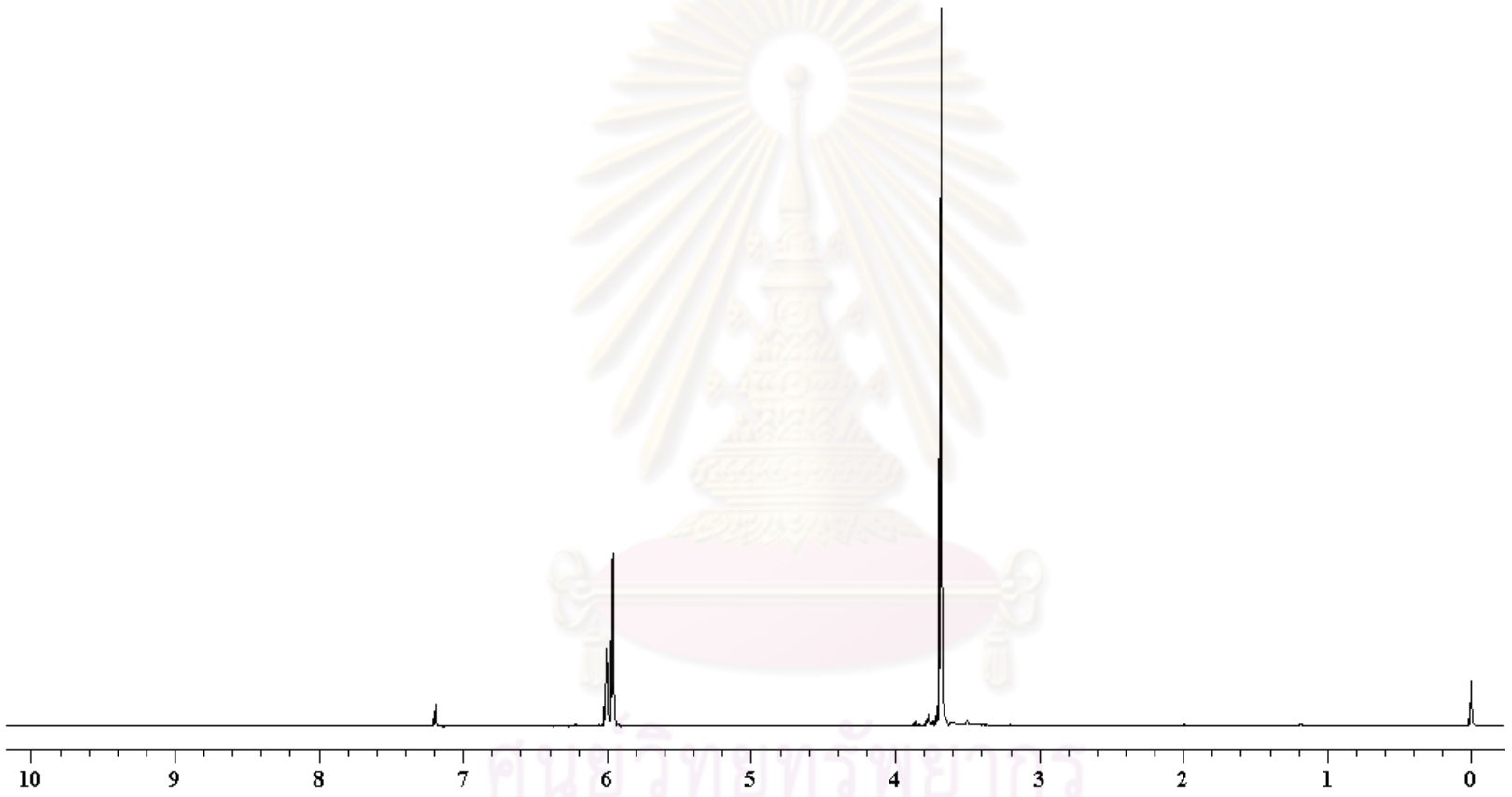

Figure A.40 ^{1}H-NMR ($CDCl_3$) spectrum of 3,5-dimethoxyphenol **43**

93

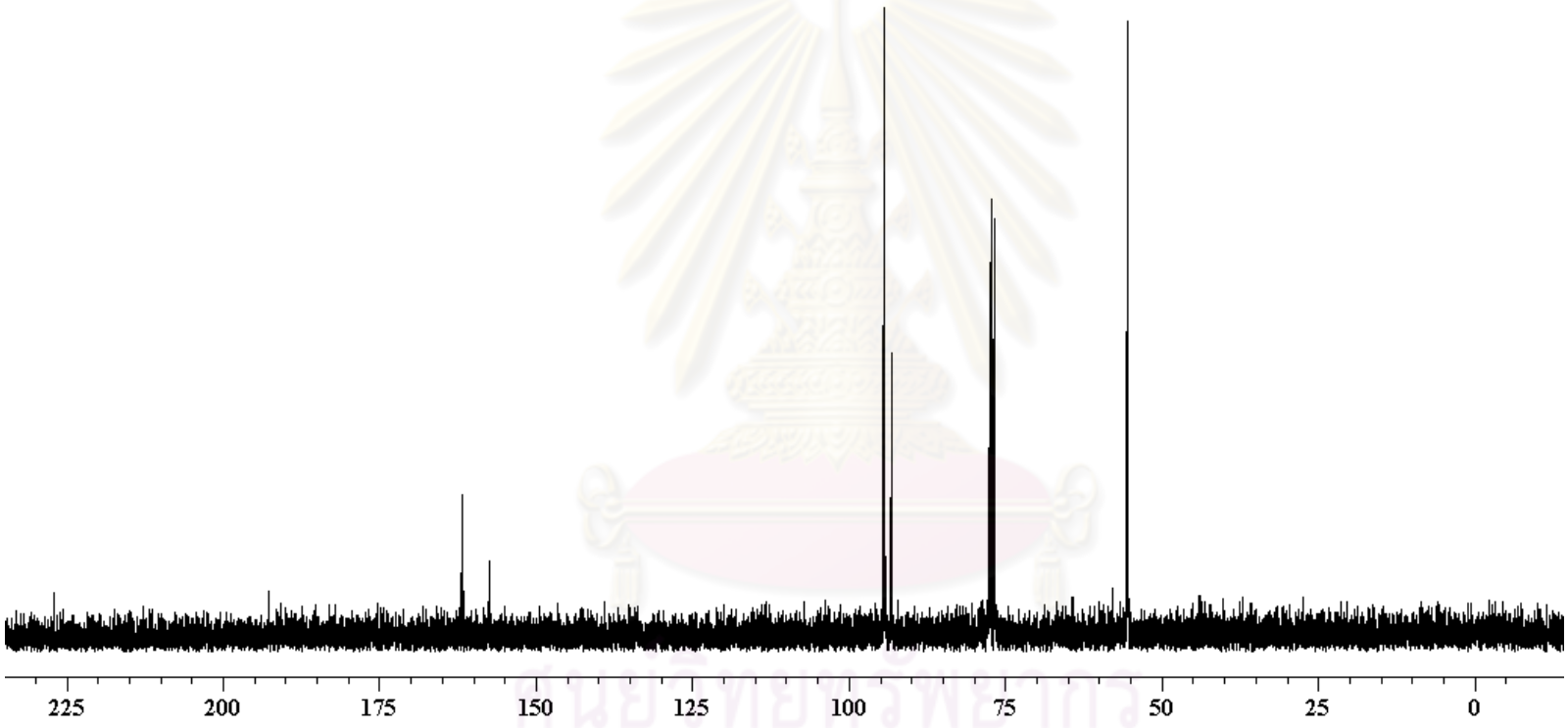

Figure A.41 ^{13}C-NMR ($CDCl_3$) spectrum of 3,5-dimethoxyphenol **43**

94

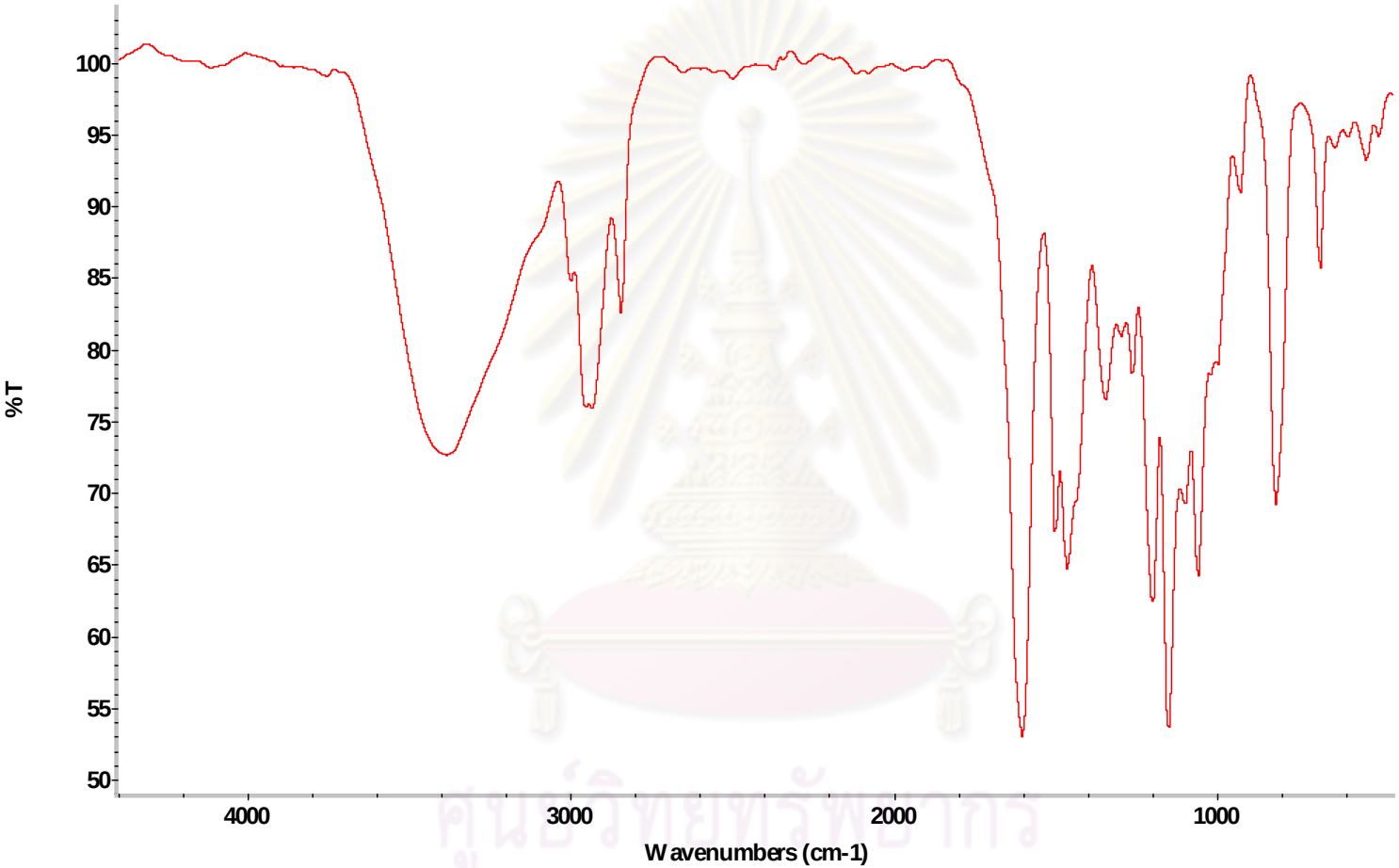

Figure A.42 IR (KBr) spectrum of 3,5-dimethoxyphenol **43**

95

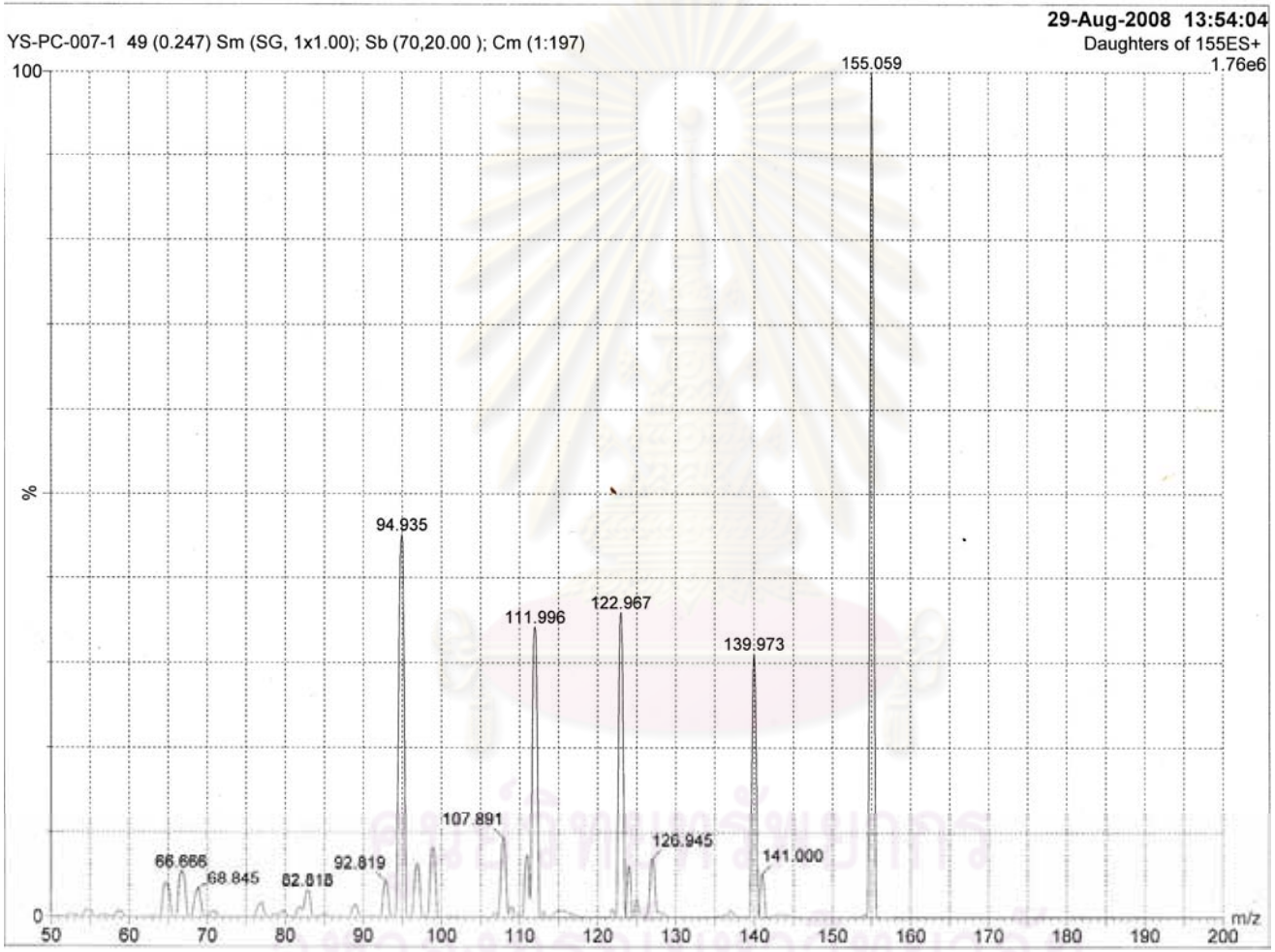

Figure A.43 Mass spectrum of 3,5-dimethoxyphenol **43**

96

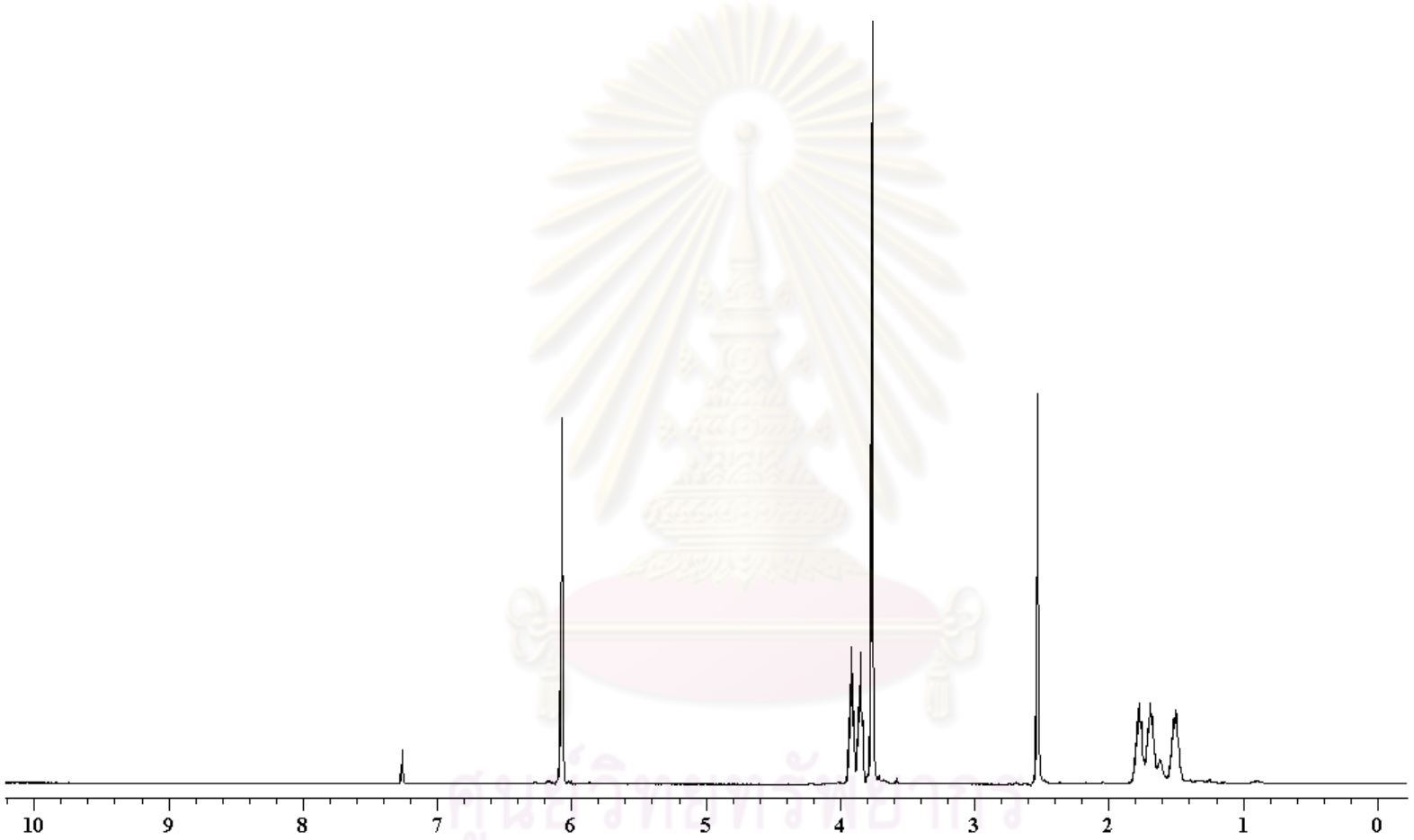

Figure A.44 ^{1}H-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy)benzene **44**

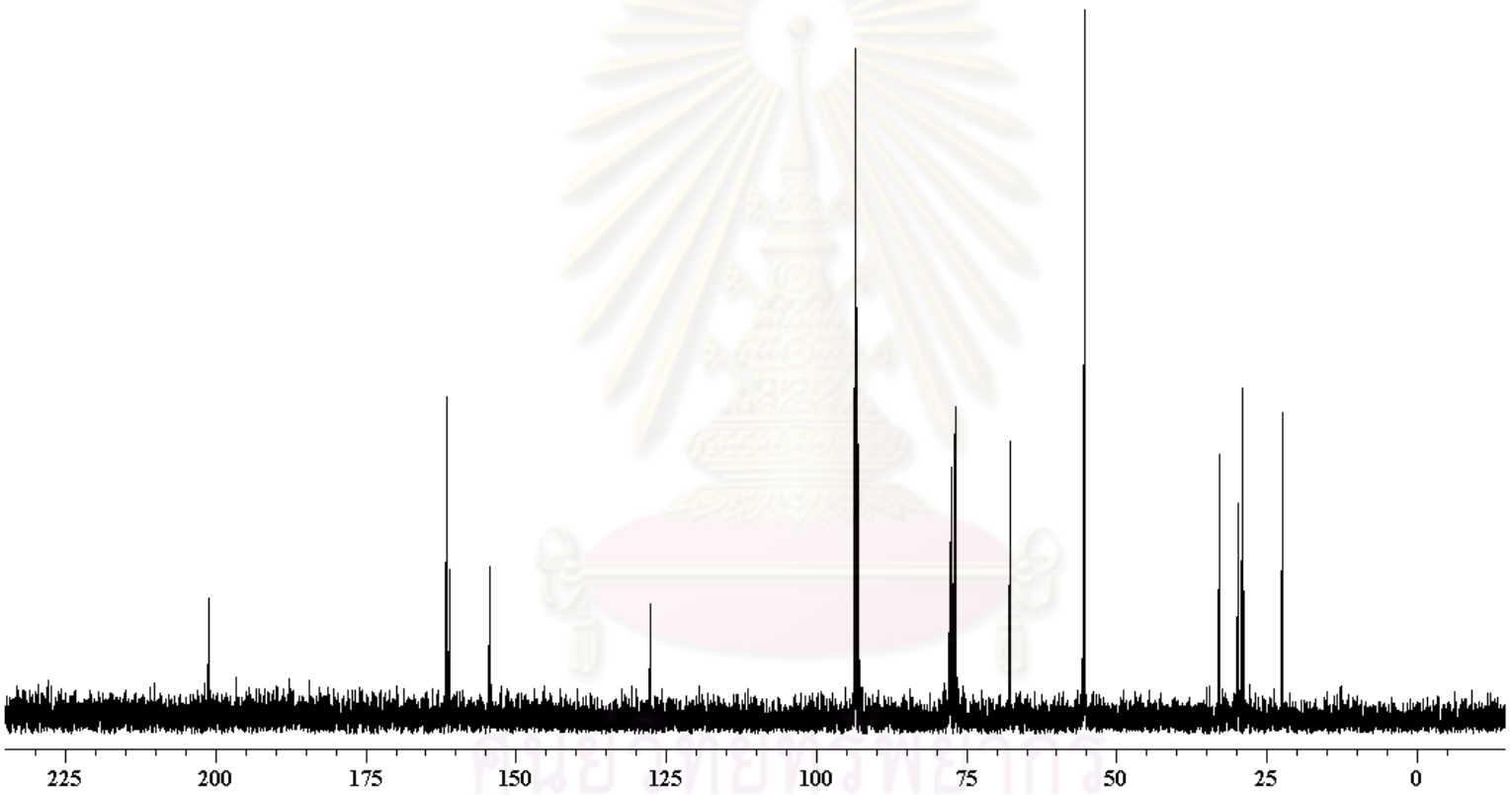

Figure A.45 ^{13}C-NMR ($CDCl_3$) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy)benzene **44**

98

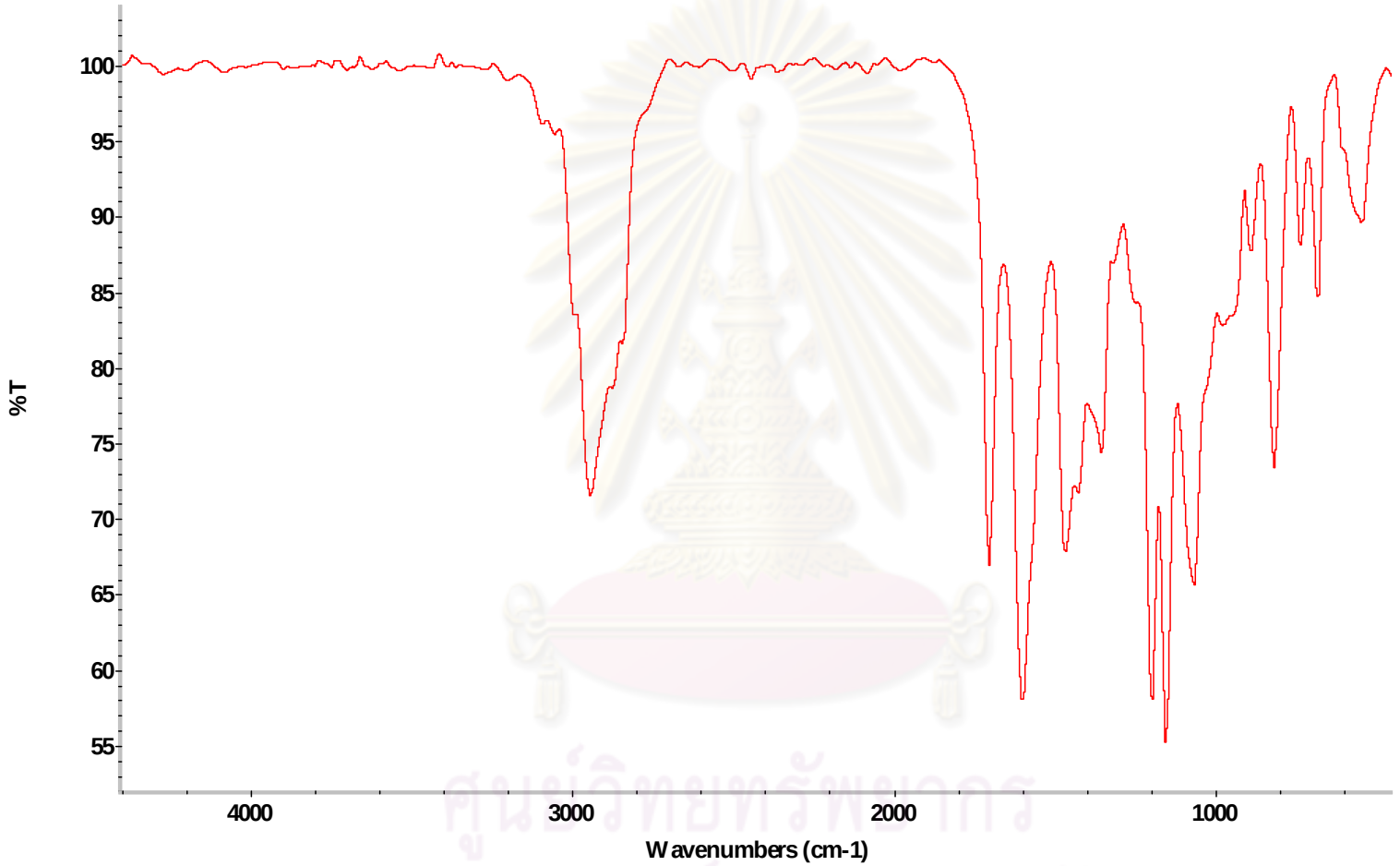

Figure A.46 IR (KBr) spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy)benzene **44**

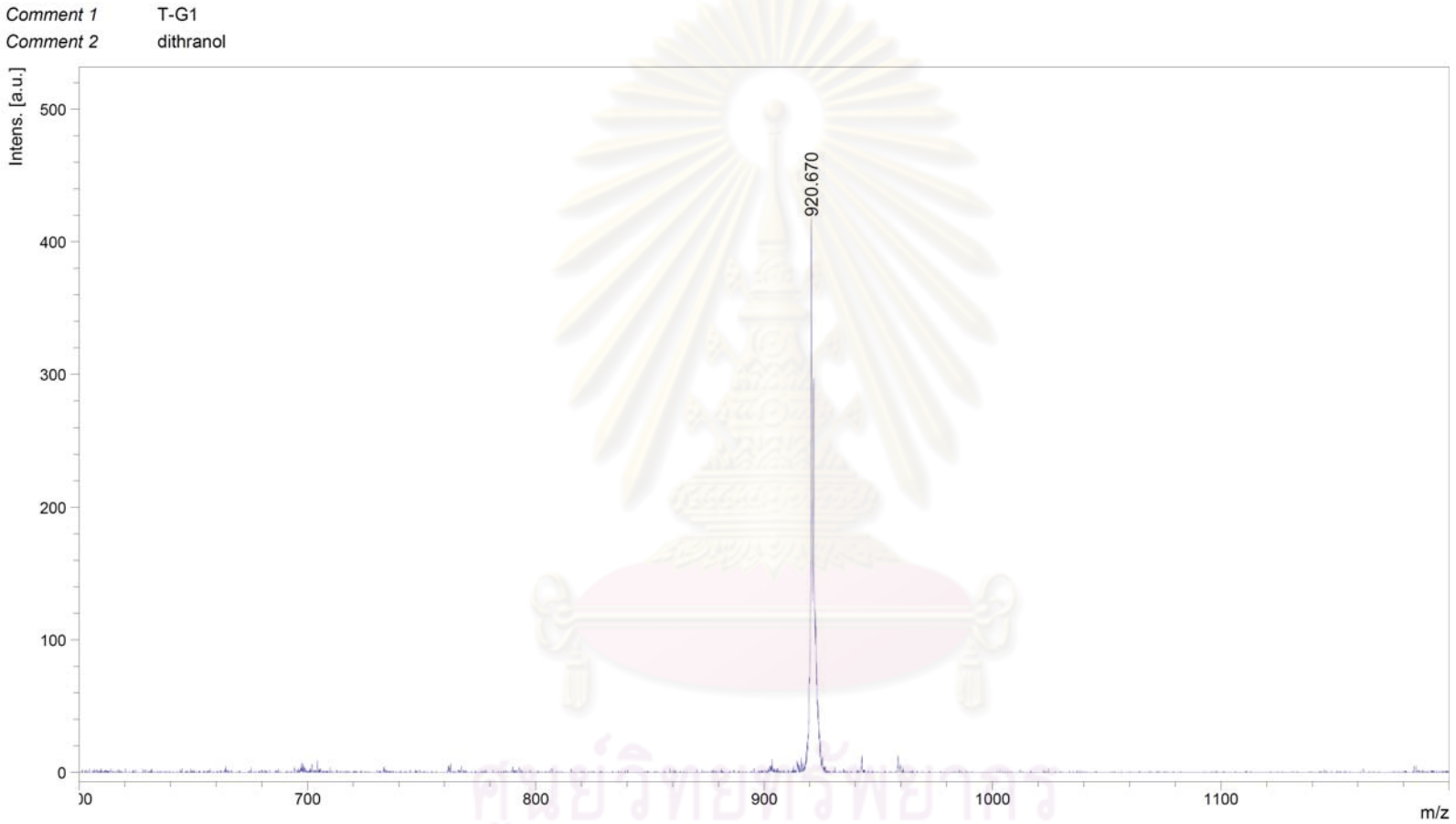

Figure A.47 MALDI-TOF MS spectrum of 1,3,5-triacetyl-2,4,6-tris(5´-(3´´,5´´-dimethoxyphenoxy)pentyloxy)benzene **44**

100

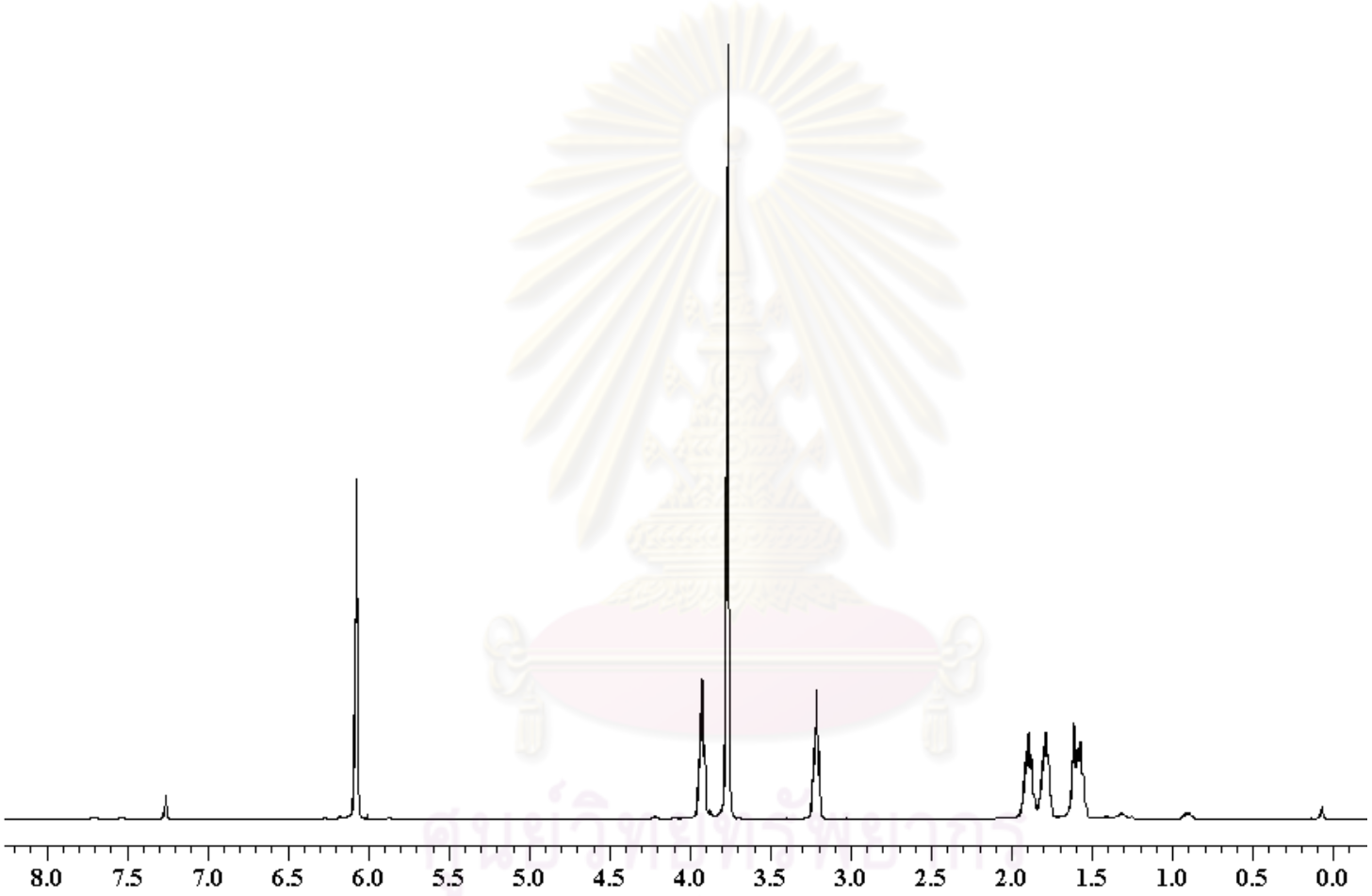

Figure A.48 ^{1}H-NMR ($CDCl_3$) spectrum of product in entry 1 **Table 3.1**

101

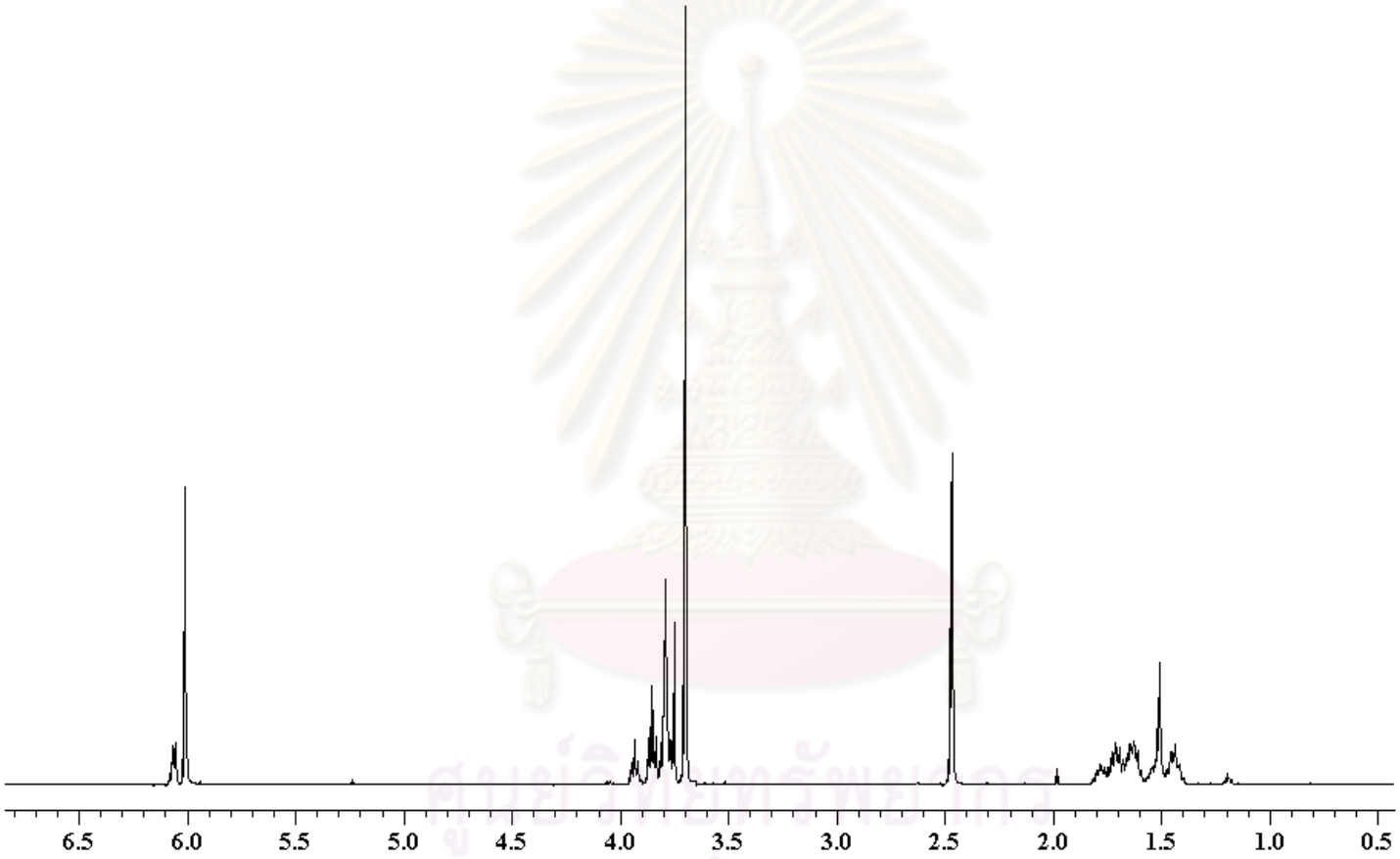

Figure A.49 ^{1}H-NMR ($CDCl_3$) spectrum of Partial demethylation product in entry 2 **Table 3.1**

102

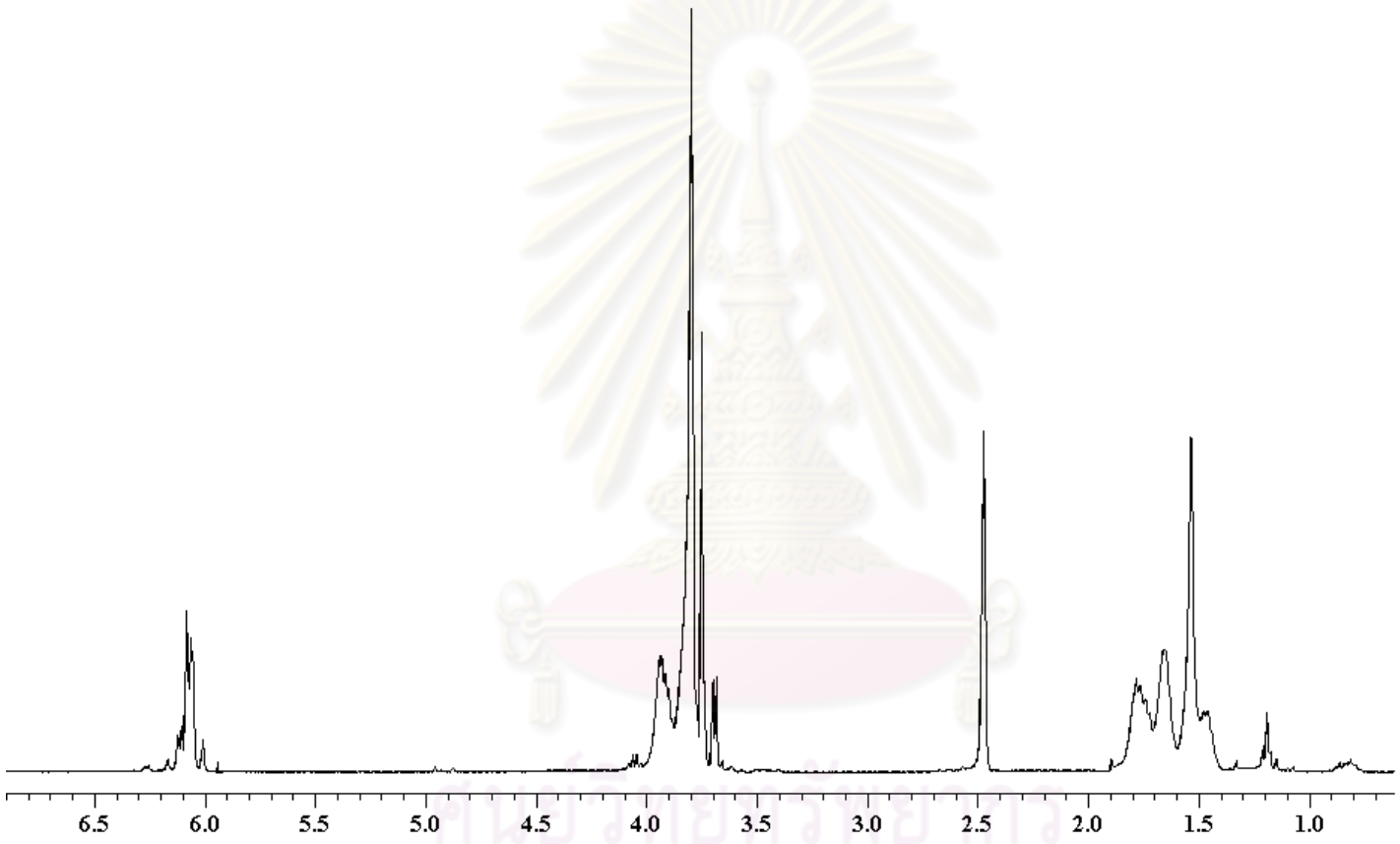

Figure A.50 ^{1}H-NMR ($CDCl_3$) spectrum of Partial demethylation product in entry 3 **Table 3.1**

103

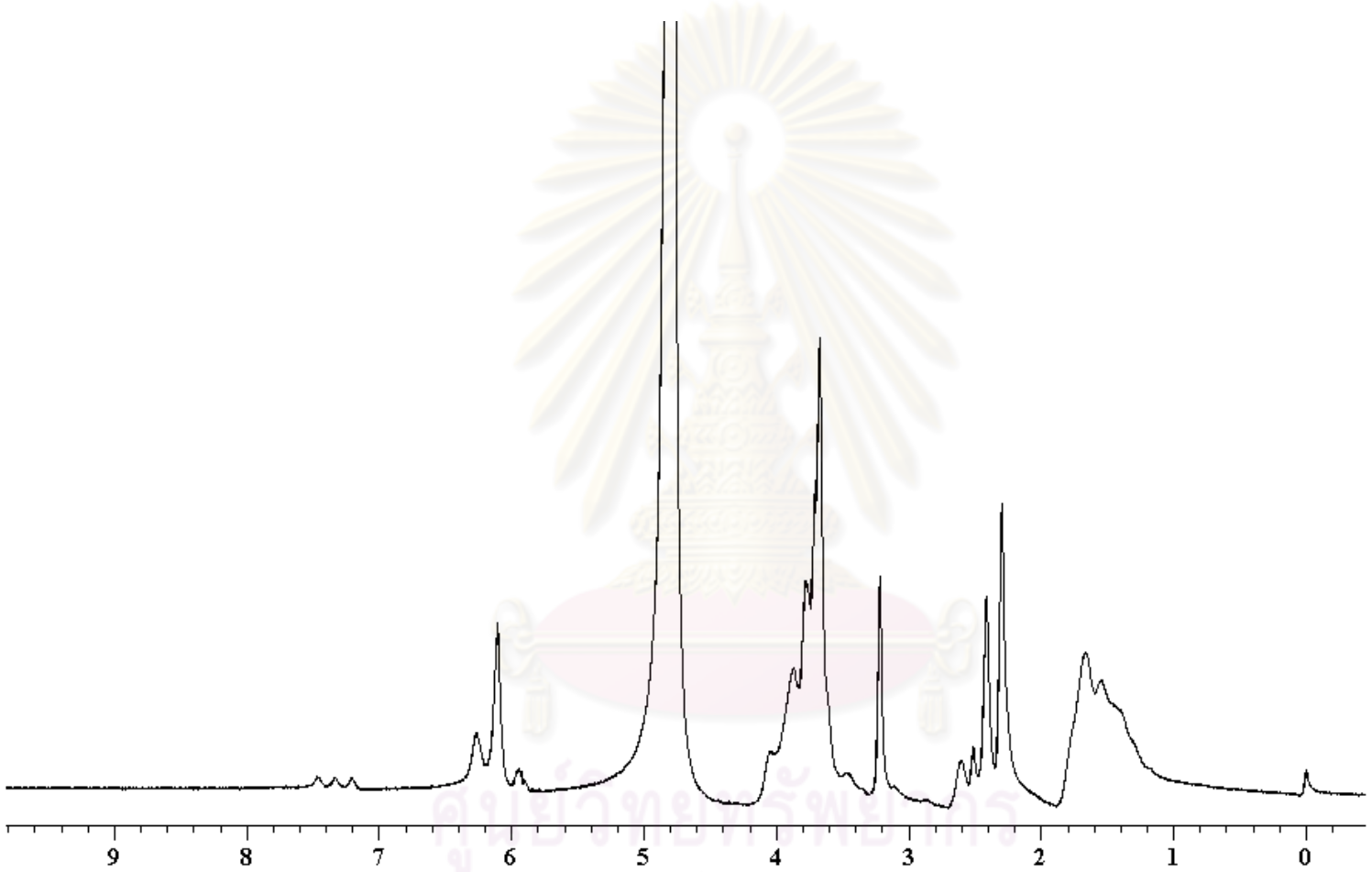

Figure A.51 ^{1}H-NMR (CD_3OD) spectrum of product in entry 4 **Table 3.1**

104

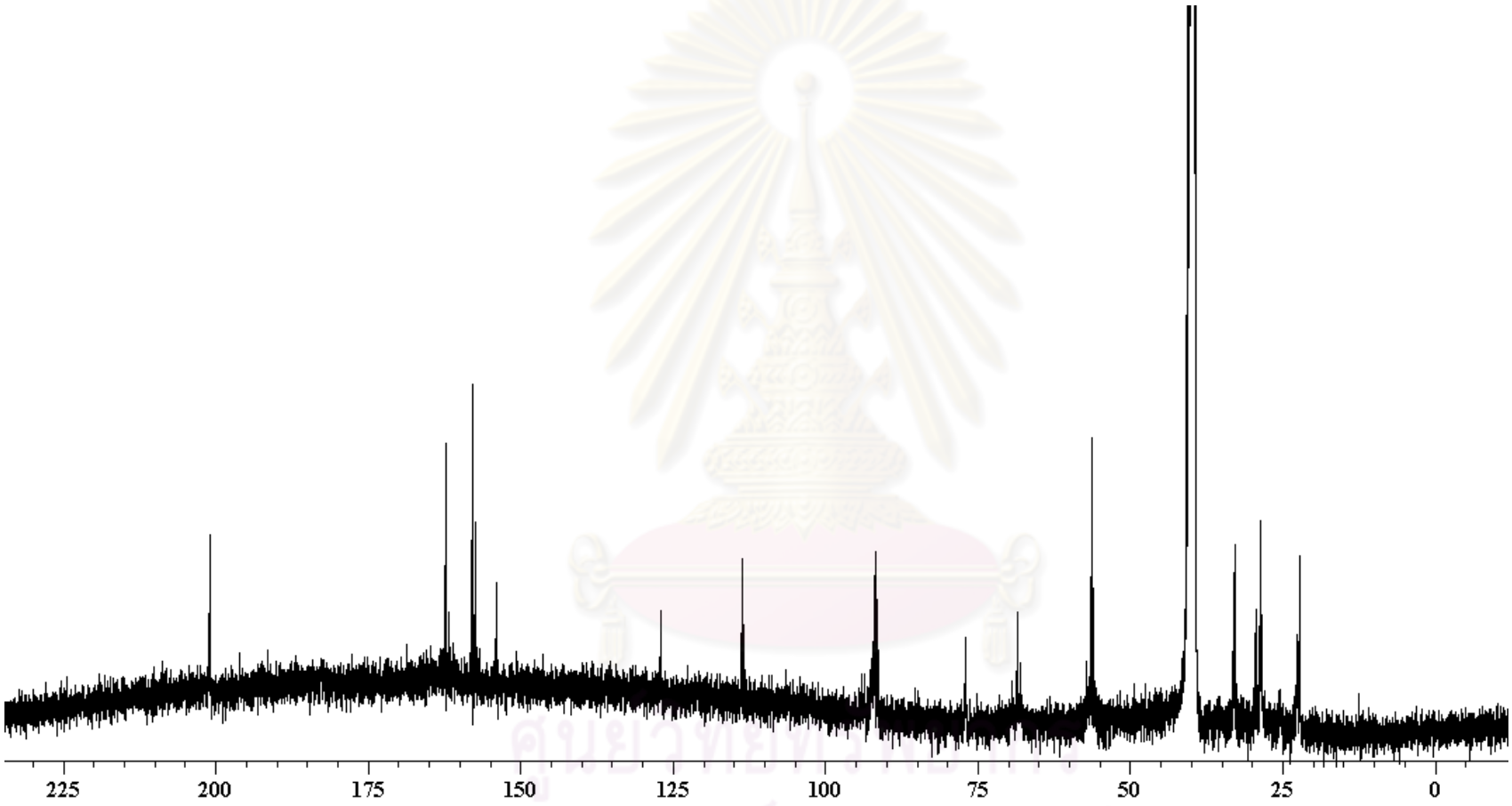

Figure A.52 ^{13}C-NMR (DMSO-d_6) spectrum of product in entry 4 **Table 3.1**

105

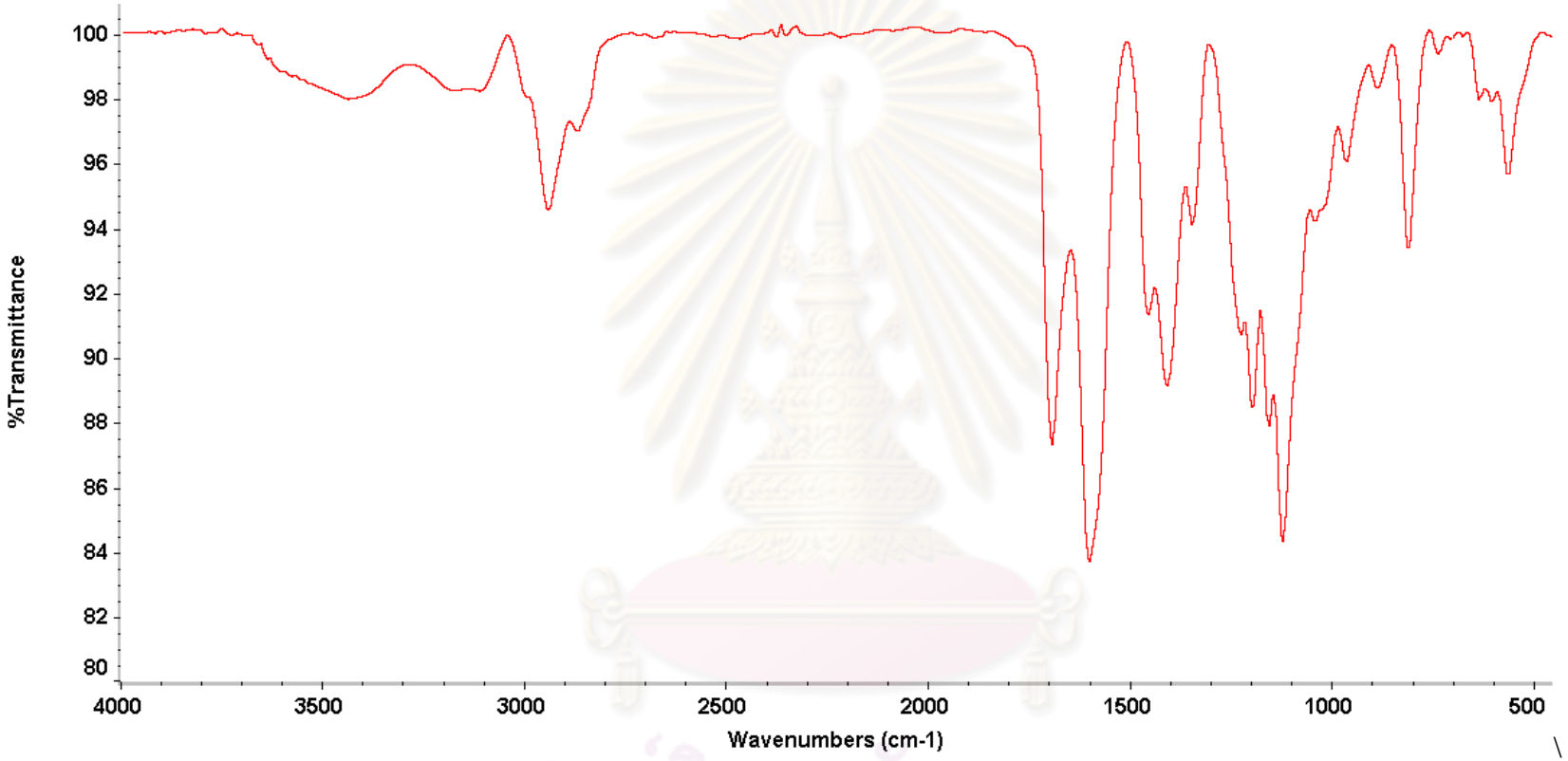

Figure A.53 IR (KBr) spectrum of of product in entry 4 **Table 3.1**

106

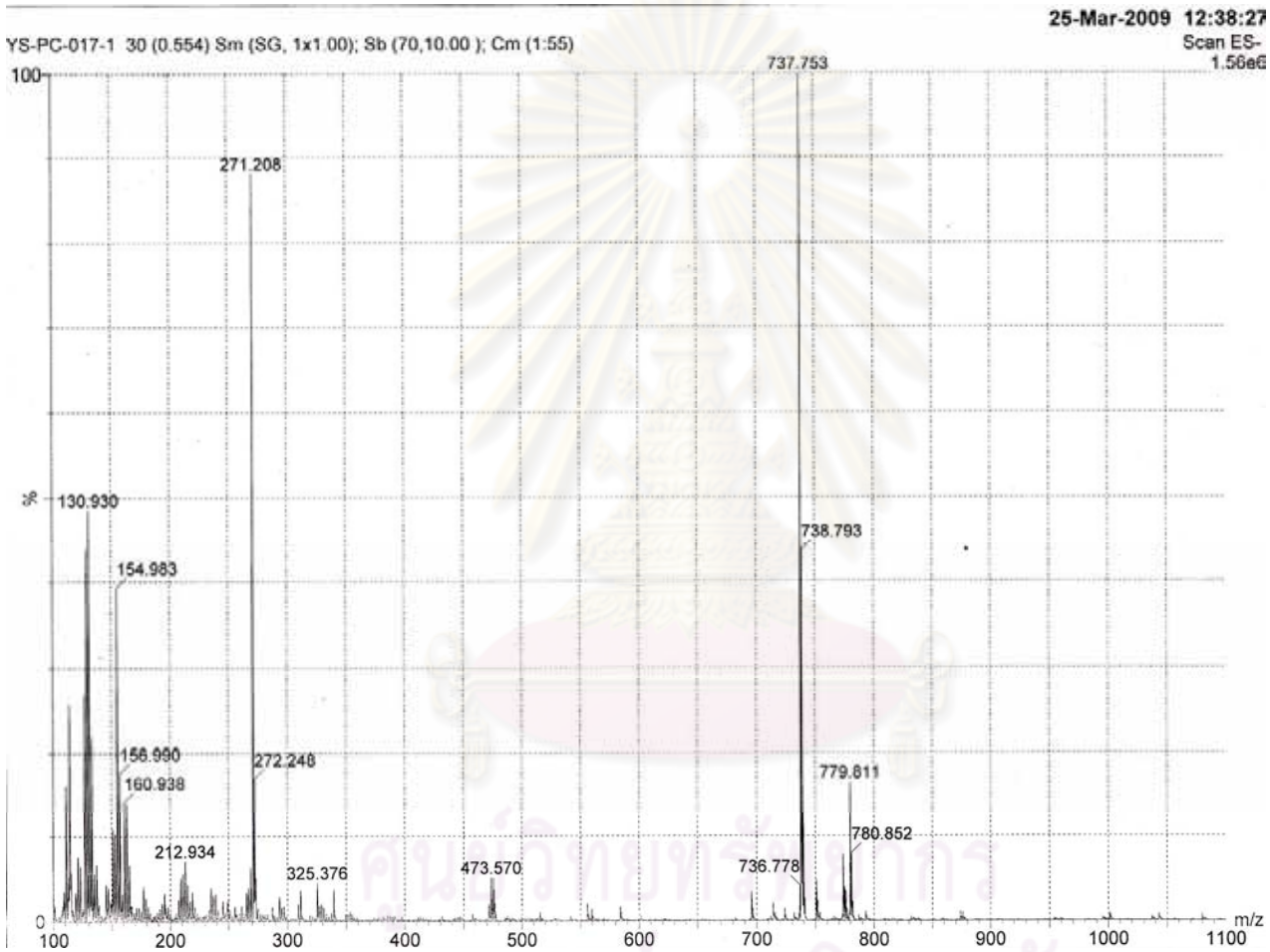

Figure A.54 Mass spectrum of product in entry 4 **Table 3.1**

107

VITA

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