การสังเคราะห์สารประกอบ 6-hydroxy-2,3,9-trimethoxy-[1]-benzopyrano [3,4-*b*][1]benzopyran-12(6H)-one

นางสาว จำเรียง ธรรมธร

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Synthesis of 6-hydroxy-2,3,9-trimethoxy-[1]-benzopyrano [3,4-*b*][1]benzopyran-12(6H)-one

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Thesis Title	SYNTHESIS OF 6-HYDROXY-2,3,9-TRIMETHOXY-[1]-BENZOPYRANO[3,4-*b*][1]BENZOPYRAN-12(6H)-ONE
By	Ms. Jumreang Tummatorn
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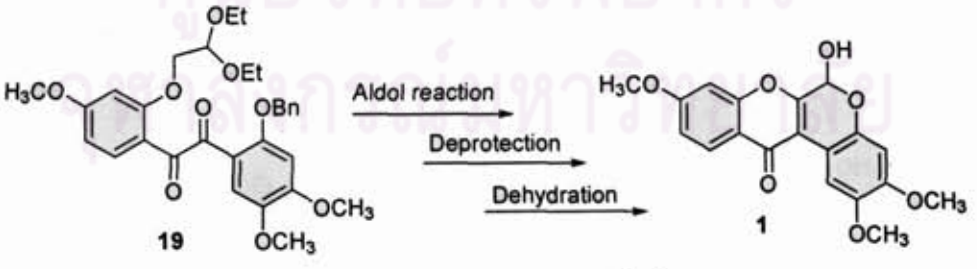
จำเรียง ธรรมธร : การสังเคราะห์สารประกอบ 6-hydroxy- 2,3,9-trimethoxy-[1]-benzopyrano[3,4-*b*][1]benzopyran-12(6H)-one (Synthesis of 6-hydroxy-2,3,9-trimethoxy-[1]-benzopyrano[3,4-*b*][1]benzopyran-12(6H)-one) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ศ. ดร. โสภณ เริงสำราญ, 197 หน้า.

การสังเคราะห์สารประกอบดีไฮโดรโรทีนอยด์ **(1)** สามารถทำได้ในสามขั้นตอนจากสารประกอบไดเอริลไดคีโตน **(19)** ที่เป็นสารตัวกลางสำคัญในการสังเคราะห์ สารตัวกลางดังกล่าวสามารถเตรียมได้จากการออกซิไดซ์สารประกอบไดเอริลอะเซทิลลีนที่ได้จากการทำปฏิกิริยาโซโนกาชิราร์ระหว่างเอริลอะเซทิลลีนและเอริลไอโอไดด์ภายใต้ ภาวะที่มีตัวเร่งปฏิกิริยารูเทเนียม สารประกอบ **19** เมื่อทำปฏิกิริยากับสารประกอบโพลีน แล้วจะเกิดการปิดวงแบบจำเพาะเจาะจง ได้สารประกอบเบนโซไพราโนนเป็นผลิตภัณฑ์ และไม่พบเบนโซไพแรนเกิดขึ้นเป็นสารผลิตภัณฑ์ข้างเคียง ในขั้นตอนสุดท้าย การเกิดปฏิกิริยาไฮโดรจิเนชั่นและดีไฮเดรชัน ตามลำดับ จะทำให้ได้สารประกอบดีไฮโดรโรทีนอยด์ **(1)** คิดเป็นเปอร์เซนต์ผลิตภัณฑ์รวมได้เท่ากับ 45 % จากสารประกอบไดเอริลไดคีโตน **(19)** เมื่อนำสารประกอบดีไฮโดรโรทีนอยด์ **(1)** และสารตัวกลางที่สังเคราะห์ได้ไปทดสอบฤทธิ์ทางชีวภาพในการยับยั้งอาการอักเสบและการยับยั้งเซลล์มะเร็ง พบว่าสารประกอบดีไฮโดรโรทีนอยด์ **(1)** ไม่มีฤทธิ์ในการยับยั้ง ในขณะที่สารประกอบ **154** สามารถยับยั้งเซลล์มะเร็งปอด เซลล์มะเร็งช่องปาก และเซลล์มะเร็งเต้านมได้ ส่วนสารประกอบ **176a, 176d, 177b, 177e,** และ **169** สามารถยับยั้งได้ทั้งเซลล์มะเร็งลำไส้ใหญ่ มะเร็งตับ มะเร็งเต้านม มะเร็งกระเพาะอาหาร และมะเร็งปอด แม้ว่าสารประกอบดีไฮโดรโรทีนอยด์ **(1)** ที่สังเคราะห์ได้ไม่มีฤทธิ์ทางชีวภาพไม่เป็นดังผลที่คาดไว้ แต่วิธีการสังเคราะห์นี้เป็นประโยชน์อย่างมากในการสังเคราะห์โครงสร้างหลักของสารประกอบไอโซฟลาวานอยด์ โรทีนอยด์ และ ดีไฮโดรโรทีนอยด์ได้หลากหลายซึ่งเป็นประโยชน์ต่อศึกษาความสัมพันธ์เชิงโครงสร้างที่มีต่อผลการออกฤทธิ์ทางชีวภาพ



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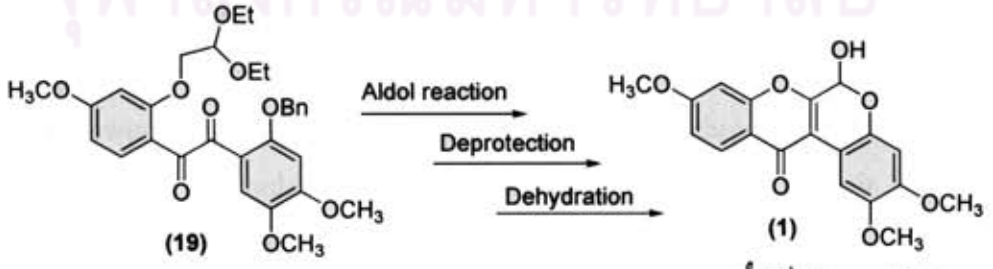
JUMREANG TUMMATORN: SYNTHESIS OF 6-HYDROXY-2,3,9-TRIMETHOXY-[1]-BENZOPYRANO[3,4-*b*][1]BENZOPYRAN-12(6H)-ONE. THESIS PRINCIPAL ADVISOR: PROF. SOPHON ROENGSUMRAN, Ph.D. 197 pp.

The total synthesis of dehydrorotenoid **(1)**, was successfully achieved in three steps through an intramolecular aldol reaction of the corresponding 1,2-diaryl diketone **(19)** as a key intermediate. The corresponding 1,2-diaryl diketone was easily accessed via the ruthenium-catalyzed oxidation of diarylacetylene which was obtained from Sonogashira coupling between monoaryl substituted acetylene and aryl iodide. Treatment of 1,2-diaryl diketone with L-proline induced a selective intramolecular aldol reaction, forming the desired benzopyranone without a byproduct benzofuran. Finally, the target dehydrorotenoid was accomplished in 45% overall yield by deprotection and dehydration reactions, respectively. The synthesized dehydrorotenoid **(1)** and intermediate compounds were evaluated for their biological activities. The results illustrate that compound **1** is inactive, while compound **154** shows activity inhibition of NCI-H187, KB and MCF7 cancer cell lines. However this compound is toxicant to normal cells. Moreover, compound **169**, **176a**, **176d**, **177b**, and **177e** have been found to potently inhibit the SW620, BT474, KATO-III, Hep-G2, CHAGA, and CH-LIVER cancer cell lines. Even the synthesized dehydrorotenoid **(1)**, target molecule, does not show the expected biological activity but this synthetic methodology provides a very useful procedure for synthesis of the most isoflavanoid, rotenoid and dehydrorotenoid core structure. Therefore, this methodology is valuable for the further study of structure-activity relationship.



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LIST OF ABBREVIATIONS

µL	microliter
µm	micrometer
$^{\circ}$C	Degree Celsius
FT-IR	Fourier Transform Infrared Spectroscopy
g	gram
h	hour
NMR	Nuclear Magnetic Resonance Spectroscopy
L	Liter
min	Minute
mg	Miligram
mL	Milliter
ppm	parts per million
%wt	percent weight
δ_H	Chemical shift of ^{1}H NMR
aq	aqueous
Bn	benzyl
Bu	butyl
Bz	benzoyl
^{13}C NMR	carbon-13-nuclear magnetic resonance
CI	chemical ionization
dil.	dilute
EI	enatiomeric excess; for a mixture of two enantiomers R ans S
EI	electron impact ionization
Equiv	electron impact ionization
Et_2O	diethyl ether
NADPH	nicotinamide adenine dinucleotide phosphate-oxide
DMSO	dimethylsulfoxide
Et_3N	triethylamine
EtOAc	ethyl acetate

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^{1}H NMR	proton nuclear magnetic resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
i-Pr	isopropyl
m-CPBA	3-chloroperoxybemzoic acid
Me	methyl
MeCN	acetonitrile
MHz	megahertz
NIS	N-iodosuccinimide
n-BuLi	n-butyllithium
OTf	trifluoromrthanesulfonyloxy (CF_3SO_2O)
TFA	trifluoroacetic acid
TLC	thin-layer chromatography
CH_2Cl_2	dichloromethane
DMF	dimethylfomamide
PPh_3	triphenylphosphine
CBr_4	tetrabromomethane
LDA	lithium diidopropylamine
TIPSCl	triisopropylchlorosilane
H_2O_2	hydrogen peroxide
K_2CO_3	potassium carbonate
MeOH	methanol
CuI	copper iodide
$FeBr_3$	iron(III) tribromide
GC-MS	gas chromotograh-mass spectrometer
LC-MS	liquid chromotograh-mass spectrometer
CO	carbon monoxide
$PdCl_2$	Palladium(II)chloride
TBAF	tetra-n-butylammonium fluoride
TCE	trichloroethylene
HPAs	homopropagyl alcohols
DHP	5,6-dihydro-2-pyrone
Tf_2O	triflic anhydride

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CHAPTER I

INTRODUCTION

1.1 Isolation of dehydrorotenoids

Rotenoids are an important class of natural products found principally in the Stemonaceae family[1] and also in certain unrelated families such as Leguminosae and Nyctaginaceae.[2] Rotenoids possess a variety of biological activities including insecticidal,[3] antiviral,[4] anticancer,[5] antiplasmodial,[6] antibacterial,[7] antifungal,[8] and anti-inflammatory activity.[9] Recent reports have revealed the pharmacological properties of the dehydrorotenoids whose structures are illustrated in Figure 1. [10-11]

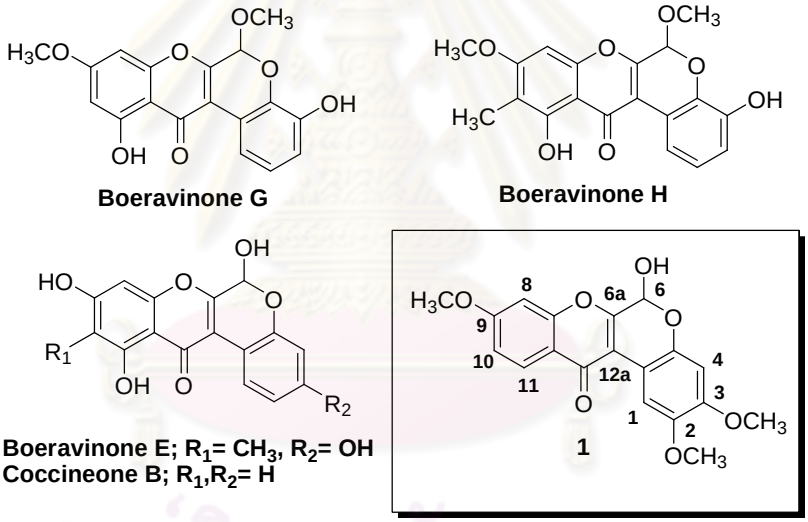


Figure 1 Naturally occurring rotenoids

Boeravinones G and H[10] have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy (IC_{50} 0.7 ± 0.07 μM for Boeravinone G and 2.5 ± 0.47 μM for Boeravinone H).[10] Boeravinone E and G[11] have anti-spasmolytic activity, inhibiting the contractions of smooth muscle induced by acetylcholine (Ach) (IC_{50} 11.0 (10.2-12.3) μg/mL for Boeravinone E and 4.44 (2.16-6.69) μg/mL for Boeravinone G).[11] Boeravinones E, G and H were isolated from the methanol extract of the roots of *Boerhaavia diffusa* L. (Nyctaginaceae)

collected in Bangalore (India). These compounds were purified by column chromatography and high-performance liquid chromatography (HPLC). 6-Hydroxy-2,3,9-trimethoxy-[1]-benzopyrano[3.4.b][1]benzo-pyran-12(6H)-one **(1)** [9a] was isolated from the ethyl acetate extract of the dried and powdered seeds of *C. fairchildiana*, collected from the Ornamental Plant Garden of the Federal University in Brazil, with an anti-inflammatory activity based on capillary permeability assay.[9]

1.2 Proposed biosythesis of dehydrorotenoids core structure [12]

The key structure of rotenoid is the tetracyclic unit, 6a,12a-dihydro-6H,12H-[1]benzopyrano[3,4-*b*][1]benzopyran-12-one, as shown in Figure 2.

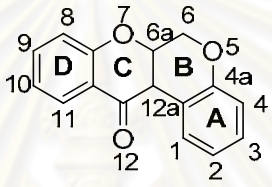
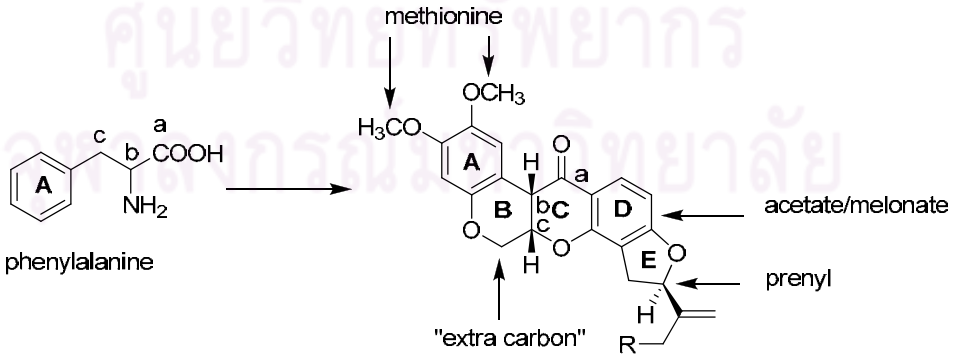


Figure 2 Rotenoid core structure

Scheme 1 illustrates the overall biosynthesis of rotenoid compound. The aryl ring-A is migrated from carbon-c of phenylalanine to carbon-b in the rotenoid core structure, thereby suggesting an isoflavonoid derivatation. Aromatic ring-D is derived from the acetate/malonate pathway and the “extra” C-6 carbon, along with the methyl groups of the two ring-A methoxy groups, is gained from the methyl group of methionine.



Scheme 1 The biosynthesis of rotenoid

The biosynthesis of rotenoid compounds is characterized in derivation as biosynthetically advanced isoflavonoids, and this agrees with the circumstantial evidence of their occurrence. Thus toxicarol **(2)** and toxicarol isoflavone **(3)** are found together in *Derris malaccensis*, while dolineone **(4)** and the isoflavanone **5** occur in *Neorautanenia pseudopachyrrhiza* as shown in Figure 3. The progress of the biosynthesis of rotenoids from primary metabolites can be divided into a number of phases as indicated in Scheme 2.

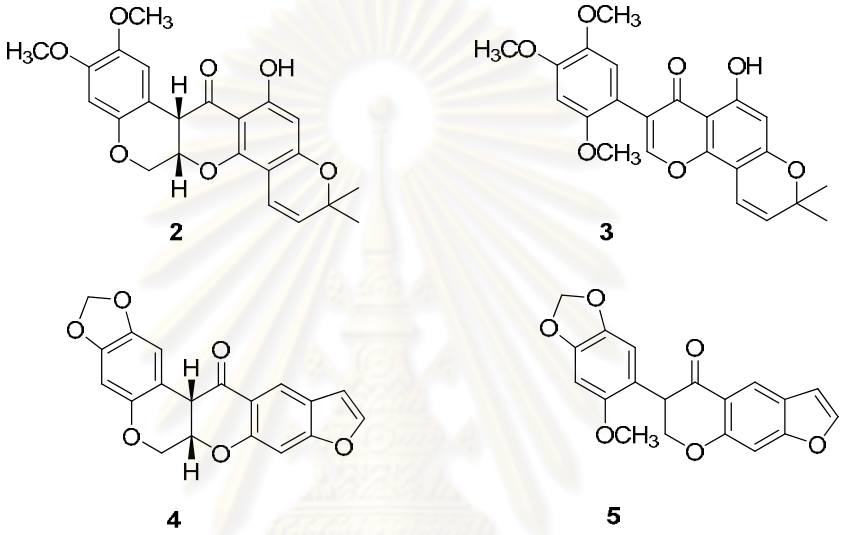


Figure 3 The structures of rotenoids and isoflavanoids

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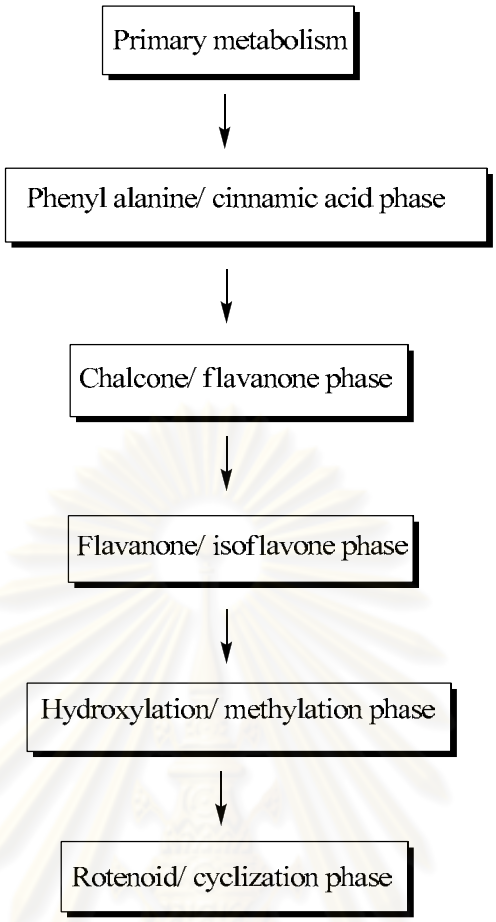
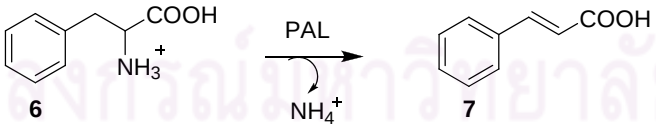


Scheme 2 Biosynthetic pathway of rotenoids

1.2.1) Phenyl alanine/cinnamic acid phase

L-phenylalanine **(6)** is converted into cinnamic acid **(7)** by the enzyme L-phenlyalanine ammonia lyase (PAL). This step involves with the enzymic elimination of ammonium ion in an antiperipalnar fashion to produce (*E*)-cinnamic acid as shown in Scheme 3.

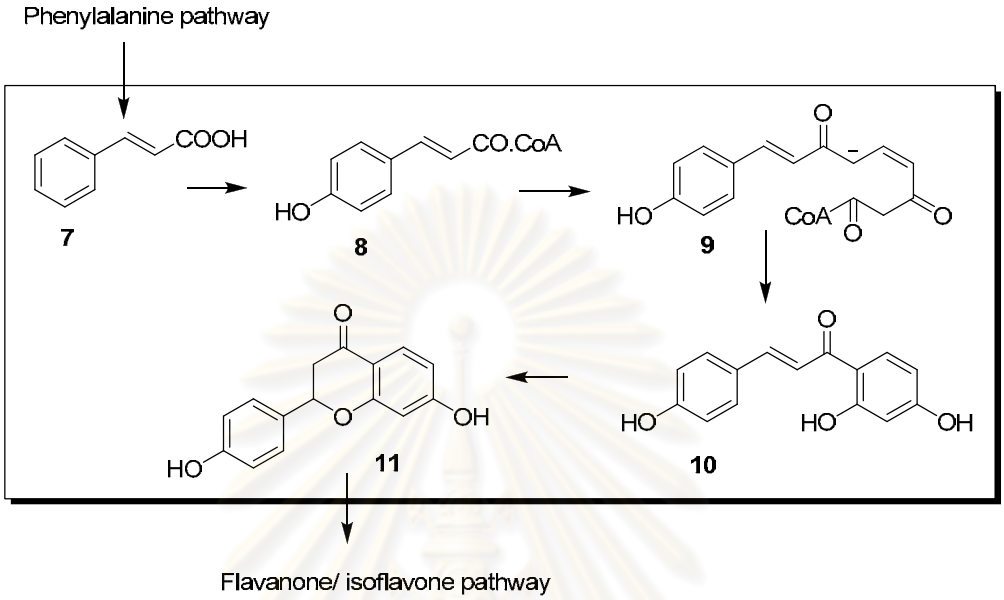


Scheme 3 Phenyl alanine/cinnamic acid phase

1.2.2) Chalcone/flavanone phase

In this phase, (*E*)-cinnamic acid **(7)** is hydroxylated by cinnamate 4-hydroxylate (a cytochrome P450 mono-oxygenase requiring NADPH and O_2) and the action of 4-coumarate CoA ligase to provide 4-coumaric acid as its CoA derivative **8**. This compound is condensed with three acetate units that derived from malonyl-CoA

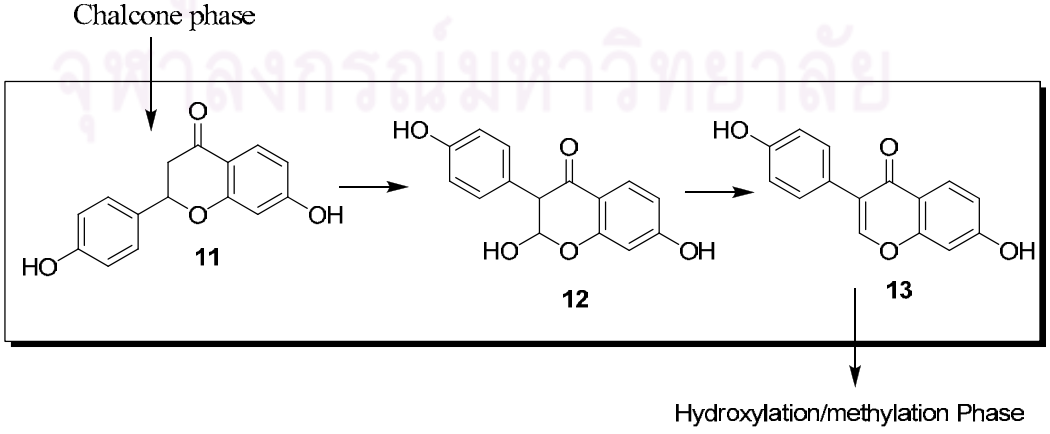
to generate compound **9**. The chalcone **10** is produced by the chalcone synthase catalyzed cyclization of compound **9** and this chalcone is converted to the flavanone structure **11** as shown in Scheme 4.



Scheme 4 Chalcone/flavanone phase

1.2.3) Flavanone/ isoflavonone phase

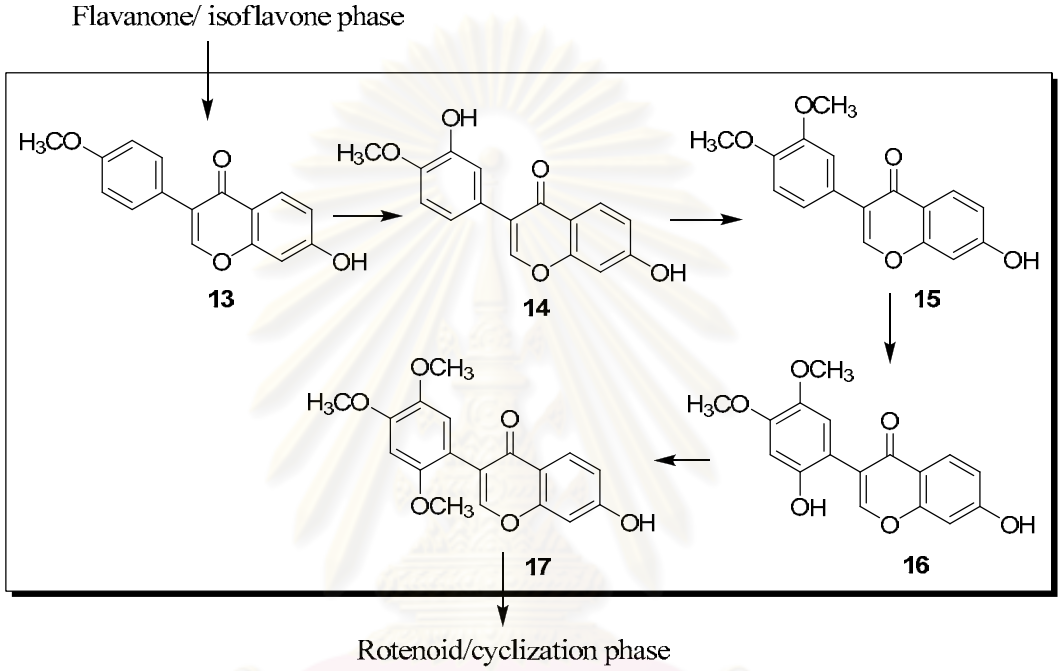
This phase of the biosynthesis involves oxidation, and the overall 1,2-rearrangement of the aryl group destine to become ring-A of the rotenoid. The flavanone **11** is initiated by isoflavone synthese, an NADPH-dependent P-450 iron-containing microsomal enzyme of the endoplasmic reticulum, to produce the hydroxyisoflavanone **12**. Next, this compound is dehydrated to give the flavone **13** by soluble dehydrase enzyme as shown in Scheme 5.



Scheme 5 Flavanone/isoflavonone phase

1.2.4) Hydroxylation/ methylation phase

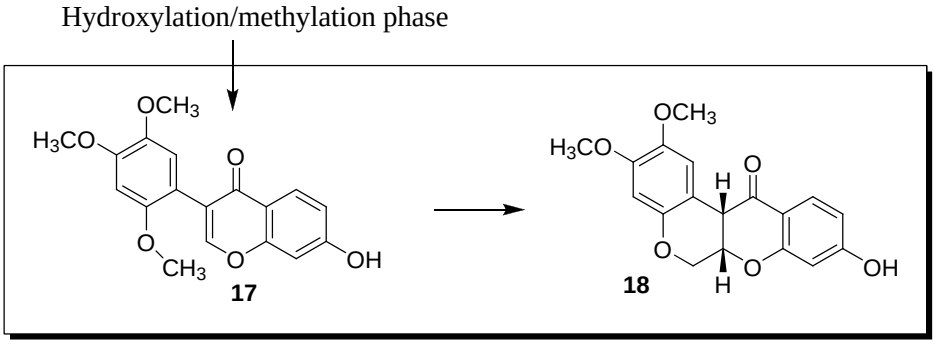
The isoflavanone **13** is taken place to generate 3′,7′-dihydroxy-4′-methoxy-isoflavanone **(14)** by ortho-hydroxylation via arene oxide mechanism. Compound **14** is then methylated by *S*-adensosylmethionine to give diether **15**. 6′-Hydroxylation of compound **15** is followed by another methylation leads to compounds **16** and **17** as shown in Scheme 6.



Scheme 6 Hydroxylation/methylation phase

1.2.5) Rotenoid/cyclisation phase

The cyclization process is presented in Scheme 7 but there is little knowledge of the enzymology, whether one or more enzymes are involved, that lays between structures **17** and **18**. It may be represented as a radical generation and addition process as shown in Scheme 7.



Scheme 7 Rotenoid/cyclization phase

1.3 Retrosynthesis of dehydrorotenoid

A variety of synthetic approaches for rotenoid syntheses have been investigated, although previous approaches do not permit access to dehydrorotenoids containing an acetal moiety in ring B. To date, the only report concerning the synthesis of this structure is the synthesis of coccineone B using 2-benzoyloxybenzyl-2,4,6,-trihydroxyphenyl ketone as key intermediate.[13] This study will focus on the methodology that provides direct access to dehydrorotenoid **(1)**, a representative compound to illustrate this synthetic strategy, from diketone intermediate.

This research described the methodological challenges associated with the synthesis of dehydrorotenoid **1**, which was achieved in three steps using the corresponding 1,2-diaryl diketone as a key intermediate. Several features of our synthetic strategy were attractive: (i) the convergent pathway minimizes the number of linear synthetic steps while maximizing product yields; (ii) the availability of functionalized 1,2-diaryl substituted diketones provided abundant starting materials using an oxidation protocol was describe herein, that could be used for the synthesis of a variety of dehydrorotenoid-based natural products, implying further uses in preparing many related compounds for biological study.

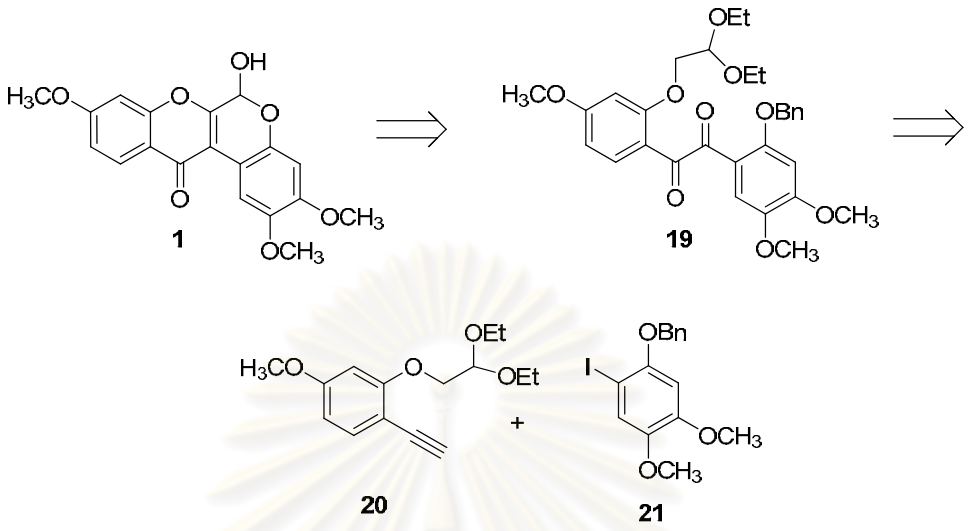
Thus, the objectives of this research are summarized as follows:

1) To develop efficient methods for the synthesis of 6-hydroxy-2,3,9-trimethoxy-[1]-benzopyrano[3,4-b][1]benzopyran-12(6H)-one **(1)** from diketone intermediate.

2) To investigate the bioactivity of synthesized compounds.

The retrosynthetic approach is adopted for compound **1** and outlined in Scheme 8. The synthetic strategy is based on two key successive intramolecular cyclization steps of 1,2-diaryl diketone **19** which can be traced back from the

corresponding substituted diaryl acetylene. The preparation of the desired substituted diaryl acetylene is accomplished by Sonogashira coupling between monoaryl substituted acetylene **20** and aryl iodide **21**.



Scheme 8 Retrosynthetic approach of compound **1**

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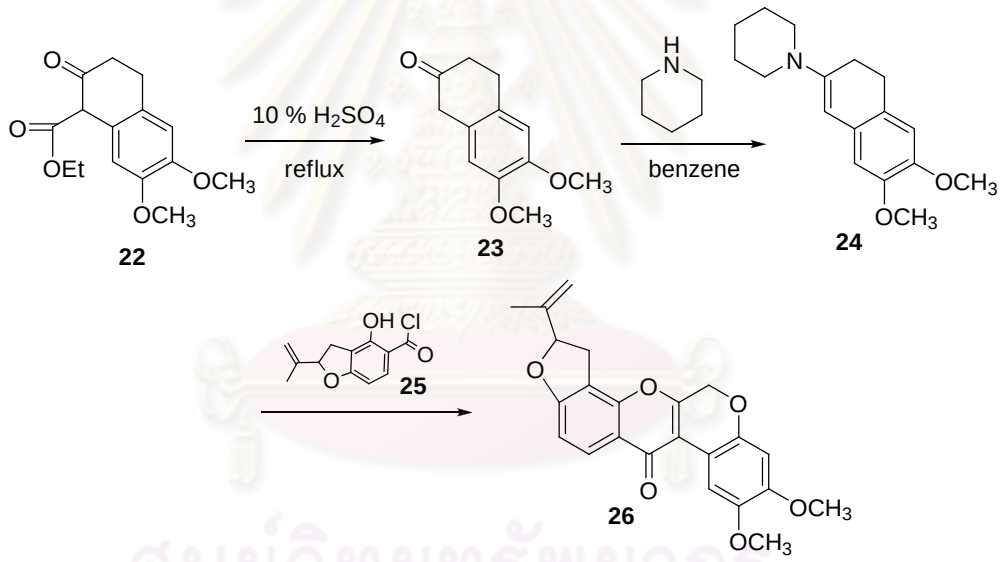
CHAPTER II

LITERATURE REVIEWS

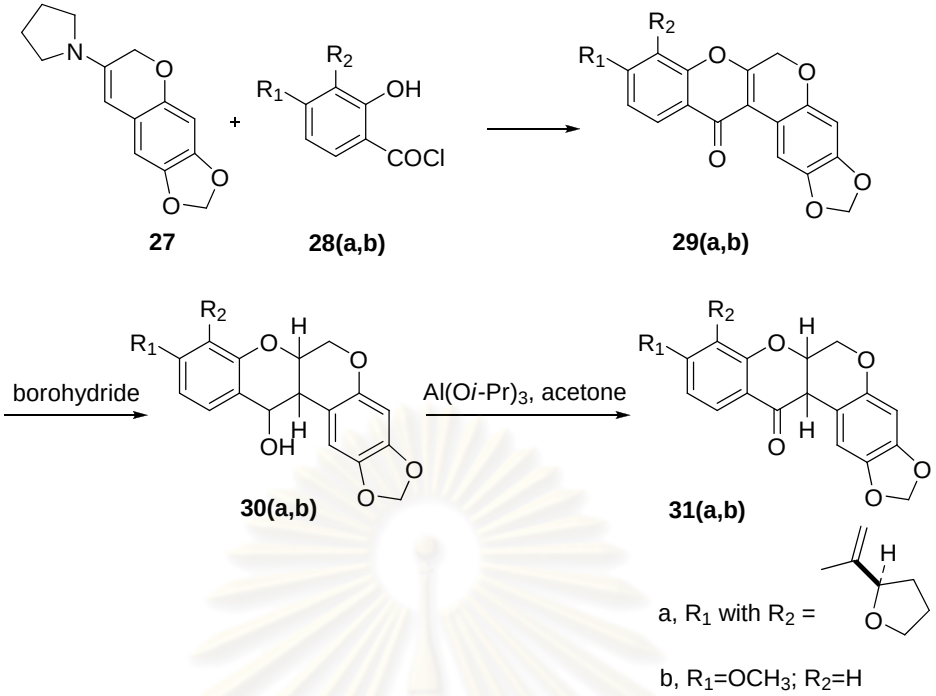
2.1 Synthetic approaches towards the rotenoid core structure

In 1965, Miyano Masatery[14] has reported the total synthesis of dehydrorotenoid **(26)** via the condensation of enamine **24** and compound **25** as key step. Initially, the β-keto ester **22** was converted to the ketone **23** under refluxing in acid condition. This ketone was reacted with pyrrolidine in benzene to provide the pyrrolidine enamine **24**. Finally, pyrrolidine enamine **24** was condensed with tubaic acid **(25)** to give dehydrorotenone product **26** as shown in Scheme 9.



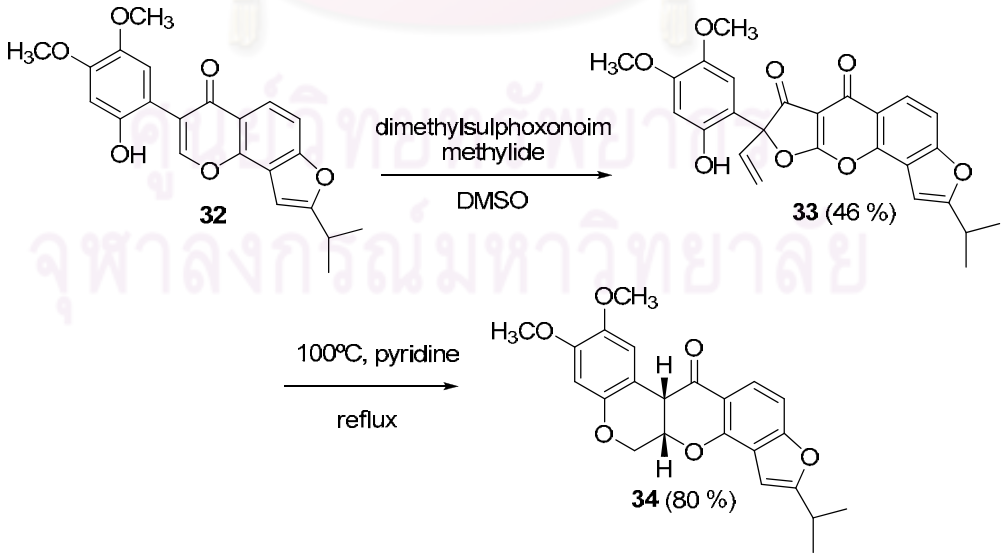
Scheme 9 Synthesis of dehydrorotenoid by the condensation of enamine and acid chloride

In 1970, Miyano Masatery[15] studied the synthesis of methylenedioxyphenyl analogs of rotenone **31a,b**. The pyrolidine enamine **27** underwent condensation with 1-butalic acid chloride **28a,b** to give **29a,b** which was reduced with borohydride to generate **30a, b** and finally reoxidized to compound **31a**,**b** by Oppenauer reaction as shown in Scheme 10.



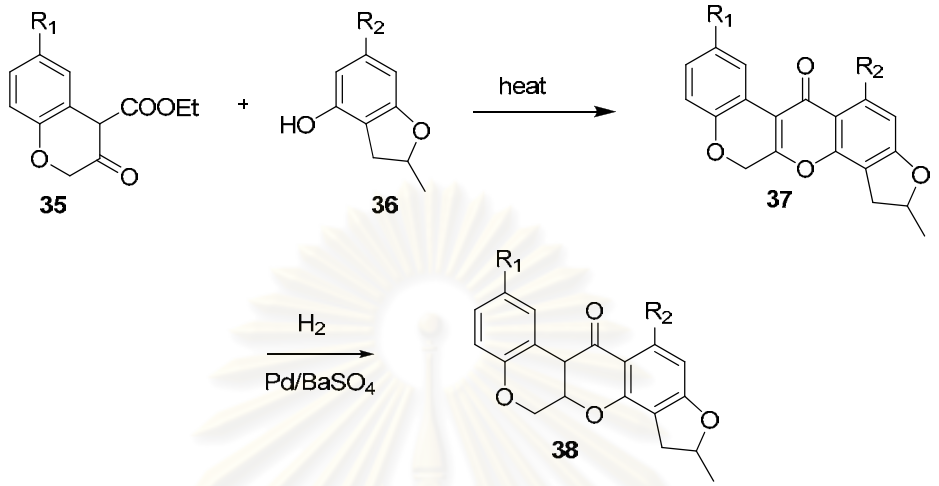
Scheme 10 The synthesis of methylenedioxyphenyl analogs of rotenone

In 1973, Crombie *et al*.[16] have described a synthesis of rotenoid **34**, which involved the conversion of isoderrital isoflavone **(32)** into the vinylcoumaranone **(33)** by treatment with dimethylsulphoxonium methylide in dimethylsulphoxide. Finally, the vinylcoumaranone **(33)** was heated at 100 °C in pyridine for 24 h to obtaine (±)-isorotenone **(34)** in 80 % yields as shown in Scheme 11.



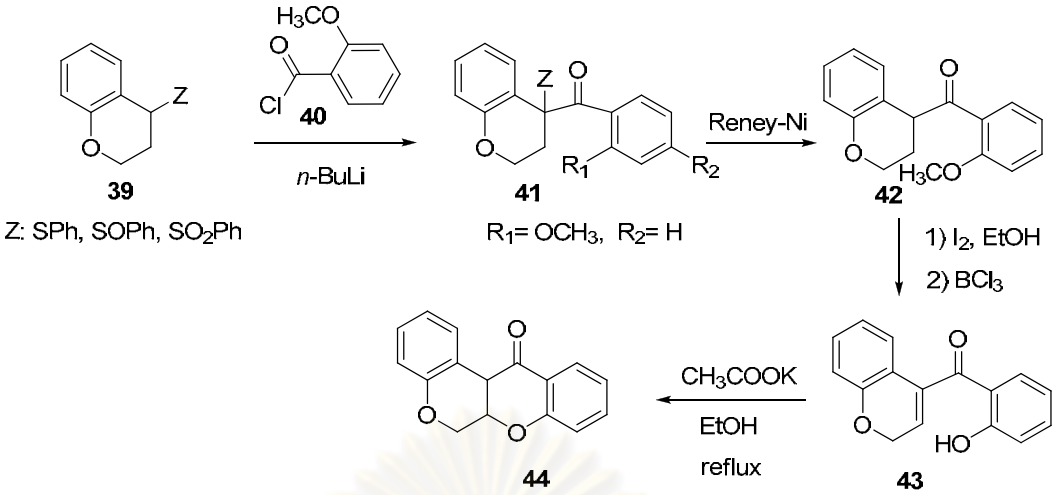
Scheme 11 Syntesis of (±)-isorotenone

In 1980, Verhe *et al*.[17] have reported the preparation of new rotenoid **38** by thermal condensation of 4-ethoxycarbonyl-3-chromanones (**35)** with *O*-heterocyclic phenols **36**, affording dehydrorotenoid **37** which was transformed into rotenoids by catalytic hydrogenation as shown in Scheme 12.



Scheme 12 The preparation of rotenoid by thermal condensation

In 1989, Steven *et al*.[18] have presented the synthesis of rotenoid ring system using 4-aroylation of the 4-phenyl-sulphonylchromans **(39)** as key step. All sulphenyl chromans **(39)** contain an anion stabilizing group Z, were prepared from the well known route. These compounds were deprotonated with *n*-BuLi to generate the desired anion and then were reacted with benzoyl chloride derivative **40** to afford the β-ketosulphones **41**. Next this compound was reductively desulphonylated using Raney nickel in quantitative yield. The product compound **42** was dehydrogenated by iodine in ethanol, and then the product chrom-3-ene was demethylated using boron trichloride to give compound **43**. The labile intermediate **43** was then cyclized by refluxing in ethanol with potassium acetate to afford the desired rotenoid **44** containing the rotenoid ring system as shown in Scheme 13.



Scheme 13 The synthesis of rotenoid ring system using 4-aroylation reaction

In 1992, Ahmad-Junan *et al.*[19] have reported a new synthesis approach to the rotenoid ring system **56**. This route commenced from condensation of 2-hydroxy-4-methoxyacetophenone **(45)** with ethyl ethoxyacetal and then acid-catalyzed cyclization gave 2-ethoxymethyl-7-methoxychromone (**46)**. This compound was converted into the desired bromo compound **47** by treatment with hydrogen bromide. Next this compound was treated with 3,4-dimethoxyphenol **(48)** to provide chromone **49**, which was iodinated to afford compound **50**. Treatment of compound **50** with sodium borohydride underwent conjugate reduction to yield the chromanol **51**, which readily dehydration with *p*-toluenesulfonic acid to the required compound **52**. The cyclization of the iodoamlchromene **52** with palladium acetate formed the tetracyclic compound **53**, which was treated with osmium tetraoxide-*N*-methylmorpholine-*N*-oxide to yield the diol **54**. Oxidation of diol **54** furnished the rotenone **55** that was followed by zinc effect deoxygenation, to afford (±) munduserone **56** as shown in Scheme 14.

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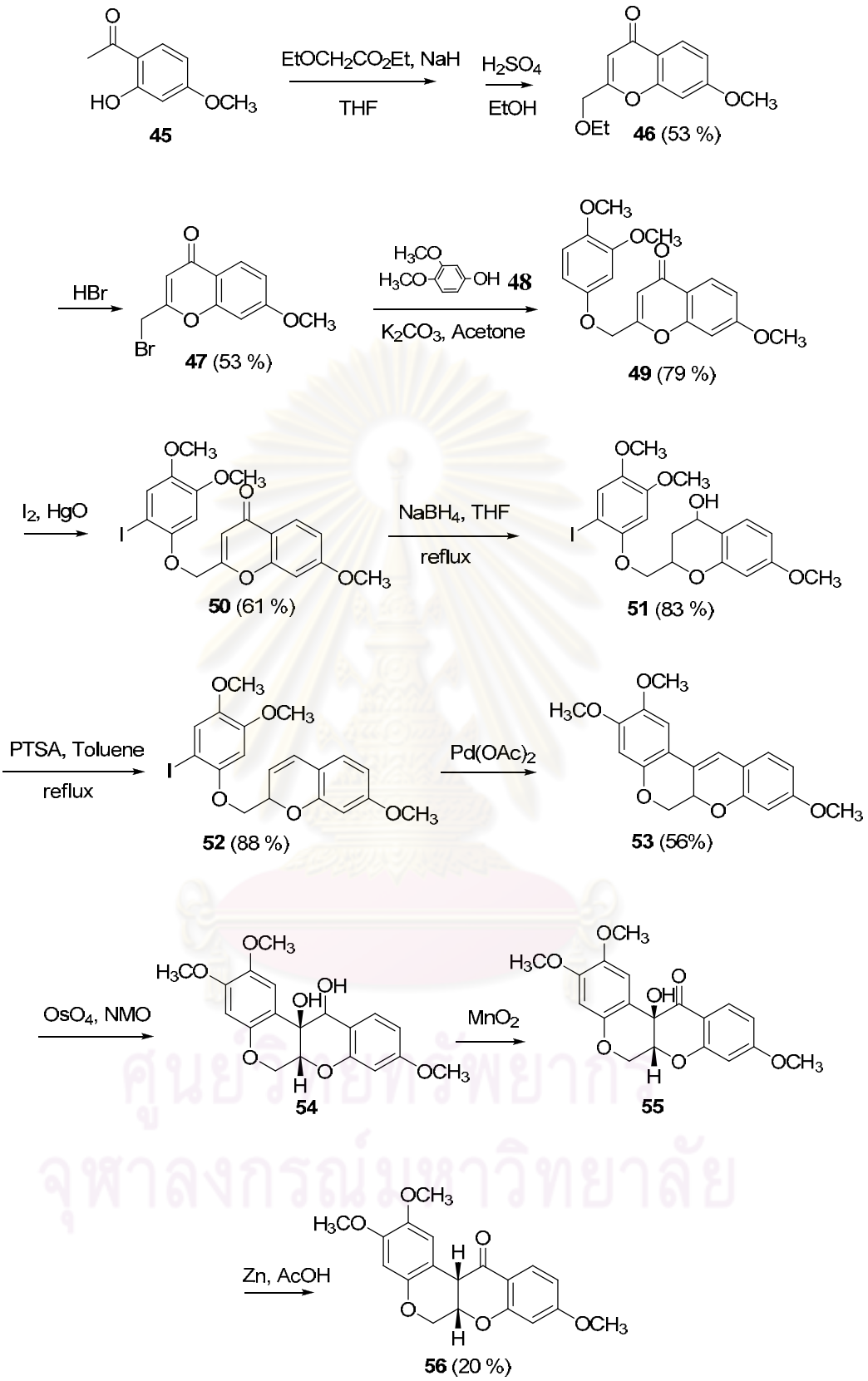

Scheme 14 Synthesis of (±) munduserone **(56)**

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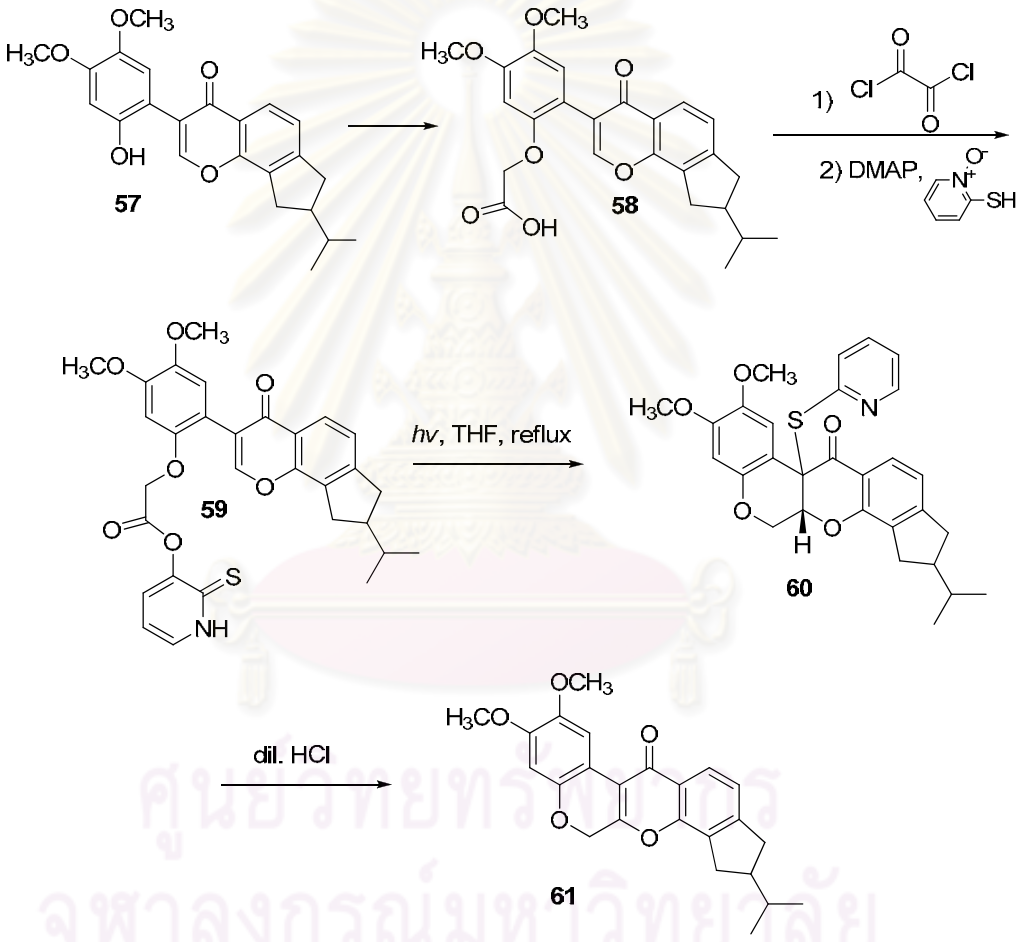
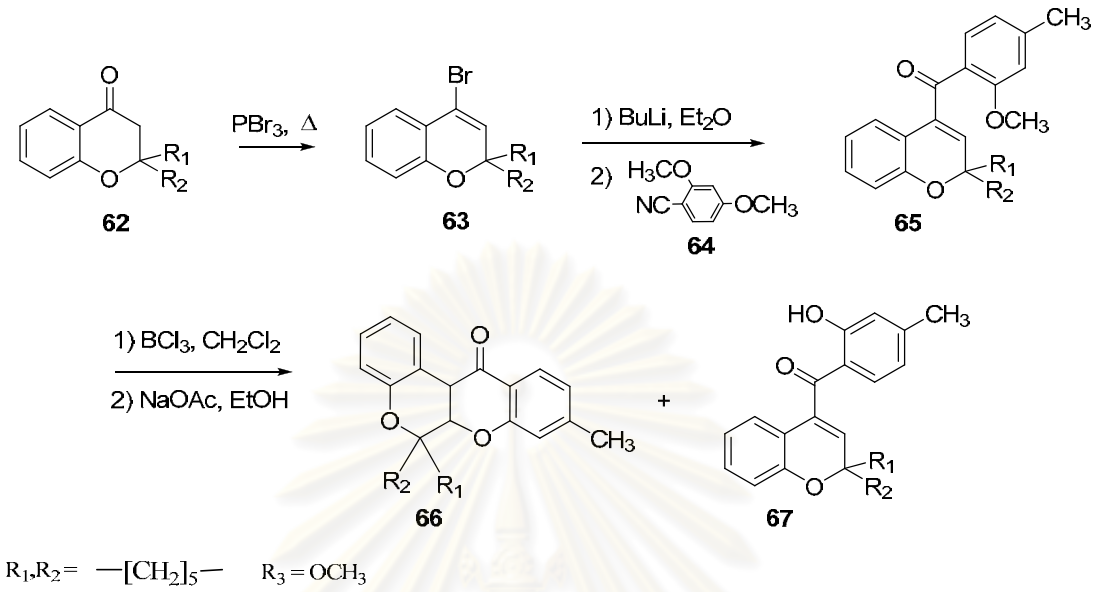
In 1992, Ahmad-Junan *et al.*[20] have reported the methodology for synthesis of rotenoid **61** via radical cyclization. Isiderritol isoflavone **(57)** was first prepared by literature methods and was converted into the corresponding aryloxy acetic acid **58**. The thioxopyridyl ester **59** was prepared in situ and was then irradiated (tungsten lamp) in refluxing tetrahydrofuran solution to afford a crude mixture of compound **60**. This crude mixture of compound **60** was treated with dilute hydrochloric acid to afford a mixture containing one major product. This proved to be dehydroisoprotenone **(61)**.



Scheme 15 Synthesis of rotenoid via radical cyclization

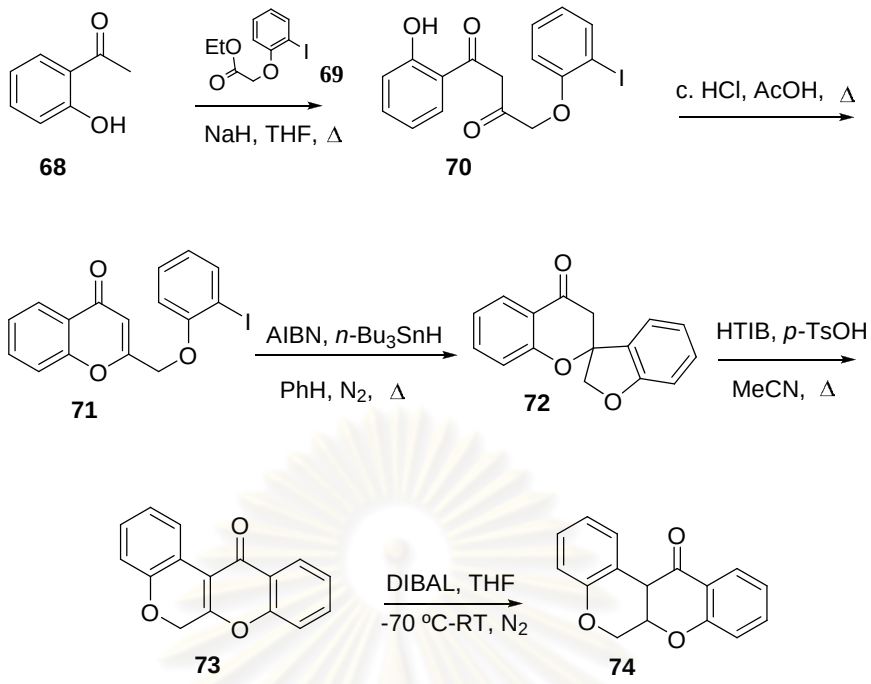
In 1994, Gabbutt *et al.*[21] have reported the synthesis of rotenoid **66** from a chroman-4-one **62**. This method commenced with the synthesis of 4-bromo-2H-chromene **(63)**, which was provided by refluxing compound **62** with phosphorus tribromide. Subsequently, compound **63** was reacted with butyllithium and then 2,4-dimethoxybenzonitrile **(64)** to obtain compound **65**. Finally, target rotenoid **66** and

side product **67** were produced from demethylation and intramolecular ring closure of compound **65** using borontrichloride and sodium acetate trihydrate, respectively as shown in Scheme 16.



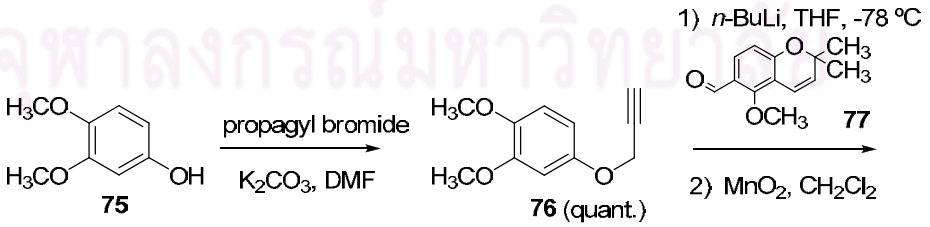
Scheme 16 Synthesis of rotenoid from chroman-4-one **62**

In 1998, Gabbutt *et al.*[22] have described the synthesis of tetracyclic rotenoid core structure **74** by using 1,2-aryl migration as a key step as shown in Scheme 17. Firstly, 2′-hydroxyacetophenone **(68)** was reacted with ethyl-(2-iodophenoxy)-acetate **(69)** *via* Claisen condensation to give the diketone **70.** This diketone was performed in acid condition to obtain 2-(2-iodophenoxymethyl)chromone (**71**) and then intramolecular radical cyclization of compound **71** was proceeded by a kinetically favored 5-exo-trig ring closure to afford the spirocyclic **72**. Next step, it was the key step for this rotenoid synthesis including the hypervalent iodine-promoted oxidation ring expansion of compound **72** to dehydrorotenoid **73**. Finally, the conjugated reduction of compound **73** was accomplished by using diisobutylaluminium hydride (DIBAL) to obtain rotenoid **74** as shown in Scheme 17.

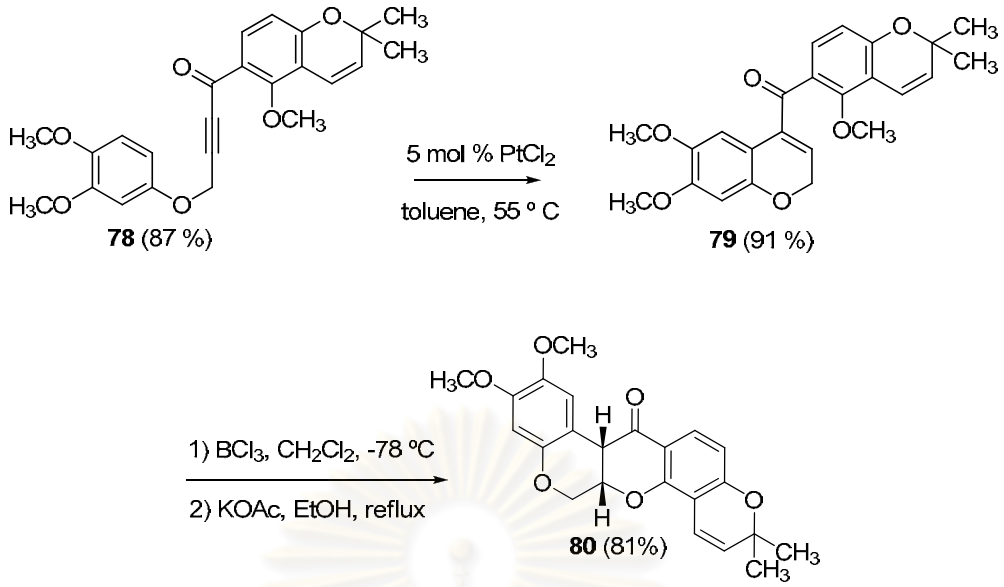


Scheme 17 Synthesis of tetracyclic rotenoid core structure

In 2003, Pastine *et al.*[23] have reported a new methodology for total synthesis of (±)-deguelin **(80)** as shown in Scheme 18. The synthesis commenced with conversion of phenol **75** to the propargyl ether **76**. Treatment of **76** with *n*-BuLi and aldehyde **77** produced the crude alcohol which was oxidized with MnO_2 to yield the alkynone **78**. The desired cyclization product **79** was achieved from the platinum catalyzed 6-endo hydroarylation of an alkynone intermediate **78**. Finally, the target molecule **80**, (±)-deguelin, was achieved by the selective demethylation of compound **79** with BCl_3, followed by base-catalyzed intramolecular oxo-Michael addition as shown in Scheme 18.

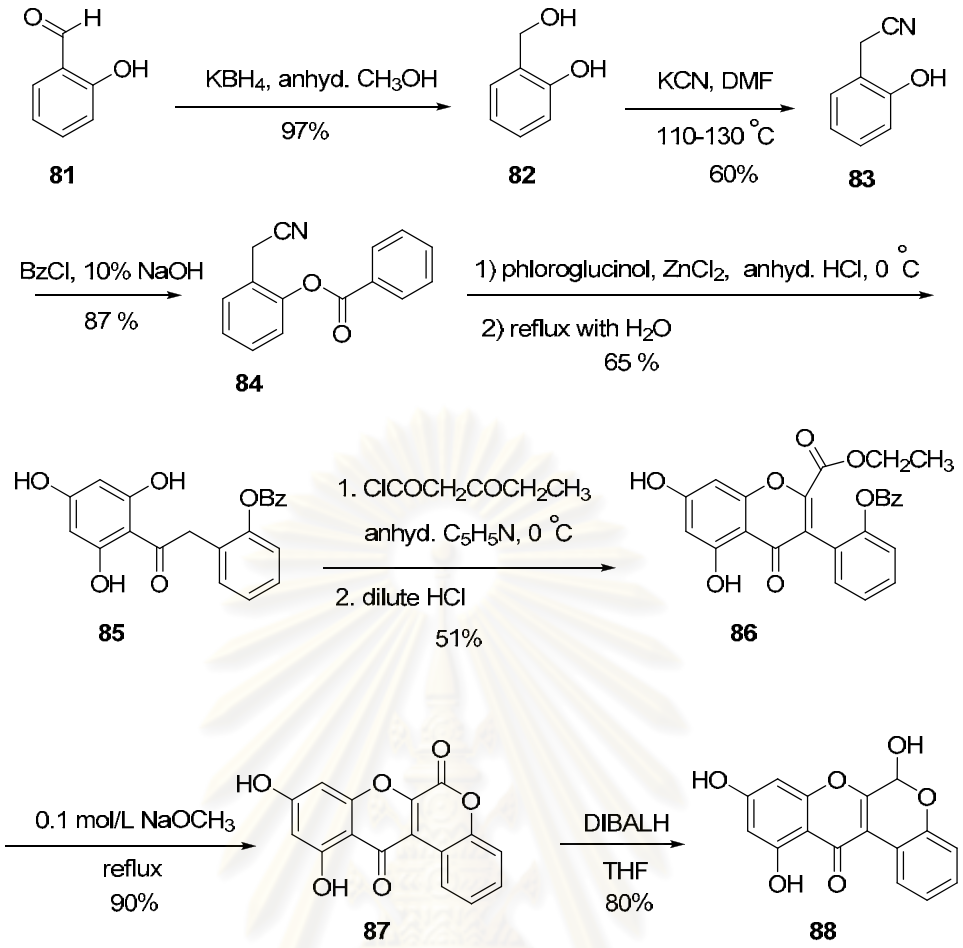


Scheme 18 Synthesis of (±)-deguelin **(80)** (continuous**)**



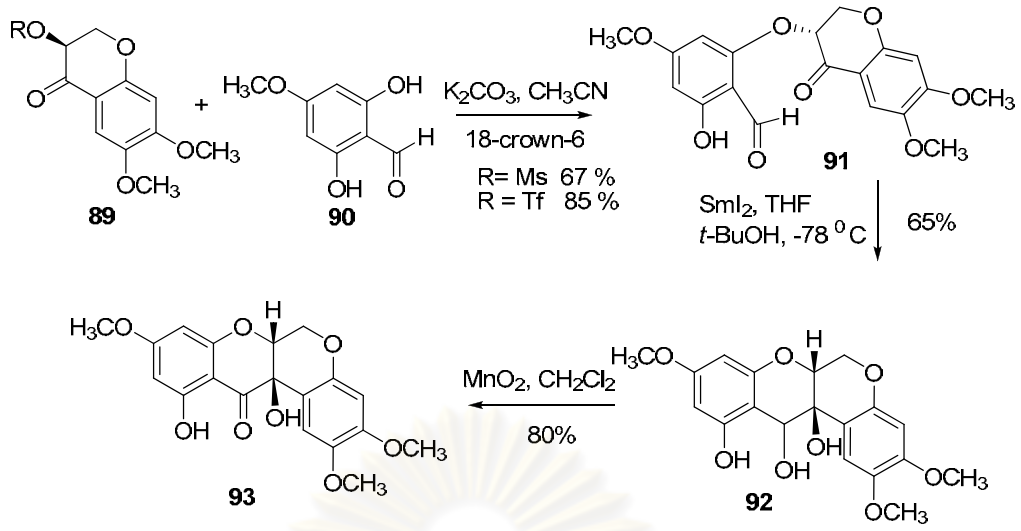
Scheme 18 Synthesis of (±)-deguelin **(80)**

In 2005, Li *et al*. [24] have reported the synthesis of 6,9,11-trihydroxy-6a,12a-dehydrorotenoid (coccineone B) **(88)**. This compound was isolated from the roots of *Boerhaavia diffusa L.*, which is a plant of the family of *Nyctaginaceae* and widely used as a traditional medicine in Nepal, Srilanka, Indian, ans East Africa. Antitumor and antiviral effects of *Boerhaavia diffusa L.* have also been investigated. The synthesis of coccineone B started from reduction reaction of 2-hydroxybenzaldehyde **(81)** with potassiumborohydride to afford 2-hydroxybenzyl alcohol **(82).** The reaction mixture of compound **82** and potassiumcyanide in DMF was heated to give 2-hydroxyphenylacetonitrile **83**. The hydroxyl group of this compound was protected with benzoyl chloride to generate compound **84**. Compound **85** was prepared by Hoesch reaction of compound **84** and phloroglucinol with a good stream of hydrogenchlorideis in the presence of $ZnCl_2.H_2O$. Condensation of compound **85** with ethoxalyl chloride in anhydrous pyridine and extraction with dilute hydrochloric acid gave compound **86**. Treatment of this compound with sodium methoxide provided lactone product **87** and then reduced to the target molecule **88** by DIBALH as outlined in Scheme 19.



Scheme 19 Synthesis of coccineone B **(88)**

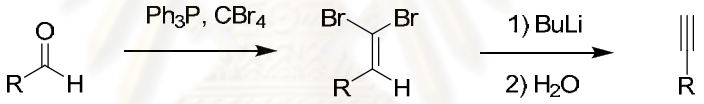
In 2006, Khorphueng *et al*. [25] have reported the total synthesis of 6-deoxyclitoriacetal **(93)** as shown in Scheme 20. Firstly, compound **89** was coupled with compound **90** to generate keto-aldehyde **91** using 18-crown-6 and K_2CO_3. Treatment of compound **91** with samarium diiodine provided a stereoselective product **92** via intramolecular keto-aldehyde Pinacol coupling. Finally, oxidation of compound **92** with MnO_2 gave 6-deoxyclitoriacetal **(93)**.



Scheme 20 Synthesis of 6-deoxyclitoriacetal **(93)**

2.2 Background on key transformations

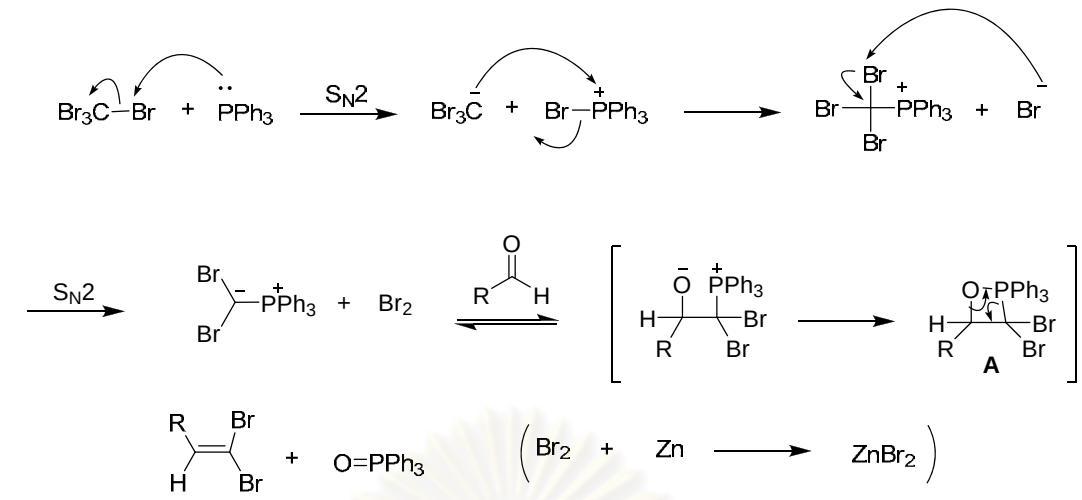
2.2.1. Corey-Fuchs reaction [26, 27]



Scheme 21 Corey-Fuchs reaction

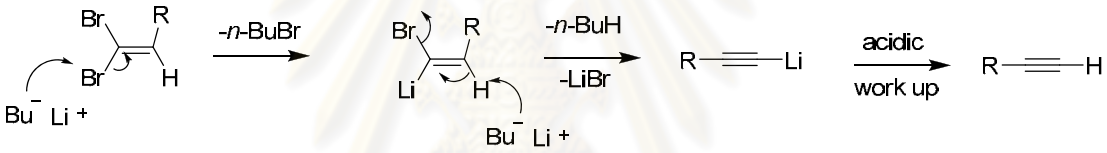
These two steps methodologies allow the preparation of terminal alkynes by one-carbon homologation of an aldehyde. In the first step, the dibrominated phosphonium ylide **A** is generated in situ by reaction of Ph_3P, CBr_4, and Zn. The reaction between ylide **A** and an added aldehyde elongates the latter to give a 1,1-dibromoalkene. This step is comparable to a Wittig Reaction. In the second phase of the reaction, the 1,1-dibromoalkene is treated with a lithium base (BuLi, LDA) to generate a bromoalkyne intermediate via dehydrohalogenation, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne upon work-up.

The mechanism of Corey-Fuchs reaction is shown in Scheme 22 and 23.



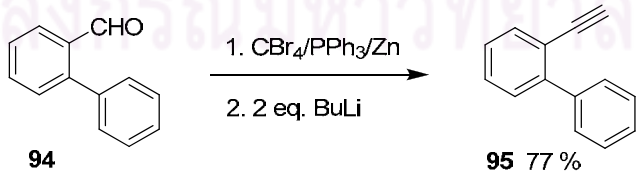
Scheme 22 Mechanism of Corey-Fuchs reaction Part A

Reaction of the dibromoalkene with BuLi:



Scheme 23 Mechanism of Corey-Fuchs reaction Part B

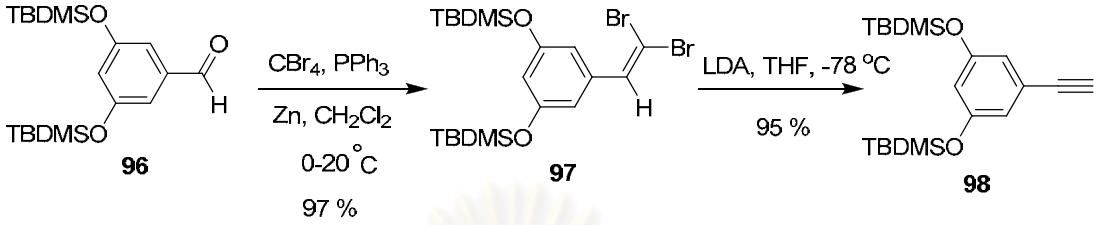
Jackson *et al.* [28] have studied the annulation selectivity reaction in the coupling of Fischer carbene complexes with *o*-ethynylbiphenyl derivative. The alkyne **95** was prepared for this study via Corey-Fuchs reaction. The aldehyde **94** was converted to alkyne compound **95** in 77 % yields as shown in scheme 24.



Scheme 24 Preparation of terminal alkyne

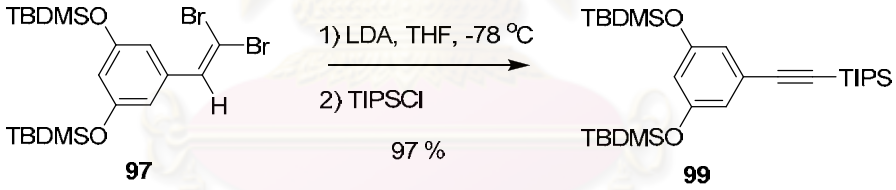
Recently, Gibtner *et al.*[29] have synthesized the terminal alkyne **98** using Corey-Fuchs reaction. The aldehyde **96** could easily be converted to the

corresponding dibromo olefin **97** in very good yield by treatment with CBr_4 and PPh_3 in CH_2Cl_2 and then was transformed unprotected alkyne compound **98** in excellent yields as shown in Scheme 25.



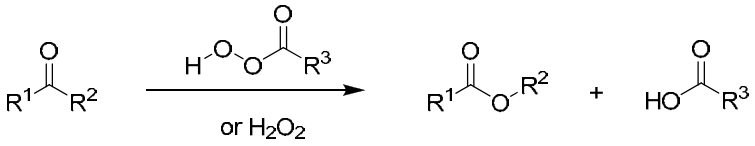
Scheme 25 Synthesis of terminal alkyne

A modification of the Corey-Fuchs reaction involves the reaction of the intermediate alkynyllithium with an electrophile prior to aqueous work-up, giving a chain extension product. Gibtner and co-workers [29] used this method for preparation triisopropylsilyl (TIPS) protected alkyne **99** in 97 % yields as shown in Scheme 26.



Scheme 26 Modification of Corey-Fuchs reaction

2.2.2. **Baeyer-Villiger oxidation**[26, 27]



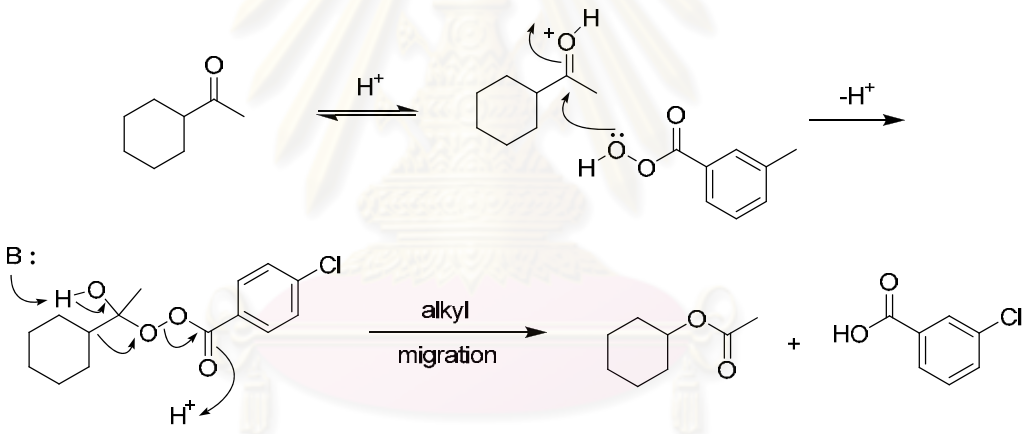
Scheme 27 Baeyer-Villiger oxidation

The Baeyer-Villiger oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The Baeyer-Villiger can be carried out with peracids, such as *m*-CBPA, or with hydrogen peroxide and a Lewis acid.

The regiospecificity of the reaction depends on the relative migratory ability of the substituents attached to the carbonyl. Substituents which are able to stabilize a positive charge migrate more readily, so that the order of preference is: tert. alkyl > cyclohexyl > sec. alkyl > phenyl > prim. alkyl > CH_3>>> H. In some cases, stereoelectronic or ring strain factors also affect the regiochemical outcome.

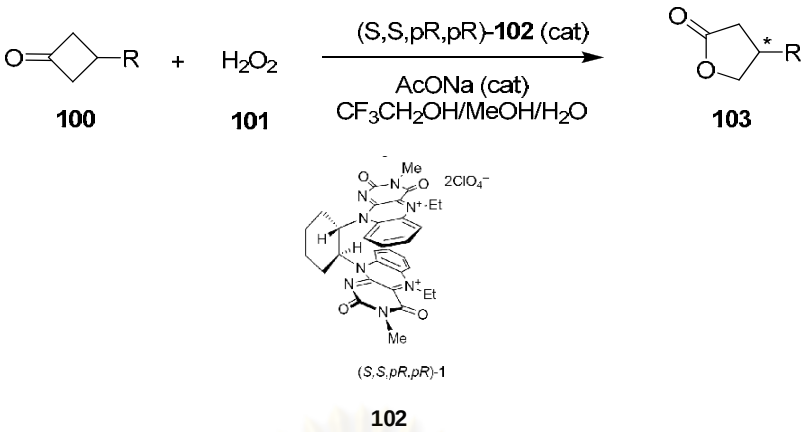
The reaction of aldehydes preferably gives formates, but sometimes only the liberated alcohol may be isolated due to the solvolytic instability of the product formate under the reaction conditions.

The mechanism of Baeyer-Villiger oxidation is shown in Scheme 28.



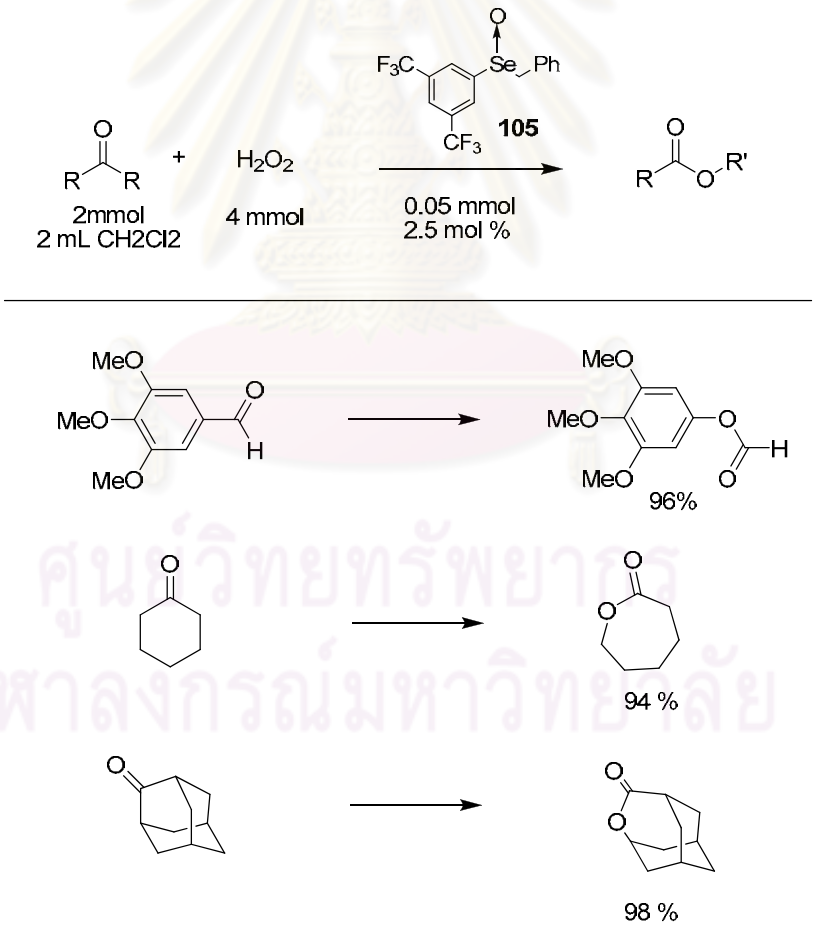
Scheme 28 Mechanism of Baeyer-Villiger oxidation

Murahashi *et al.*[30] have developed a novel method for the asymmetric Baeyer-Villiger reaction. They were demonstrated that novel planar-chiral bisflavinium perchlorate **(102)** catalyzes the Baeyer-Villiger reaction of cyclobutanones with hydrogen peroxide to give the corresponding optically active lactones **(103)** with up to 74 % ee as shown in Scheme 29.



Scheme 29 Preparation of lactone compounds

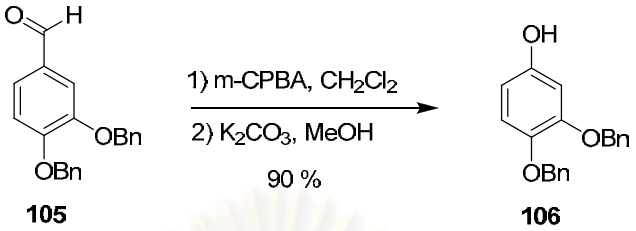
Goodman *et al.*[31] have described that the organoselenoxide **(105)** are efficient catalyst for Baeyer-Villiger oxidation of various carbonyl-containing compounds using the environmentally benign oxidant H_2O_2 as shown in Scheme 30.



Scheme 30 Baeyer-Villiger oxidation using organoselenoxide

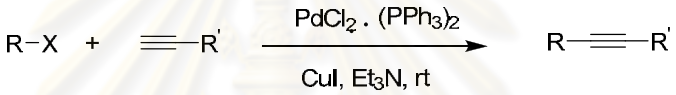
ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Li, *et al.*[32] was reported the preparation of phenol **106** using Baeyer-Villiger oxidation reaction. Compound **105** was treated with *m*-CPBA and then hydrolyzed to generate the desired product **106** in good yield as shown in Scheme 31.



Scheme 31 Preparation of phenol compound

2.2.3. **Sonogashira reaction** [26. 27]

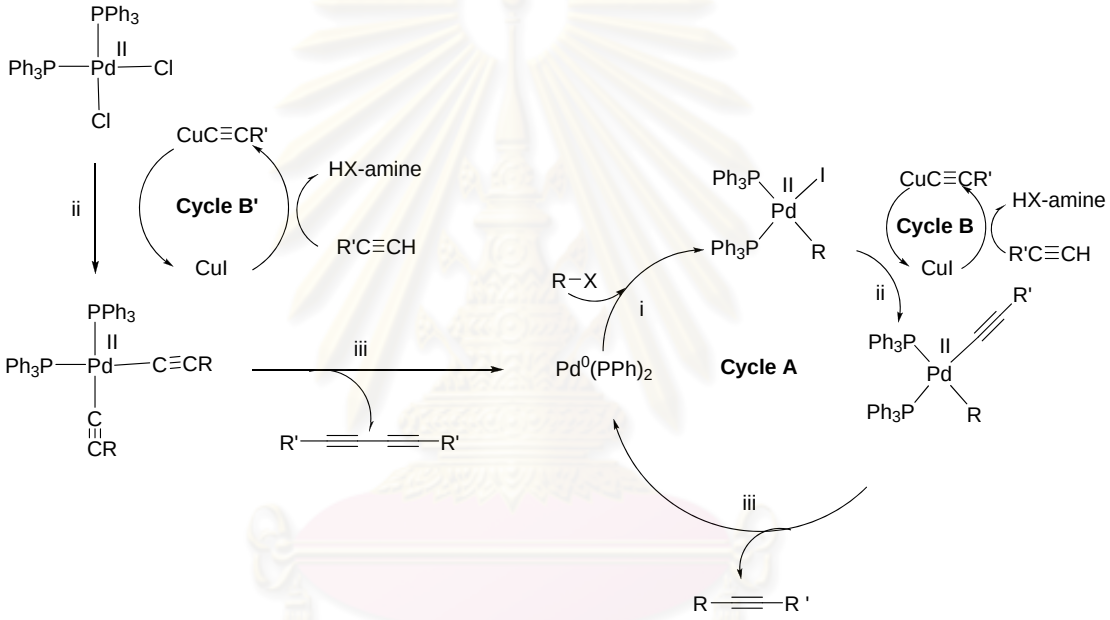


Scheme 32 Sonogashira reaction

Sonogashira coupling is a coupling reaction of terminal alkynes with aryl or vinyl halides using a palladium catalyst. The mechanism of this reaction is illustrated in scheme **32**. The catalytic process requires the use of a palladium (0) complex. $PdCl_2(PPh_3)_2$, a Pd(II) complex, can be handle more conveniently and is usually employed, since this complex is reduced immediately to provide the Pd (0) complex in the presence of base, and generally uses copper iodide as a co-catalyst. Under these conditions the acetylene will form at least a small equilibrium amount of an ammonium acetylide. A substoichiometric amount of CuI is added to capture the small equilibrium concentration of the ammonium acetylide as a copper acetylide as shown in cycle B'. The copper acetylide represents a substantially improved nucleophile in comparison to the free acetylene. Without the CuI addition, the acetylide content of the reaction mixture is so small that a reaction occurs only at higher temperatures. The amine as well as the terminal alkyne or its respective acetylide ion can act as the reducing reagent. The amine as a reductant would be oxidized to give an imminium ion while the acetylene as a reductant would be

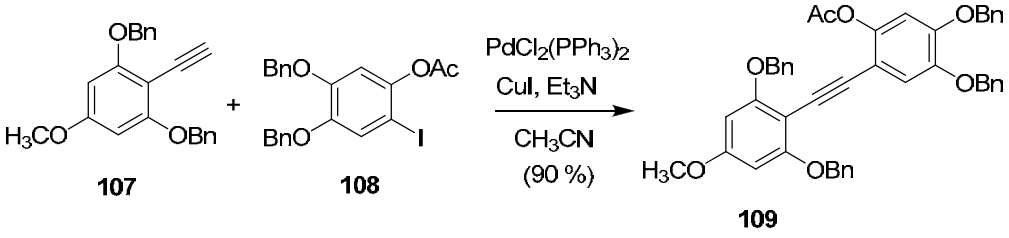
converted into a 1,3-diyne, that is, the product of an oxidative dimerization (Glaser coupling).

The catalytic cycles starts with the formation of a π-complex between the catalytically active Pd (0) complex and arylating agent and then the oxidative addition of this complex gives a Pd (II) complex with a σ-bonded aryl moiety (cycle A-i). The second step is the transmetallation. The alkynyl-Pd compound is formed from the alkynyl copper (generated from the therminal alkyne, base, and copper iodide; cycle B) via ligand exchange. The third step, reductive elimination with coupling of the two organic ligands gives the product and regenerates the palladium (0) catalyst. [26, 27]



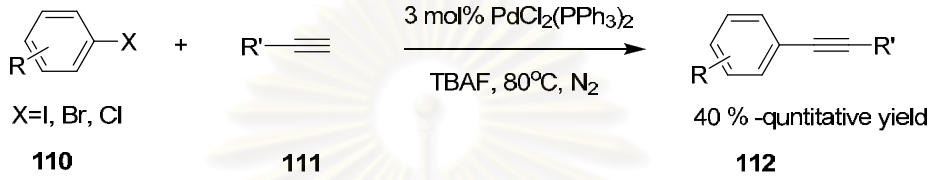
Scheme 33 Mechanism of Sonogashira reaction

Li *et al.* [32] used the Sonogashira reaction for the preparation of diaryacetylene **109** which is the important intermediated for the total synthesis of wedelolactone. The coupling reaction between compound **107** and **108** give the desired product in 90 % yields as shown in Scheme 34.



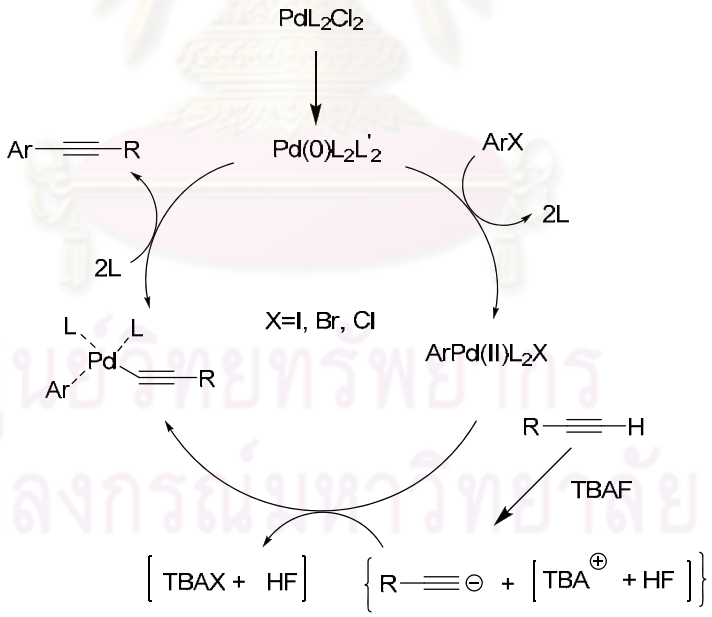
Scheme 34 Synthesis of diaryacetylene

Liang *et al.*[33] have developed a new system for the rapid Sonogashira cross-coupling reaction. This methodology could be applied to the reactions of deactivated aryl chlorides. In the presence of 3 mol % of $PdCl_2(PPh_3)_2$ and 2 equiv of TBAF aryl halides **110**, a number of ArX species (X=I, Br, Cl) were coupled with terminal alkynes **111** to give the corresponding products **112** in moderate to excellent yields under copper-, amine-, and solvent-free conditions as shown in Scheme 35.



Scheme 35 New condition of Sonogashira cross-coupling reaction

The mechanism of this reaction was proposed as shown in Scheme 36

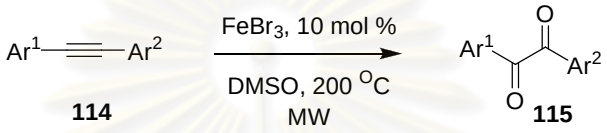


Scheme 36 Reaction mechanism of Sonogashira cross-coupling reaction

2.2.4. Transforming alkyne to 1,2-diarydiketones

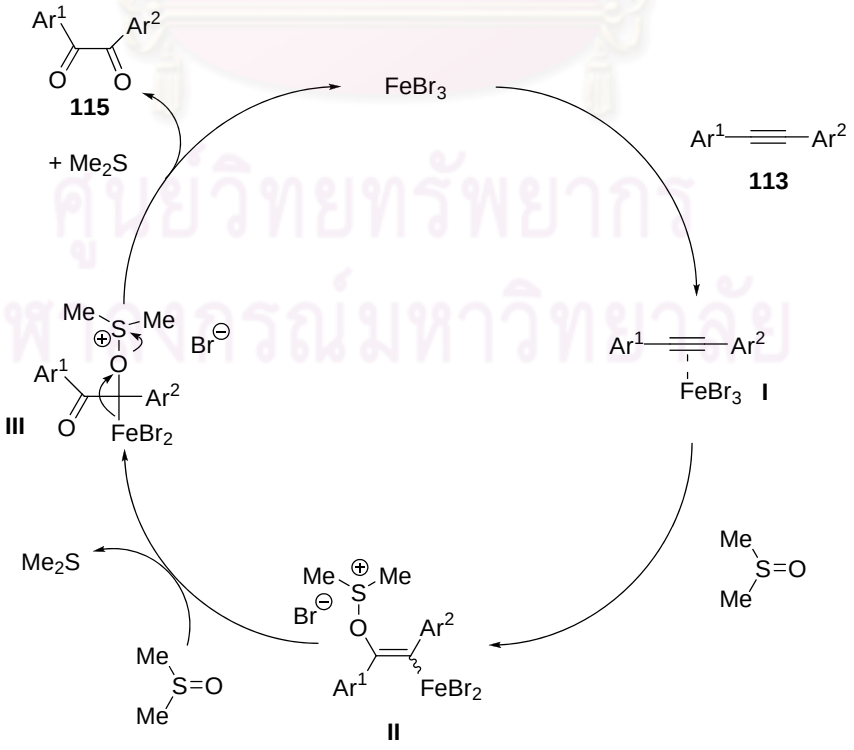
The conversion of alkyne to 1,2-diketone is well precedent and a wide array of reagent systems have been reported.

Giraud *et al.*[34] have reported the oxidation of functionalized diaryalkyne with DMSO in the presence of $FeBr_3$ catalyst as shown in Scheme 37. The procedure has been applied successfully under microwave irradiation gave product in 0-75 % yields. However, this procedure shows the efficiency only the oxidation of protected-phenolic arylalkyne substrate. In the case, the hydroxyl group was protected with the acetyl group, generating the cleavage of the acetoxyester group diketone product.



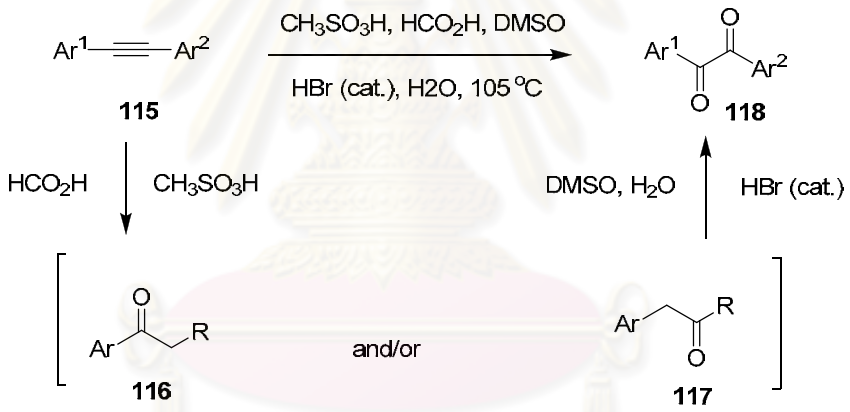
Scheme 37 Synthesis of 1,2-diaryl diketone using $FeBr_3$

The plausible mechanism was proposed as shown in scheme 38. The triple bond of aryl alkyne **113** may activate by Fe (III) to generate **I** and allowed successive addition of DMSO. After a first addition, a vinyl iron species **II** (or its cationic equivalent) would be formed and then trapped by a second molecule of DMSO. The species **III** formed would evolve to afford the desired benzyl **114** together with Me_2S and regenerated the catalyst.



Scheme 38 Proposed pathway for the oxidation of arylalkyne

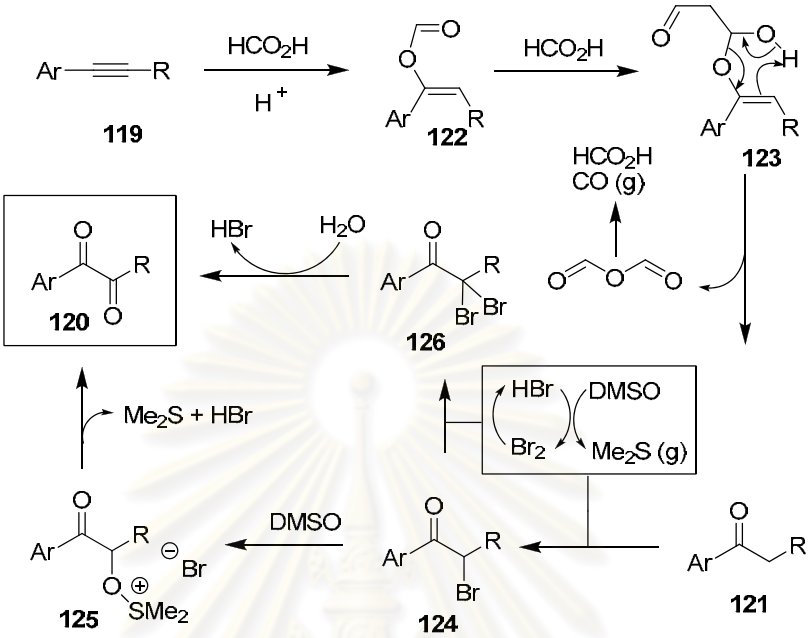
Wan *et al.*[35] have explained the oxidation of alkynes to 1,2-diketone derivatives through a one-pot procedure via a Bronsted acid-promoted and a DMSO-based oxidation as shown in Scheme 39. The diphenylacetylene **115** bearing a variety of substituents (1 equiv.) was treated with 1 mL/mmol of 88% formic acid, 5 equiv. of DMSO, 1 equiv of methanesulfonic acid and 0.1 equiv. of 48% HBr under refluxing condition at 105 °C. The reaction is stepwise in nature, all the reagent could be added at the same time at the beginning. Alkyne with electron-rich or electron-poor diary substituents, an aryl with an unprotected free amine, or a free acid all underwent a smooth transformation to form the corresponding 1,2-dicarbonyl derivatives in good to excellent yields.



Scheme 39 Synthesis of 1,2-diaryl diketone in acid condition

Moreover, they also studied the oxidation reaction mechanism by detecting the off gas with headspace GC-MS and the reaction intermediates with liquid chromatography mass spectrometry (LC-MS). They found that CO and Me_2S evolved from the reaction media. Reaction intermediates, the monoketone **121** and the bromoketone **124**, were detected by LC-MS. The reaction mechanism was proposed in Scheme 40. The formic acid was added to an alkyne to form the vinyl formate **123**, which decomposes to form the monoketone **121** by liberating CO. The ensuing DMSO-based oxidation of **121** using HBr/Br_2 as a catalyst affords the expected dicarbonyl **120** by liberating Me_2S gas, alkoxydimethyl sulfonium salt **125**, α-dibomoketone **12**6. It is also plausible that enol formate **122** undergo bromination

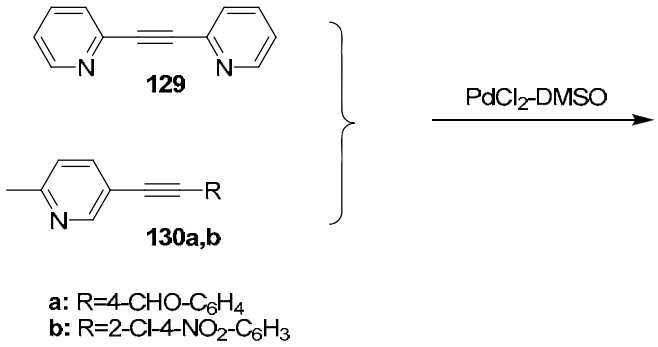
directly to afford the bromoketone **124**, which would readily undergo the DMSO oxidation.



Scheme 40 Mechanism of acid-catalyzed for synthesis 1,2-diaryl diketone

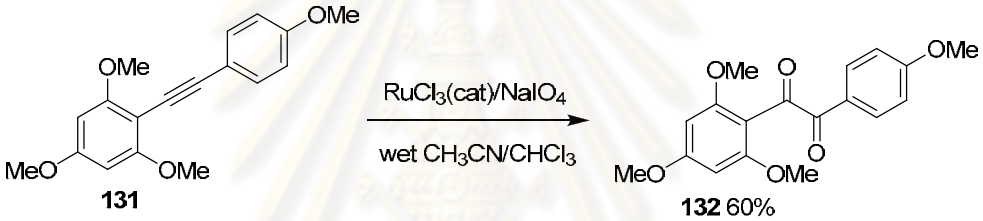
Yusubov *et al.*[36] have informed the conversion of alkynyl derivatives to 1,2-diketones using the reagent combination $PdCl_2$-DMSO. The results showed that the acetlenic derivatives of crown-ethers **127a,b** were oxidized very successfully to give the corresponding 1,2-diketones **128a,b** in excellent yields (79-84%). In contrast, this reagent was ineffective when oxidized the alkynlpyridine **129a, b** and **130**. In this case, only formation of a complex mixture of products was observed.

Scheme 41 Oxidation reaction of $PdCl_2$ for preparation of 1,2-diketone



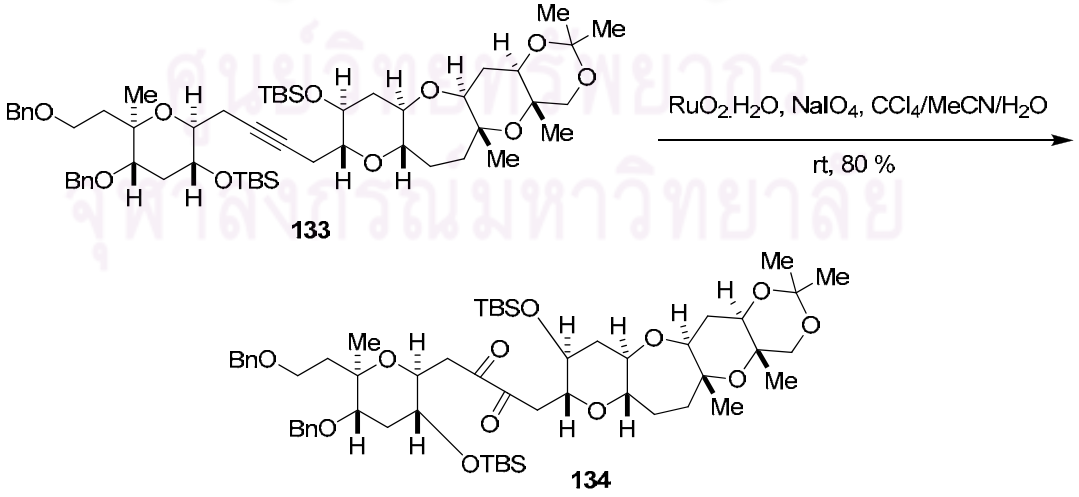
Scheme 41 Oxidation reaction of $PdCl_2$ for preparation of 1,2-diketone (continuous)

Magnus *et al.*[37] have described the conversion of diarylalkyne to 1,2-diketone using a ruthenium catalyst. The alkyne **131** was oxidized with $RuCl_3$ (catalyst)/ NaIO4/wet $CH_3CN/CHCl_3$ to give diketone **132** in 60 % yields as shown in Scheme 42.



Scheme 42 Oxidation reaction of diarylalkyne using ruthenium catalyzed

Mori *et al.*[38] have demonstrated the synthesis of diketone **134** through the oxidation of the disubstituted acetylene **133** with RuO_2-$NaIO_4$ as shown in Scheme 43.



Scheme 43 Oxidation reaction of diarylalkyne using RuO_2

Srinivasan *et al.*[39] have reported a simple method for the oxidation of alkynes to the 1,2-diketones using potassium permanganate in aqueous acetone solutions as shown in Table 1. This condition was necessary to maintain an approximately neutral solution to obtain good yield. This could be achieved by addition of definite amounts of sodium bicarbonate and magnesium sulfate. The added salts served as a buffer (pH 7.0-7.5 initially) and neutralize hydroxide ions which was produced during the reduction of permanganate.

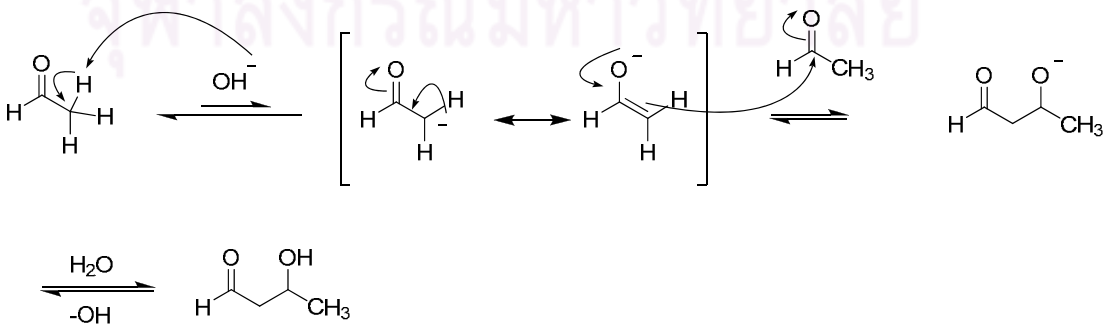
Table 1. Oxidation of Alkynes by Potassium Permanganate in Aqueous Acetone

Alkyne	Time(h)	Product	% yield
5-decyne	4	5,6-decanedione	40
7-tetradecyne	4	7,8-tetradecanedione	69
8-hexadecyne	4	8,9-hexadecanedione	81
1-phenyl-1-pentyne	1.75	1-phenyl-1,2-pentanedione	77
diphenylacetylene	3	1,2-diphenyl-1,2-ethanedione	88

2.2.5. **Aldol reaction** [26, 27]

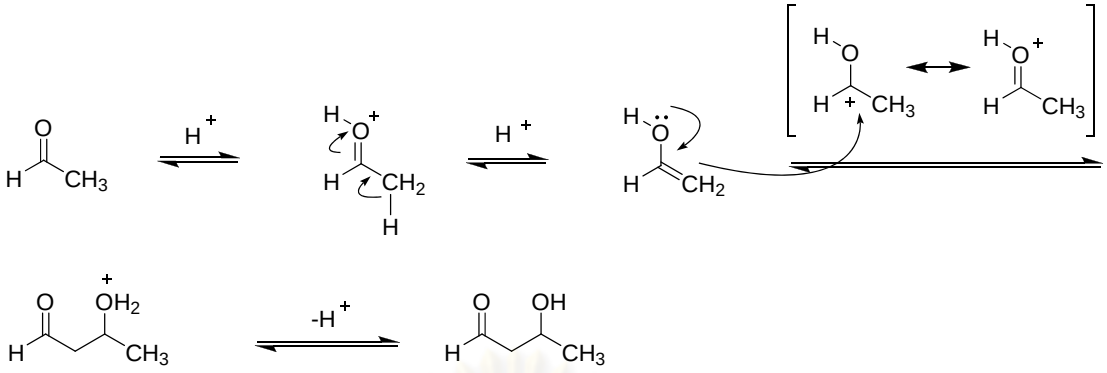
Aldol reaction is a reaction between the two carbonyl compounds in which one carbonyl compound plays the role of a nucleophile while the other carbonyl compound acts as an electrophile. When the enolate of an aldehyde or a ketone reacts at the α-carbon with the carbonyl of another molecule under basic or acidic conditions to obtain β-hydroxy aldehyde or ketone, this reaction is called Aldol Reaction. The reaction mechanism has been shown Scheme 44 and 45.

Base catalyzed:



Scheme 44 Reaction mechanism of Aldol reaction in base catalyzed

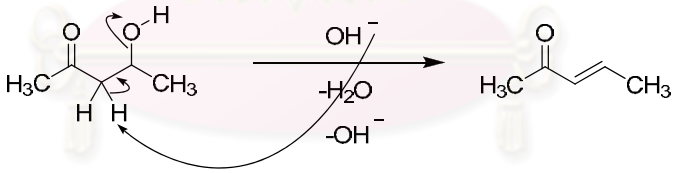
Acid catalyzed:



Scheme 45 Reaction mechanism of Aldol reaction in acid catalyzed

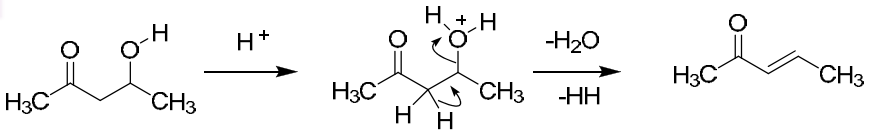
In some cases, the adducts obtained from the Aldol Addition can easily be converted (in situ) to α,β-unsaturated carbonyl compounds, either thermally or under basic or acidic catalysis as shown in Scheme 46 and 47. The formation of the conjugated system is the driving force for this spontaneous dehydration. Under a variety of protocols, the condensation product can be obtained directly without isolation of the Aldol product.

Base catalyzed:



Scheme 46 Synthesis of α,β-unsaturated carbonyl compound in base catalyzed

Acid catalyzed:

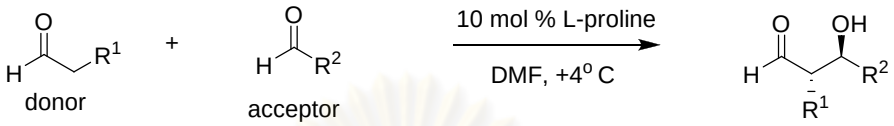


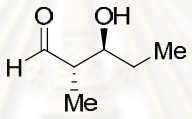
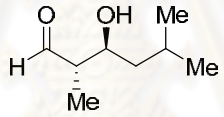
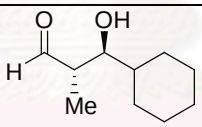
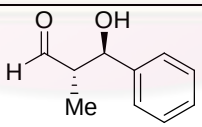
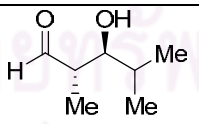
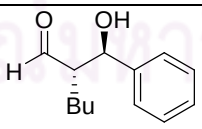
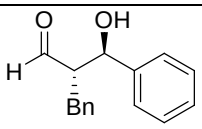
Scheme 47 Synthesis of α,β-unsaturated carbonyl compound in acid catalyzed

Throughout the development of catalytic asymmetric Aldol reaction, L-proline and its structural analogues have been reported. In 2002, Northrup, *et al.*[40] studied

the enantioselective cross-Adol reaction of aldehydes using L-proline catalysis. This method allowed enantioselective access to β-hydroxy aldehydes with high % ee which these results were illustrated in Table 2.

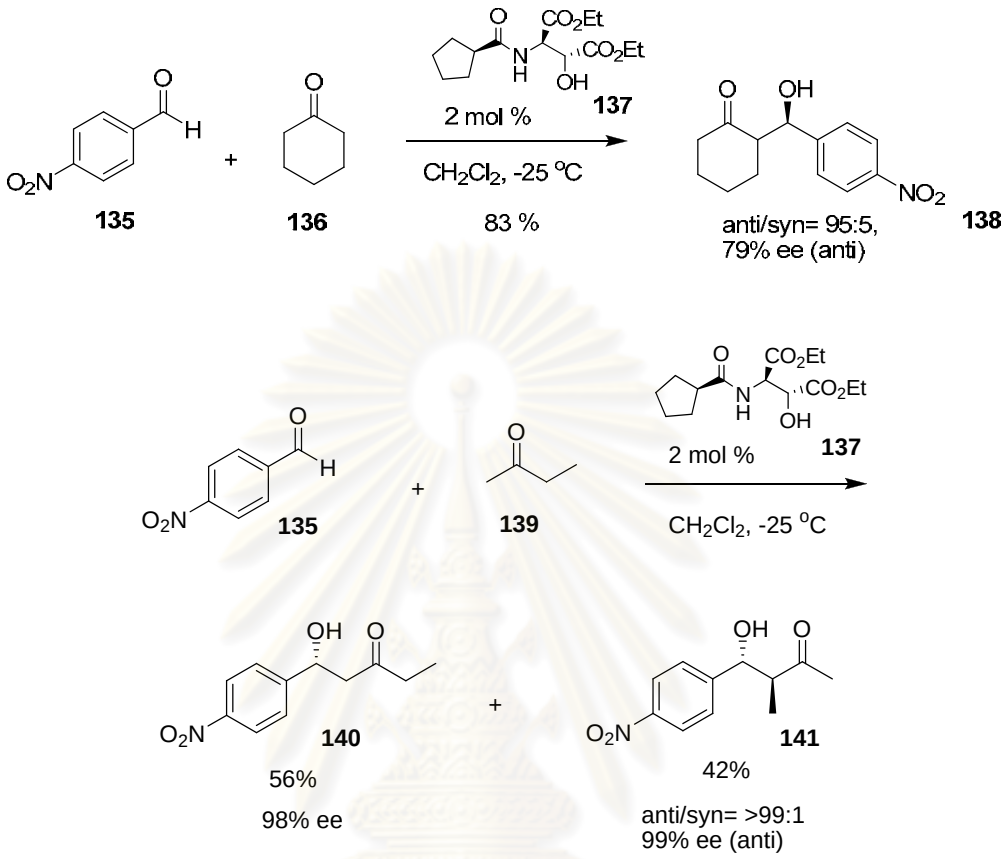
Table 2 Enantioselective direct aldehyde cross-Aldol reaction



entry	R^1	R^2	product	% yield	Anti: Syn	% ee
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6	*n*-Bu	*i*-Pr		80	24:1	98
7	Bn	*i*-Pr		75	19:1	91

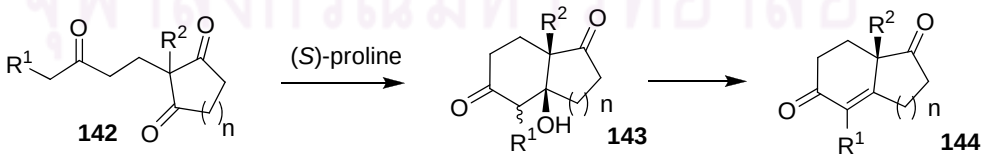
In 2005, Tang, *et al.*[41] evaluated a family of L-proline amides for their ability to catalyze the direct Aldol reaction of a wide range of aldehyde and ketone compounds. The results showed that the catalyst **136** gave the *β*-hydroxy ketones with

very high enantioselective ranging from 96% to > 99% ee. The examples of this reaction are presented in Scheme 48.



Scheme 48 Synthesis of *β*-hydroxy ketones (continuous)

Moreover, Hajos *et al*.[42] published a series of papers and patents involving the S-proline catalyzed intramolecular Aldol condensation of triketones **142** as shown in Scheme 49. This result illustrated that the Aldol adducts **143** was dehydrated to generate the asymmetric synthesis of enediones **144**.



Scheme 49 S-proline catalyzed intramolecular Aldol condensation

CHAPTER III

EXPERIMENTALS

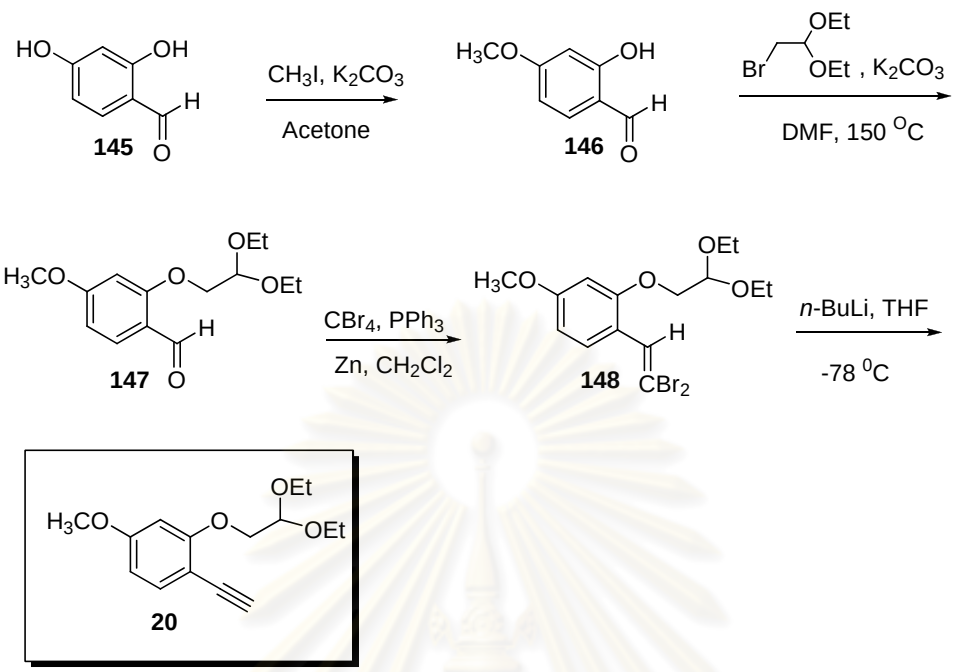
3.1 Instruments and Equipments

General Methods

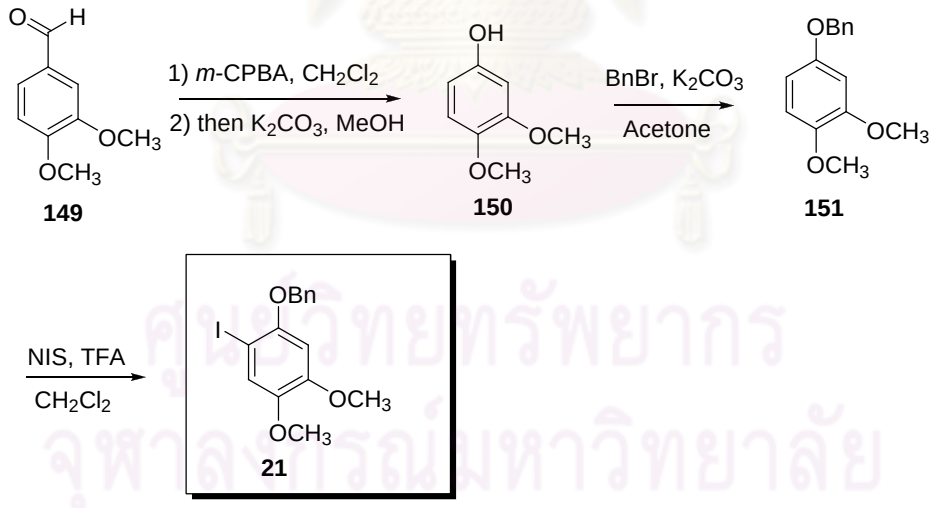
All reactants and reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous solvents were distilled immediately prior to use: tetrahydrofuran (THF) from sodium/benzophenone, dichloromethane and acetonitrile from calcium hydride. Flash chromatography was performed on silica gel 60 (Merck, 230-400). The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer operated at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Moreover COSY, NOESY, HSQC and HMBC experiments were performed on this spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used for NMR data: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad. The infrared spectra were recorded on a Nicolet Impact 410 Fourier Transform Infrared Spectrophotometer. Spectra of solid samples were recorded as KBr pellets and liquid samples as thin film on NaCl cells. High-resolution mass spectra (ESI-TOF MS) and low resolution mass spectra (ESI-MS) were obtained. Melting points of crystalline compounds are uncorrected. The optical rotation was measured on a Perkin-Elmer 341 polarimeter in $CHCl_3$.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

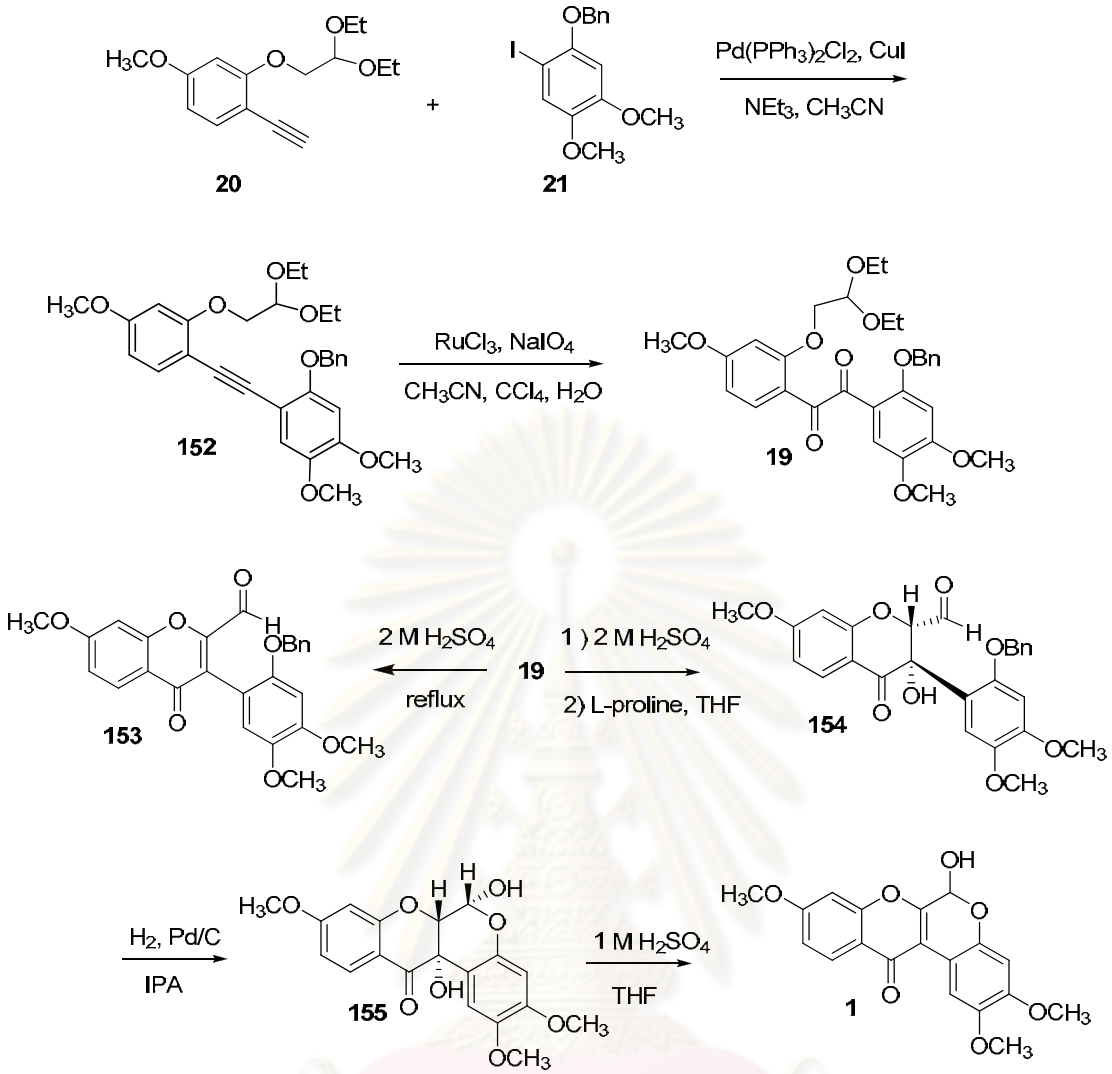
3.2 Synthesis of target compound 1 overview



Scheme 50 Synthesis of compound **20**

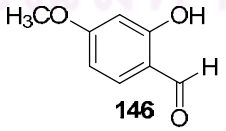


Scheme 51 Synthesis of compound **21**



Scheme 52 Synthesis of compound **1**

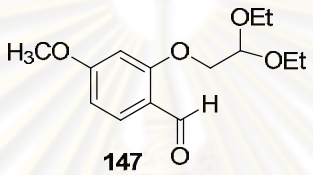
Synthesis of 2-Hydroxy-4-methoxy-benzaldehyde (146) [43]



2,4-dihydroxybenzaldehyde (**145**) (1.5 g, 10.81 mmol) and K_2CO_3 (1.5 g, 10.81 mmol) were first dissolved in acetone (20 mL) then treated with methyl iodide (677 µL, 10.81 mmol), and the mixture was stirred at room temperature for 24 h. After removal of solvent, the residue was dissolved in EtOAc (2 x 50 mL) and then washed

with H_2O (2 x 50 mL) and brine (2 x 20 mL) and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to provide compound **146** (1.05 g, 64 %) as a white solid, m.p. 39 °C TLC, R_f 0.55 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) 11.48 (s, 1H), 9.70 (s, 1H), 7.42 (d, 1H, J = 8.4 Hz), 6.53 (dd, 1H, J = 8.4, 2.4 Hz), 6.42 (d, 1H, J = 2.4 Hz), 3.84 (s, 3H) ^{13}C-NMR (100 MHz, CDCl3) 194.4, 166.8, 164.5, 135.3, 115.4, 108.4, 100.6, 55.7 IR (neat) 3081, 2850, 1638 cm^{-1}; MS- ESI calcd for $C_8H_9O_3$ (M+H)+ m/z 153.16, found 153.33.

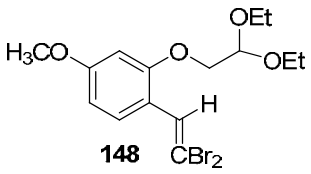
Synthesis of 2-(2,2-Diethoxy-ethoxy)-4-methoxy-benzaldehyde (147) [44]



147

To a solution of compound **146** (508.8 mg, 3.34 mmol) in DMF (3 mL) was added K_2CO_3 (1.8469 g, 13.38 mmol) and bromoacetaldehyde diethyl acetal (410 µL, 3.68 mmol). The mixture was stirred under refluxing at 150 ^{o} C for 2 h. The reaction mixture was worked up with ice, neutraled with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (3 x 15 mL), the combined organic extract was washed with H_2O (2 x 10 mL) and brine (1 x 20 mL) and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to give compound **147** (813 mg, 91 %) as a yellow oil. TLC, R_f 0.43 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.78 (d, 1H, *J* = 8.8 Hz), 6.53 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.42 (d, 1H, *J* = 2.0 Hz), 4.86 (t, 1H, *J* = 5.6 Hz), 4.05 (d, 2H, *J* = 5.6 Hz), 3.83 (s, 3H), 3.77 (m, 2H), 3.63 (m, 2H), 1.23 (t, 6H, *J* = 6.8 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 188.2, 166.1, 162.7, 130.3, 119.1, 106.7, 100.4, 98.6, 69.2, 63.2×2, 55.6, 15.3×2 IR (neat) 2968, 2875, 1684, 1597, 1438 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}O_5$ $(M+H)^+$ m/z 269.1389, found 269.1380.

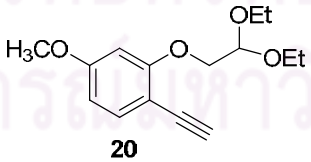
Synthesis of 1-(2,2-Dibromo-vinyl)-2-(2,2-diethoxy-ethoxy)-4-methoxy-benzene (148) [28]



148

A mixture of Zn dust (0.8863 g, 13.56 mmol), triphenylphosphine (3.0676 g, 13.56 mmol), and carbon tetrabromide (4.4956 g, 13.56 mmol) in dried CH_2Cl_2 (35 mL) was stirred at room temperature under N_2 for 6 h. To this mixture was added compound **147** (1.2124 g, 4.52 mmol) and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed to give a residue. This mixture was dissolved in EtOAc 80 mL and filtered to obtain filtrate. The solvent was removed and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to yield compound **148** (1.6828 g, 88 %) as a yellow solid, m.p. 40 °C TLC, R_f 0.63 (EtOAc/hexane, 3:7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* = 9.2 Hz), 7.47 (s, 1H), 6.43 (dd, 1H, *J* = 9.2, 2.4 Hz), 6.34 (d, 1H, *J* = 2.4 Hz), 4.76 (t, 1H, *J* = 5.6 Hz), 3.90 (d, 2H, *J* = 5.6 Hz), 3.72 (s, 3H), 3.71 (m, 2H), 3.58 (m, 2H), 1.19 (t, 6H, *J* = 6.8 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 161.1, 156.9, 132.3, 129.6, 117.4, 105.1, 100.6, 99.1, 87.7, 69.3, 63.3×2, 55.4, 15.4×2 IR (neat) 2972, 2890, 1617 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Br_2O_4Na$ $(M+Na)^+$ m/z 444.9626 found 444.9636.

Synthesis of 2-(2,2-Diethoxy-ethoxy)-1-ethynyl-4-methoxy-benzene (20) [28]

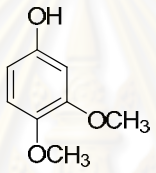


20

Compound **148** (1.6828 g, 3.97 mmol) was dissolved in dried THF (10 mL) at -78 ^{o} C under N_2, then *n*-Butyllithium (15 mL of a 0.56 M hexane solution, 8.34 mmol) was added and the solution was stirred at -78 ^{o} C for 30 min. The reaction mixture was worked up with water (5 mL) and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic extract was washed with water (20 mL) and brine (20 mL) and

finally dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:9 EtOAc/hexane) to obtain compound **20** (839 mg, 80 %) as yellow solid, m.p. 67 °C TLC, R_f 0.53 (EtOAc/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, 1H, *J* = 9.6, 1.6 Hz), 6.41 (d, 1H, *J* = 9.6 Hz), 6.40 (d, 1H, *J* =1.6 Hz), 4.83 (t, 1H, *J* = 5.6 Hz), 4.01 (d, 2H, *J* = 5.6 Hz), 3.78 (m, 2H), 3.75 (s, 3H), 3.66 (m, 2H), 3.14 (s,1H), 1.22 (t, 6H, *J* = 7.2 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 161.3, 161.0, 134.7, 105.8, 104.2, 100.8, 99.5, 80.1, 79.6, 69.9, 63.4×2, 55.4, 15.3×2 IR (neat) 3281, 2983, 2880, 2110 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}O_4$ $(M+H)^+$ m/z 265.1440 found 265.1447.

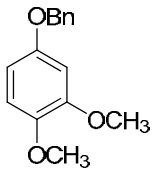
Synthesis of 3,4-dimethoxyphenol (150) [32]



150

To a solution of 3,4-dimethoxybenzadehyde **(149**) (2.00 g, 12.04 mmol) in CH_2Cl_2 (32 ml) was added *m*-chloroperbenzoic acid (3.26 g with 25-30 % of H_2O, ca 13.24 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with dimethyl sulfide (1 mL) and then successively washed with saturated aqueous Na_2SO_3 solution (3 x 20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in MeOH (30 mL), then treated with K_2CO_3 (3.3217 g, 24.07 mmol), and the mixture was stirred at room temperature for 30 min. After removal of MeOH, the residue was dissolved in EtOAc (30 mL), washed with H_2O (2 x 20 mL) and brine (20 mL), and dried over Na_2SO_4. The organic phase was filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:1 EtOAc/hexane) to provide compound **150** (1.7854 g, 96 %) as a white solid, m.p. 80-82 °C TLC, Rf 0.50 (EtOAc/hexane, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.70 (d, 1H, *J* = 8.8 Hz), 6.46 (d, 1H, *J* = 2.4 Hz), 6.34 (dd, 1H, *J* = 8.8, 2.4 Hz), 5.84 (bs, 1H), 3.79 (s, 3H), 3.76 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) 150.3, 149.8, 142.9, 112.5, 105.9, 100.6, 56.6, 55.7 IR (neat) 3726-3034, 2983, 2839, 1608, 1508, 1465 cm^{-1}; MS (ESI) calcd for $C_8H_{11}O_3$ $(M+H)^+$ m/z 155.07 found 155.33.

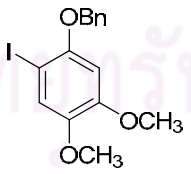
Synthesis of 4-Benzyloxy-1,2-dimethoxy-benzene (151) [45]



151

Compound **150** (857 mg, 5.56 mmol) and K_2CO_3 (844 mg, 6.11 mmol) were first dissolved in acetone (20 mL) then treated with benzyl bromide (727 µL, 6.12 mmol), and the mixture was stirred at room temperature for 24 h. After removal of solvent, the residue was dissolved in water (30 mL). The aqueous phase was extracted with EtOAc (2 x 30 mL), brine (2 x 20 mL) and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **151** (1.3064 g, 96 %) as a white solid, m.p. 43.5 °C TLC, R_f 0.48 (EtOAc/hexane, 3:7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-7.31 (m, 5H), 6.77 (d, 1H, *J* = 8.4 Hz), 6.62 (d, 1H, *J* = 1.6 Hz), 6.48 (dd, 1H, *J* = 8.4, 1.6 Hz), 5.00 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.4, 149.9, 143.7, 137.2, 128.6×2, 128.0, 127.6×2, 111.8, 104.1, 101.2, 70.6, 56.4, 55.8 IR (neat) 2834, 1611, 1519, 1463 cm^{-1}; MS (ESI) calcd for $C_{15}H_{17}O_3$ $(M+H)^+$ m/z 245.12 found 245.31.

Synthesis of 1-Benzyloxy-2-iodo-4,5-dimethoxy-benzene (21) [46]

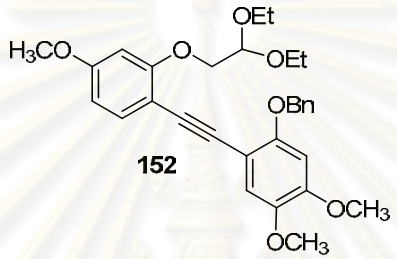


21

To a solution of compound **151** (556.7 mg, 2.28 mmol) in dried CH_2Cl_2 (4 mL) was added *N*-iodosuccinimide (446.2 mg, 2.51 mmol) and TFA (5.2 µL, 0.58 mmol) at room temperature for 2 h. The reaction mixture was quenched with aqueous $NaHSO_3$ (1 mL). The resulting was washed with H_2O (2 x 10 mL), brine (10 mL), and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to give compound **21** (827.1 mg, 98 %) as a white solid, m.p. 51 °C TLC, R_f 0.30

(EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, *J* = 7.2 Hz) 7.39 (t, 2H, *J* = 7.2 Hz), 7.32 (t, 1H, *J* = 7.2 Hz), 7.21 (s, 1H), 6.51 (s, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.0, 150.0, 144.6, 136.7, 128.5×2, 128.0, 127.4×2, 121.5, 100.2, 74.4, 72.4, 56.6, 56.1 IR (neat) 2939 2847 1508 1439 1208 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}IO_3Na$ $(M+Na)^+$ m/z 392.9964 found 392.9969.

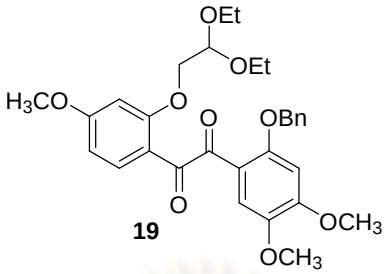
Synthesis of 1-Benzyloxy-2-[2-(2,2-diethoxy-ethoxy)-4-methoxy-phenylethynyl]-4,5-dimethoxybenzene (152) [32]



152

To a N_2-degassed solution of CH_3CN (5 mL) and triethylamine (500 µL) were added compound **20** (338.4 mg, 1.28 mmol), compound **21** (338.5 mg, 0.91 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 2 % mol) and CuI (3 mg, 1.7 % mol), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **152** (456.5 mg, 98 %) as a brown solid, m.p. 53 °C TLC, R_f 0.28 (EtOAc/hexane, 3:7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 6.8 Hz), 7.38-7.26 (m, 4H), 6.97 (s, 1H), 6.51 (s, 1H), 6.48-6.47 (m, 2H), 5.20 (s, 2H), 4.79 (t, 1H, *J* = 6.0 Hz), 4.06 (d, 2H, *J* = 6.0 Hz), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (m, 2H), 3.64 (m, 2H), 1.18 (t, 6H, *J* = 7.2 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 160.2, 154.2, 149.7, 143.6, 137.4, 133.9, 128.4×2, 127.8, 127.4×2, 115.4, 106.1, 105.9, 101.1, 100.8×2, 99.7, 88.9, 88.4, 72.6, 70.1, 63.3×2, 56.3, 55.9, 55.4, 15.4×2 IR (neat) 2967, 2372, 1606, 1514 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}O_7Na$ $(M+Na)^+$ m/z 529.2202 found 529.2208.

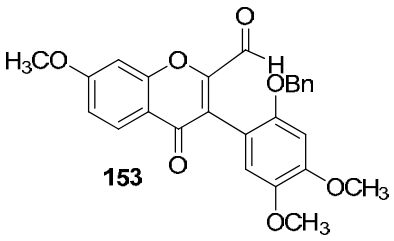
Synthesis of 1-(2-Benzyloxy-4,5-dimethoxy-phenyl)-2-[2-(2,2-diethoxy-ethoxy)-4-methoxy-phenyl]-ethane-1,2-dione (19) [47]



19

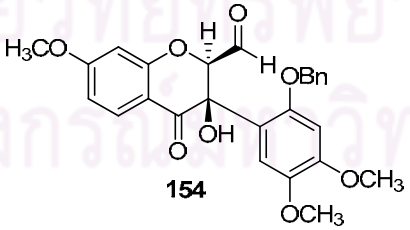
To a mixture of compound **152** (50 mg, 0.0987 mmol), $NaHCO_3$ (4 mg, 0.0476 mmol), $MgSO_4$ (18 mg, 0.15 mmol), and $NaIO_4$ (64.34 mg, 0.2961 mmol), in CCl_4 (1 mL), CH_3CN (1 mL), and water (1 mL) were added $RuCl_3$ stock solution (205 μl, 1 mol %, 0.0048 M). The reaction mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was extracted with EtOAc (2×10 mL), washed with H_2O and dried over Na_2SO_4. After removed organic solvent, the crude residue was purified by flash chromatography on silica gel (elution with 1:1 EtOAc/hexane) to obtain compound **19** (46.5 mg, 88%) as yellow solid, m.p. 119.5 °C TLC, R_f 0.43 (EtOAc/hexane, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 9.2 Hz), 7.57 (s, 1H), 7.14-7.11 (m, 3H), 7.05 (d, 2H, *J* = 6.8 Hz), 6.48 (s, 1H), 6.43 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.29 (d, 1H, *J* = 2.0 Hz), 4.87 (s, 2H), 4.20 (t, 1H, *J* = 5.6 Hz), 3.91 (s, 3H), 3.86 (s, 3H), 3.82 (d, 2H, *J* = 5.6 Hz), 3.81 (s, 3H), 3.47 (m, 2H), 3.21 (m, 2H), 1.07 (t, 6H, *J* = 7.2 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.7, 191.4, 165.7, 161.0, 155.8, 155.1, 143.9, 135.3, 132.3, 128.2×2, 127.8, 127.6×2, 116.9, 115.8, 111.3, 107.1, 100.3, 98.9, 97.7, 71.9, 70.1, 62.8×2, 56.3, 56.1, 55.6, 15.2×2 IR (neat) 2967, 1647, 160, 1514, 1442 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}O_9Na$ $(M+Na)^+$ m/z 561.2101 found 561.2105.

3-(2-(benzyloxy)-4,5-dimethoxyphenyl)-7-methoxy-4-oxo-4H-chromene-2-carbaldehyde (153)



To a solution of 0.5 M H_2SO_4 in THF was added compound **19** (200 mg, 0.37 mmol), and the reaction mixture was stirred at room temperature for 24 h. This mixture was diluted with H_2O, and then extracted with EtOAc (2×15 mL). The combined organic layer was concentrated, and the mixture was purified by flash chromatography on siliga gel (elution with 1:4 EtOAc/hexane) to give compound **153** (131 mg, 79 % yield) as a yellow solid, m.p.=127-128 °C TLC, R_f 0.48 (EtOAc/hexane, 1:1); ^{1}H-NMR ($CDCl_3$) δ 9.59 (s, 1H), 8.13 (d, 1H, J = 9.6 Hz), 7.21-7.19 (m,5H), 7.02 (s, 1H), 7.01 (d, 1H, J = 9.6 Hz), 6.86 (s,1H), 6.67 (s, 1H), 4.99 (d, 1H, J = 11.6 Hz), 4.93 (d, 1H, J = 11.6 Hz), 3.93 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H) ^{13}C-NMR ($CDCl_3$) δ 186.3, 177.4, 165.1, 157.1, 151.9, 151.2, 150.9, 143.7, 136.4, 128.5×2, 128.0, 127.8, 127.7, 127.5×2, 118.1, 115.7, 115.3, 109.2, 100.3×2, 72.7, 56.4, 56.1, 56.0 IR (neat) 3396, 1741, 1661, 1604, 1579, 1268 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{22}O_7Na$ (M+Na)+ m/z 469.1263 found 469.1275.

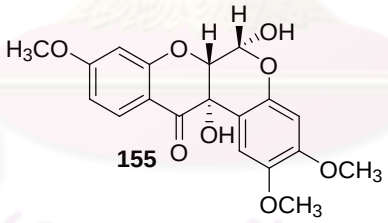
3-(2-Benzyloxy-4,5-dihydroxy-phenyl)-3-hydroxy-7-methoxy-4-oxo-chroman-2-carbaldehyde (154) [48]



To a solution of 2 M H_2SO_4 in H_2O (1 mL) and THF (4 mL) was added compound **19** (200 mg, 0.3713 mmol), and the reaction mixture was stirred at room temperature for 18 h. This mixture was diluted with H_2O (30 ml), then extracted with EtOAc (2×20 mL), washed sequentially with water (4×20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to give aldehyde crude. This crude was

dissolved in THF (4 mL), followed by addition of L-proline (3 mg, 0.371 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was added with H_2O 15 mL and then the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (2×10 mL). The combined organic phase (THF and $CHCl_3$) was washed with H_2O (2×15 mL), then dried over Na_2SO_4, filtered and concentrated. The residue was recrystaled with hexane and EtOAC to give compound **154** with a white solid (122 mg, 71 %), m.p. 193 °C TLC, R_f 0.28 (EtOAc/hexane, 1:1); $[\alpha]^{20}_D$ 0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.69 (d, 1H, *J* = 8.8 Hz) 7.18-7.16 (m, 6H), 6.62 (s, 1H), 6.58 (d, 1H, *J* = 8.8 Hz), 6.52 (s, 1H), 5.39 (s, 1H), 4.98 (d, 1H, *J* = 11.2 Hz), 4.89 (d, 1H, *J* = 11.2 Hz), 3.86 (s, 6H), 3.84 (s, 3H) 3.42 (s, 1H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.6, 186.7, 166.3, 161.0, 150.1, 148.8, 143.7, 135.8, 129.8, 128.4×2, 128.0, 127.4×2, 117.1, 113.1, 111.5, 111.1, 100.8, 99.1, 84.8, 76.1, 71.6, 56.5, 56.1, 55.8 IR (neat) 3560-3242, 1747, 1682, 1600, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}O_8Na$ $(M+Na)^+$ m/z 487.1369 found 487.1376.

6,12a-Dihydroxy-2,3,9-trimethoxy-6a,12a-dihydro-6H-chromeno[3,4-b]chromen-12a-one (155) [49]

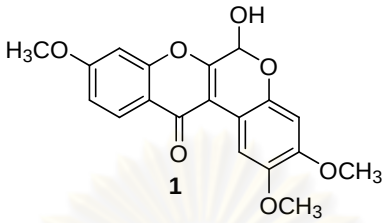


155

To a solution of compound **154** (100 mg, 0.2671 mmol) in distilled isopropanol (2 mL) was added Pd-C (10% on charcoal, 10 mg), and the mixture was stirred under a balloon pressure of H_2 at room temperature for 12 hours. The mixture was filtered and concentrated to give compound **155** (68.62 mg, 80%) as white solid, m.p. 84-86 °C TLC, R_f 0.23 (EtOAc/hexane, 1:1); $[\alpha]^{22.5}_D$ +4 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ7.86 (d, 1H, *J* = 8.8 Hz), 7.73 (s, 1H), 6.66 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.55 (d, 1H, 2.4), 6.42 (s, 1H), 5.81 (bs, 1H), 5.34 (d, 1H, *J* = 6.0 Hz), 4.57 (d, 1H, *J* = 2.8 Hz), 4.28 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) 186.1, 166.2, 161.9, 151.2, 145.0, 144.1, 130.5, 113.3, 112.8, 111.1, 110.0,

101.1, 100.6, 91.8, 76.8, 67.3, 56.3, 55.9, 55.8 IR (neat) 3686, 3070, 1617, 1582, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}O_8Na$ $(M+Na)^+$ m/z 397.0899 found 397.0905.

6-Hydroxy-2,3,9-trimethoxy-6H-chromeno[3,4-b]chromen-12-one (1)



1

To a solution of 0.5 M H_2SO_4 in THF was added compound **155** (50 mg, 0.1336 mmol), and the reaction mixture was stirred at room temperature for 24 h. This mixture was diluted with H_2O, and then extracted with EtOAc (2×15 mL). The combined organic layer was concentrated, and the mixture was purified by flash chromatography on siliga gel (elution with 95:5 $CHCl_3$/MeOH) to give compound **1** (44.3 mg, 93 % yield) as a yellow solid, m.p. 211 °C TLC, R_f 0.48 ($CHCl_3$/MeOH, 95:5); $[\alpha]^{20}_D$ +4 (*c* 0.1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$+$(CD_3)_2SO$) δ 8.48 (s, 1H), 8.03 (d, 1H, *J* = 8.8 Hz), 6.87 (dd, 1H, *J* = 8.8, 2.0 Hz), 6.77 (d, 1H, *J* = 2.0 Hz), 6.53 (s, 1H), 6.04 (s, 1H Hz), 3.81 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$+$(CD_3)_2SO$) δ 175.4, 164.0, 156.8, 155.1, 149.0, 143.8, 143.2, 127.2, 118.1, 114.7, 110.5, 109.5, 108.8, 101.2, 100.2, 88.9, 56.2, 55.8×2 IR (neat) 3286, 2913, 1626, 1591, 1513, 1447 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}O_7Na$ $(M+Na)^+$ m/z 379.0794 found 379.0795.

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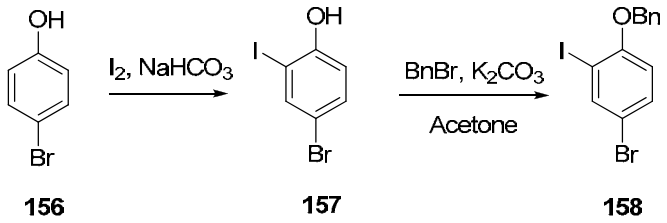
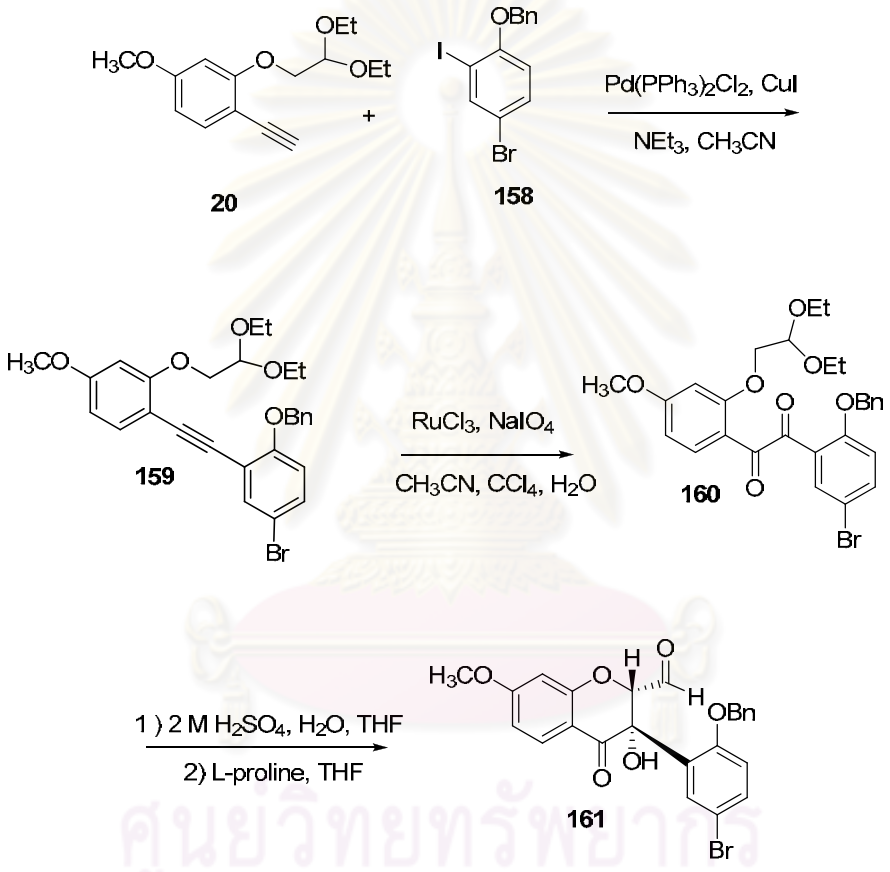
3.3 Synthesis of isoflavanone derivative 161



Scheme 53 Synthesis of compound **158**



Scheme 54 Synthsis of compound **161**

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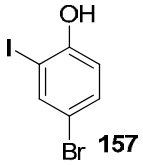
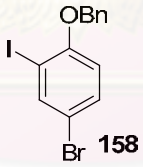
Synthesis of compound 157 [50]



157

To a solution of 4-bromophenol **156** (1.00 g, 5.78 mmol) in THF/H_2O (25:25 mL) was added I_2 (1.61 g, 6.36 mmol) and $NaHCO_3$ (0.73 g, 8.67 mmol). The reaction mixture was stirred at room temperature for 48 h. This reaction was quenched by saturated NaS_2O_3. The mixture reaction was extracted with EtOAc. The combined organic layer was concentrated, and the mixture was purified by flash chromatography on siliga gel (elution with 1:9 EtOAc/hexane) to give compound **157** (1.485 mg, 86 % yield) as a yellow solid, m.p. 81 °C TLC, R_f 0.48 (1:9 EtOAc/hexane; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1H, *J* = 2.3 Hz), 7.33 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.86 (d, 1H, *J* = 8.6 Hz), 5.37 (s, 1H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.2, 139.8, 133.0, 116.3, 113.0, 86.1 IR (neat) 3433, 2943, 2835, 1601, 1460, 954 cm^{-1}.

Synthesis of compound 158

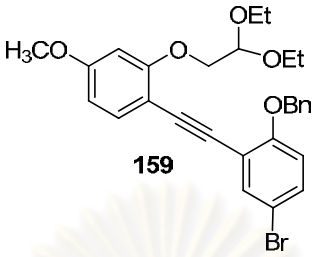


158

Compound **(157)** (1.00 g, 3.4656 mmol) and K_2CO_3 (554.0 mg, 4.0147 mmol) were first dissolved in acetone (30 mL) then treated with benzyl bromide (420.0 μL, 30.41 mmol), and the mixture was stirred at room temperature for 12 h. After remove of solvent, the crude was dissolved in water (50mL). The aqueous phase was extracted with ethyl acetate (2×50 mL) and the wash with brine (2×20 mL) and dried over Na_2SO_4. The organic phase were filtrated and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **158** (1.4481 g, 95%) as a white solid., m.p. 93 °C TLC, R_f 0.43 (EtOAc/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, *J* = 3.1 Hz), 7.49 (d, 2H, *J* = 7.8 Hz), 7.44-7.34 (m, 4H), 6.70 (d, 1H, *J* = 9.4 Hz), 5.12 (s, 2H) ^{13}C-NMR

(100 MHz, $CDCl_3$) δ 156.5, 141.3, 136.0, 132.2, 128.7×2, 128.1, 127.0×2, 113.8, 113.7, 87.7, 71.1 IR (neat) 1652, 1594, 1259, 1064, 677.

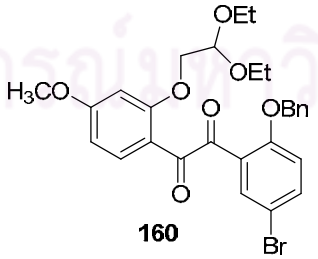
Synthesis of compound 159



159

To a N_2-degassed solution of CH_3CN (20 mL) and triethylamine (500 µL) were added compound **20** (611.9 mg, 2.3135 mmol), compound **158** (600 mg, 1.5423 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 2 % mol) and CuI (6 mg, 2 % mol), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **159** (721.2 mg, 89 %) as a brown solid, m.p. 87 °C TLC, R_f 0.45 (EtOAc/hexane, 3:7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 2.3 Hz), 7.49 (d, 2H, *J* = 7.0 Hz), 7.38-7.26 (m, 5H), 6.78 (dd, 1H, *J* = 8.6, 1.6 Hz), 6.48 (d, 1H, *J* = 9.4 Hz), 6.47 (s, 1H), 5.17 (s, 2H), 4.80 (t, 1H, *J* = 5.5 Hz), 4.05 (d, 2H, *J* = 5.5 Hz), 3.81 (s, 3H), 3.76 (m, 2H), 3.67 (m, 2H), 1,22 (t, 6H, *J* = 8.6 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.3, 160.4, 157.9, 136.7, 135.3, 134.2, 131.6, 128.5×2, 127.8, 126.9×2, 116.4, 114.6, 112.7, 105.9, 105.3, 100.9, 99.5, 91.7, 87.0, 70.7, 70.2, 63.6×2, 55.5, 15.4×2. IR (neat) 2975, 2222, 1613, 1509, 1457, 1213, 1018, 741.

Synthesis of compound 160



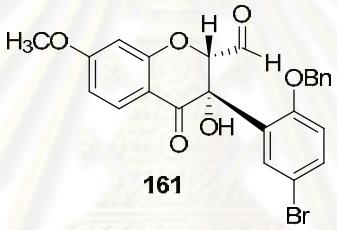
160

General procedure was followed employing 650 mg (1.24 mmol) of 1-(2-Benzyloxy-5-bromophenylethynyl)-2-(2,2-diethoxyethoxy)-4-methoxy-benzene**(159)**.

Purification by flash chroma tography on silica gel (elution with EtOAc/hexane, 2:3)

to give 1-(2-Benzyloxy-5-bromo-phenyl)-2-[2-(2,2-diethoxy-ethoxy)-4-methoxy-phenyl]-ethane-1,2-dione **160** (572 mg, 83 % yield) as a white solid, m.p. 84-85 °C TLC, R_f 0.33 (EtOAc/hexane, 1:1); ^{1}H-NMR ($CDCl_3$) δ 8.18 (d, 1H, *J* =2.3 Hz), 7.67 (d, 1H, *J* =8.6 Hz), 7.60 (dd, 1H, *J* =8.6, 2.3 Hz), 7.15-7.10 (m, 3H). 7.03 (d, 2H, *J* =6.2 Hz), 6.87 (d, 1H, *J* =8.6 Hz), 6.43 (dd, 1H, *J* =8.6, 1.6 Hz), 6.25 (s, 1H), 4.87 (s, 2H), 4.18 (t, 1H, *J* =4.7 Hz), 3.18 (s, 3H), 3.77 (d, 2H, *J* =4.7 Hz), 3.49 (q, 2H, *J* =7.8 Hz) 3.20 (q, 2H, *J* =7.8 Hz), 1.06 (t, 6H, *J* =7.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 191.0, 190.7, 165.9, 161.0, 158.3, 137.7, 134.5, 133.2, 132.2, 128.3×2, 128.0, 127.7×2, 125.3, 116.4, 114.9, 113.6, 107.2, 100.1, 98.8, 71.3, 69.9, 62.9×2, 55.6, 15.2×2; IR (neat) 2978, 2927, 1668, 1704, 1653 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{29}O_7BrNa$ (M+Na)+ m/z 579.0989 found 579.0997.

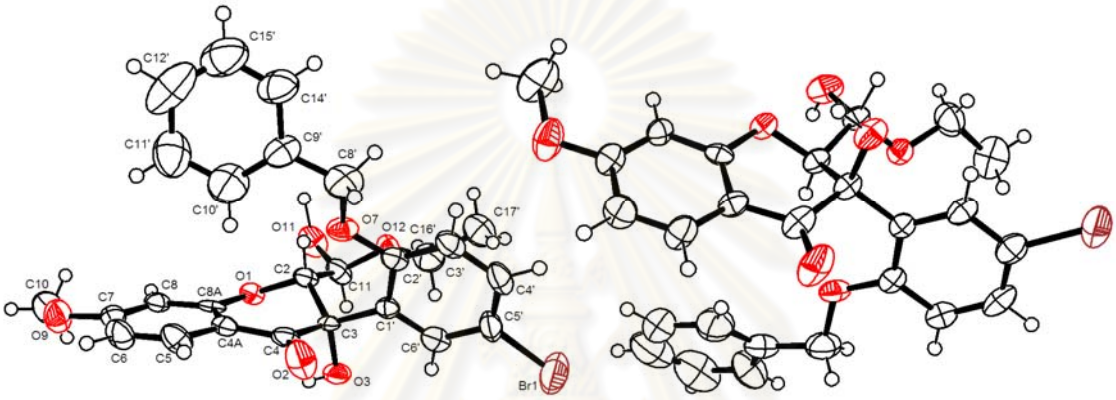
Synthesis of compound 161



161

To a solution of 2 M H_2SO_4 in H_2O (1 mL) and THF (4 mL) was added compound **160** (130 mg, 0.2327 mmol), and the reaction mixture was stirred at room temperature for 18 h. This mixture was diluted with H_2O (30 ml), then extracted with EtOAc (2×20 mL), washed sequentially with water (4×20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to give aldehyde crude. This crude was dissolved in THF (4 mL), followed by addition of L-proline (3 mg, 0.371 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was added with H_2O 15 mL and then the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (2×10 mL). The combined organic phase (THF and $CHCl_3$) was washed with H_2O (2×15 mL), then dried over Na_2SO_4, filtered and concentrated. The residue was recrystaled with hexane and EtOAC to give compound **161** with a white solid (150 mg, 75 %), m.p. 190-192 °C TLC, R_f 0.30 (EtOAc/hexane, 1:1); $[\alpha]^{20}_D$ +10 (c 1.0, $CHCl_3$);); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.77 (d, 1H, *J* = 2.0 Hz), 7.70 (d, 1H, *J* = 8.8 Hz), 7.48 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.19-7.11 (m, 5H), 6.88 (d, 1H, *J* = 8.4 Hz), 6.66 (dd, 1H, *J* =

8.8, 2.0 Hz), 6.52 (d, 1H, *J* = 2.0 Hz), 5.33 (s, 1H), 4.98 (d, 1H, *J* = 11.2 Hz), 4.90 (d, 1H, *J* = 11.2 Hz) 3.85 (s, 3H); ^{13}C-NMR (100 MHz, $(CD_3)_2SO$) δ 196.7, 187.0, 166.2, 161.1, 154. 1, 136.1, 132.6, 131.1, 129.9, 129.8, 128.5×2, 128.1, 127.7×2, 115.2, 113.1, 112.1, 111.4, 101.2, 84.6, 75.8, 70.7, 56.4 IR (neat) 3674-3172, 2950, 1738, 1659, 1602-1446, 1256 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}O_6BrNa$ (M+Na)+ m/z 505.0263 found 505.0257. Compound **161** was recrystallized from dichloromethane and ethanol (1:4) to give single crystals. The structure was investigated using X-ray crystallography which result was illustrated in Figure 4.



162 **163**

Figure 4 ORTEP diagram for compounds **162** and **163.**

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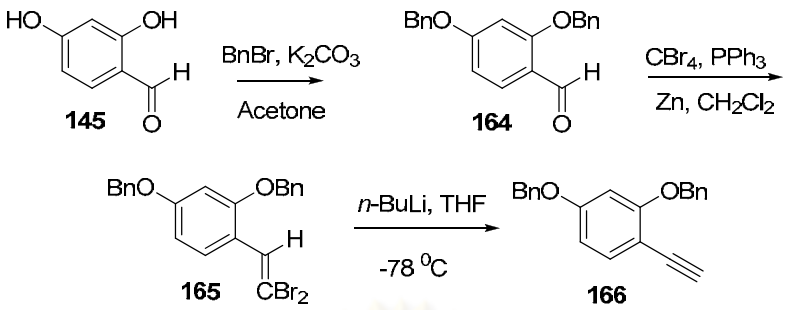
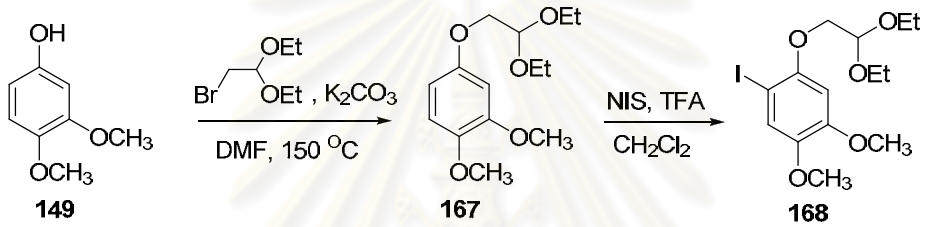
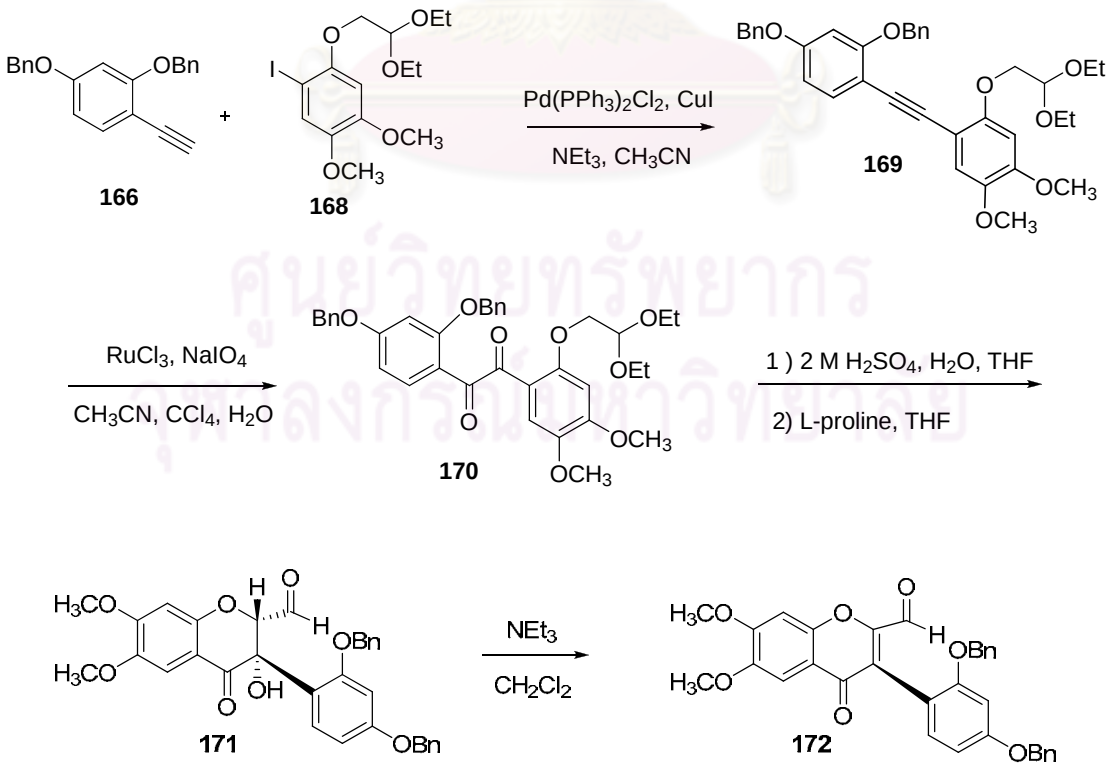
3.4 Synthesis of compound 172 overview



Scheme 55 Synthesis of compound **166**

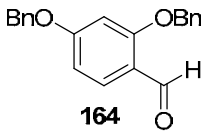


Scheme 56 Synthesis of compound **168**



Scheme 57 Synthesis of Compound **172**

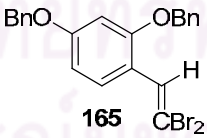
Synthesis of compound 164



164

Dihydroxybenzadehyde **(145)** (2.00 g, 14.48 mmol), $^{n}Bu_4NI$ (0.1 g, 0.28 mmol) and K_2CO_3 (6.0 g, 43.44 mmol) were first dissolved in acetone (30 mL) then treated with benzyl bromide (3.61 mL, 30.41 mmol), and the mixture was stirred at room temperature for 24 h. After remove of solvent, the crude was dissolved in water (50mL). The aqueous phase was extracted with ethyl acetate (2×50 mL) and the wash with brine (2×20 mL) and dried over Na_2SO_4. The organic phase were fillered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **164** (4.38 g, 95%) as a white solid., m.p. 67 °C TLC, R_f 0.43 (EtOAc/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.88 (d, 1H, *J* = 8.6, 2.3 Hz), 7.45-7.41 (m, 10H), 6.68 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.64 (d, 1H, *J* = 2.3 Hz), 5.17 (s, 2H), 5.14 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) 188.3, 165.2, 162.7, 135.9, 135.8, 130.5×2, 128.7×2, 128.4, 128.3×2, 127.6×2, 127.3×2, 119.4, 107.0, 100.0, 70.4×2 IR (neat) 2953, 1677, 1600, 1456, 1259, 1109, 1020, 820, 735 cm^{-1}; MS (ESI) calcd for $C_{21}H_{19}O_3$ $(M+H)^+$ m/z 319.13 found 319.13.

Synthesis of compound 165

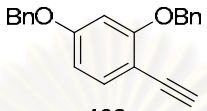


165

A mixture of zinc dust (308.04 mg, 4.71 mmol), triphenylphosphine (1.56 g, 4.71 mmol) and carbontetrabromide (1.24 g, 4.71 mmol) in dichloromethane (8 mL) was stirred at room temperature under nitrogen for 2 h. To this solution was added compound **164** (500 mg, 1.57 mmol) and the reaction was filtered and concentrated. The residue was purified by flash chromatography on silica gel (elution with 2:8 EtOAc/hexane) to give compound **(165)** (685.7 mg, 92%) as a brown solid., m.p. 67 °C TLC, R_f 0.53 (EtOAc/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1H, *J* =

8.6 Hz), 7.64 (s, 1H), 7.45-7.36 (m, 10H), 6.63 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.60 (d, 1H, *J* = 2.3 Hz), 5.09 (s, 2H), 5.08 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) 160.4, 157.1, 136.6, 136.5, 132.3, 129.9, 128.8×2, 128.2×2, 128.1×2, 127.7×2, 127.3×2, 117.9, 105.7, 100.6, 88.1, 70.4, 70.2 IR (neat) 2943, 2835, 1601, 1460, 954 cm^{-1}; MS (ESI) calcd for $C_{22}H_{18}Br_2NaO_2$ $(M+Na)^+$ m/z 497.17 found 265.497.35.

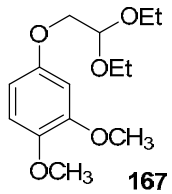
Synthesis of compound 166



166

Compound **165** (1.3212 g, 2.78 mmol) was dissolved in dried THF (20 mL) at -78 ^{o} C under N_2, then *n*-Butyllithium (10.0 mL of a 0.56 M hexane solution, 5.56 mmol) was added and the solution was stirred at -78 ^{o} C for 30 min. The reaction mixture was worked up with water (5 mL) and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic extract was washed with water (20 mL) and brine (20 mL) and finally dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:9 EtOAc/hexane) to obtain compound **166** (863.97 mg, 80 %) as yellow solid, m.p. 71 °C TLC, R_f 0.48 (EtOAc/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49-7.23 (m, 11H), 6.56 (s, H), 6.54 (dd, 1H, *J* = 8.6, 2.3 Hz), 5.16 (s, 2H), 5.03 (s, 2H), 3.27 (s, 1H) ^{13}C-NMR (100 MHz, $CDCl_3$) 160.9, 160.4, 136.6, 136.4, 128.7×2, 128.6×2, 128.2×2, 127.9×2, 127.6×2, 126.9×2, 106.3, 104.7, 101.0, 80.2, 80.0, 70.3, 70.2 IR (neat) 2100, 1613, 1506, 1454, 1171, 1034 cm^{-1}; MS (ESI) calcd for $C_{22}H_{19}O_2$ $(M+H)^+$ m/z 315.14 found 315.30.

Synthesis of compound 167

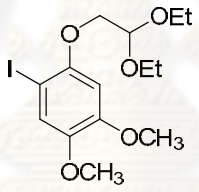


167

To a solution of compound **149** (400 mg, 2.60 mmol) in DMF (3 mL) was added K_2CO_3 (1.7922 g, 12.99 mmol) and bromoacetaldehyde diethyl acetal (605 µL, 3.90

mmol). The mixture was stirred under refluxing at 150 ^{o} C for 2 h. The reaction mixture was worked up with ice, neutraled with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (3 x 15 mL), the combined organic extract was washed with H_2O (2 x 10 mL) and brine (1 x 20 mL) and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **167** (568 mg, 81 %) as a yellow oil. TLC, R_f 0.52 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.77 (d,1H, *J* = 8.6 Hz), 6.59 (d, 1H, *J* = 3.1 Hz), 6.42 (dd, 1H, *J* = 8.6, 3.1 Hz), 4.84 (t, 1H, *J* = 5.5 Hz), 3.98 (d, 2H, *J* = 5.5 Hz), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (m, 2H), 3.66 (m, 2H), 1.27 (t, 6H, *J* = 7.0 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 153.2, 149.8, 143.6, 111.6, 103.9, 101.0, 100.4, 68.9, 62.4×2, 56.4, 55.8, 15.3×2 IR (neat) 2968, 2875, 1431, 1230 cm^{-1}; MS (ESI) calcd for $C_{14}H_{23}O_5$ $(M+H)^+$ m/z 271.15, found 271.25.

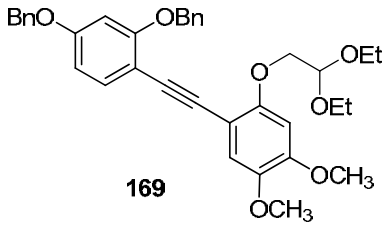
Synthesis of compound 168



168

To a solution of compound **167** (150 mg, 0.5563 mmol) in dichloromethane (3 mL) was added N-iodosuccinamide (108.92 mg, 0.6119 mmol) and trifluoroacetic acid (13 μL, 0.1669 mmol) at room temperature for 2 h. The reaction mixture was quenched with aqueous NaHSO3 (1mL) and the resulting was washed sequentially with water (2×20 mL), and brine (10 ml), and dried over anhydrous Na_2SO_4. The residue was filtered, concentrated, and purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **168** (196.1 mg, 89 %) as a white solid. TLC, R_f 0.52 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.49 (s, 1H), 4.80 (t, 1H, *J* = 5.5 Hz), 3.94 (d, 2H, *J* = 5.5 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 3.73 (m, 2H), 3.64 (m, 2H), 1.20 (t, 6H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 152.3, 150.1, 144.5, 121.5, 100.9, 99.4, 73.7, 71.5, 63.5×2, 56.6, 56.1, 15.4×2 IR (neat) 2953, 1497, 723 cm^{-1}; MS (ESI) calcd for $C_{14}H_{22}IO_5$ $(M+H)^+$ m/z 397.05, found 397.14.

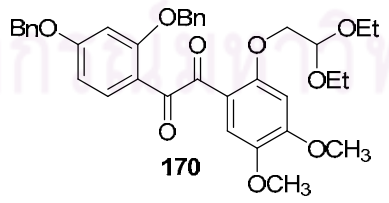
Synthesis of compound 169



169

To a N_2-degassed solution of CH_3CN (5 mL) and triethylamine (500 µL) were added compound **166** (165 mg, 0.4661 mmol), compound **168** (167 mg, 0.3107 mmol), $Pd(PPh_3)_2Cl_2$ (4 mg, 2 % mol) and CuI (1 mg, 2 % mol), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **169** (164 mg, 90 %) as a brown solid, m.p. 73 °C TLC, R_f 0.45 (EtOAc/hexane, 3:7); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, *J* = 7.8 Hz), 7.47-7.28 (m, 9H), 6.97 (s, 1H), 6.63 (m, 3H), 5.20 (s, 2H), 5.07 (s, 2H), 4.84 (t, 1H, *J* = 4.7 Hz), 4.17 (d, 2H, *J* = 4.7 Hz), 3.92 (s, 3H), 3.84 (s, 3H), 3.79 (m, 2H), 3.68 (m, 2H), 1.24 (t, 6H, *J* = 7.8 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 160.2, 159.9, 154.4, 149.8, 143.4, 137.0, 136.5, 133.7, 128.7×2, 128.5×2, 128.2×2, 127.8, 127.6×2, 127.0×2, 115.4, 106.8, 106.5, 105.3, 101.3, 101.1, 100.1, 88.9, 88.7, 71.6, 70.5, 70.2, 63.2, 56.3, 56.0 15.4×2 IR (neat) 2978, 2939, 2210, 1604, 1515, 1460, 744 cm^{-1}; MS (ESI) calcd for $C_{36}H_{39}O_7$ $(M+H)^+$ m/z 583.27 found 583.36.

Synthesis of compound 170

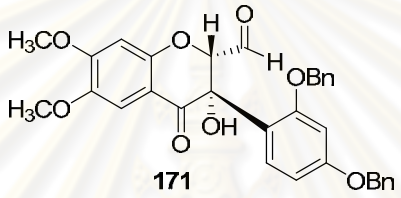


170

General procedure was followed employing 400 mg (0.6865 mmol) of 1,2-diphenylacethylene **169**. Purification by flash chromatography on silica gel (elution with EtOAc /hexane, 1:4) to give 1,2-diphenyl-ethane-1,2-dione **(170)** (422.0 mg, 87 % yield) as a light yellow crystal, m.p. 105-106 °C TLC, R_f 0.42 (EtOAc/hexane,

2:3); ^{1}H-NMR ($CDCl_3$) δ 8.10 (d,1H, *J*=8.6 Hz), 7.77-7.38 (m, 5H), 7.21 (t, 1H, *J* = 7.0 Hz), 7.19 (s, 1H), 7.13 (t, 2H, *J* = 7.8 Hz), 7.05 (d, 2H, *J* = 7.0 hz), 6.75 (dd, 1H, *J* = 8.6, 1.6 Hz), 6.60 (d, 1H, *J* = 1.6 Hz), 6.44 (s, 1H), 5.15 (s, 1H), 4.87 (s, 2H), 4.21 (t,m 1H, *J* = 5.5 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 3.81 (d, 2H, *J* = 5.5 Hz), 3.52 (m, 2H), 3.27 (m, 2H), 1.11 (t, 6H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 160.2, 159.9, 154.4, 149.8, 143.4, 137.0, 136.5, 133.7, 128.7×2, 128.5×2, 128.2×, 127.8, 127.6×2, 127.0×2, 115.4, 106.8, 106.5, 105.3, 101.3, 101.1, 100.1, 88.9, 88.7, 71.6, 70.5, 70.2, 63.2, 56.3, 56.0, 15.4×2 IR (neat) 2978, 2927, 1703, 1653 cm^{-1}. ; MS (ESI) calcd for $C_{36}H_{39}O_9$ $(M+H)^+$ m/z 615.26 found 615.36.

Synthesis of compound 171



171

To a solution of 2 M H_2SO_4 in H_2O (1 mL) and THF (4 mL) was added compound **170** (200 mg, 0.3254 mmol), and the reaction mixture was stirred at room temperature for 18 h. This mixture was diluted with H_2O (30 ml), then extracted with EtOAc (2×20 mL), washed sequentially with water (4×20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to give aldehyde crude. This crude was dissolved in THF (4 mL), followed by addition of L-proline (3 mg, 0.371 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was added with H_2O 15 mL and then the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (2×10 mL). The combined organic phase (THF and $CHCl_3$) was washed with H_2O (2×15 mL), then dried over Na_2SO_4, filtered and concentrated. The residue was recrystaled with hexane and EtOAC to give compound **171** with a white solid (176 mg, 66 %), m.p. 197 °C TLC, R_f 0.30 (EtOAc/hexane, 1:1); $[\alpha]^{20}_D$ 0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.57 (d, 1H, *J* = 8.09 Hz), 7.44-7.34 (m, 6H), 7.16-7.08 (m, 4H), 6.91 (s, 1H), 6.68 (dd, 1H, *J* = 10, 1.7 Hz), 6.47 (s, 1H), 5.32 (s, 1H), 5.06 (s, 2H), 4.94 (d, 1H, *J* = 11.0 Hz), 4.83 (d, 1H, *J* = 11 Hz), 3.90 (s, 3H), 3.75 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) 195.9, 188.9, 160.7, 156.2, 155.5, 155.3, 145.0, 136.6, 135.4, 128.8,

128.7×2, 128.2×2, 127.9×2,127.6×2, 127.4×2, 118.7, 111.7, 106.9, 105.9, 101.1, 100.1, 84.9, 76.0, 70.7, 70.2, 56.4, 55.9. IR (neat) 3421, 1736, 1680, 1623, 1501, 1454, 732 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{28}O_8Na$ $(M+Na)^+$ m/z 563.1682 found 563.1660.

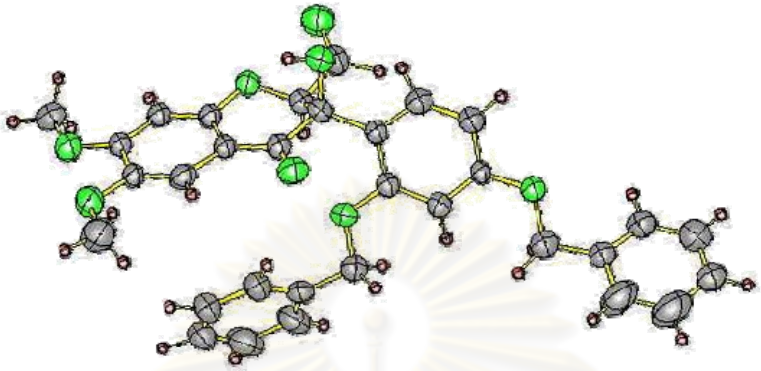
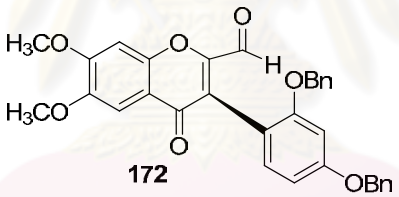


Figure 5 ORTEP diagram for compounds **171**

Synthesis of compound 172

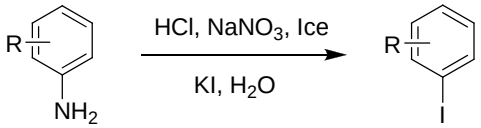


172

To a solution of compound **171** in CH_2Cl_2 3 mL was added NEt_3 (102.8 mg, 0.1902 mmol). The reaction mixture was stirred at room temperature for 10 mins. The reaction was added water 10 mL and then extracted with CH_2Cl_2 (2×10 mL). The combined organic layers was washed with water 10 mL and died over $NaSO_4$. The organic solvent was evaporated and the crude product was purified by flash chromatography on silica gel (elution with EtOAc /hexane, 3:7) to give 3-(2,4-bis(benzyloxy)phenyl)-6,7-dimethoxy-4-oxo-4H-chromene-2-carbaldehyde **(172)** (98 mg, 99 % yield) as a light yellow crystal, m.p. 176-180 °C TLC, R_f 0.45 (EtOAc/hexane, 3:7); ^{1}H-NMR ($CDCl_3$) δ 9.63 (s, 1H), 7.54 (s, 1H), 7.45-7.35 (m, 5H), 7.25-7.22 (m, 6H), 7.03 (s, 1H), 6.73 (m, 2H), 5.08 (s, 2H), 5.01 (s, 2H), 3.98 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 186.3, 177.0, 161.2, 157.8, 155.5, 151.6, 151.4, 148.1, 136.5, 136.2, 133.6, 128.7, 128.5, 128.2, 128.0, 127.9, 127.6, 127.3, 117.9, 110.4,

106.4, 104.5, 101.5, 100.1, 70.9, 70.3, 56.6, 56.4 IR (neat) 2981, 1716, 1675, 1501, 1454, 738cm^{-1}.

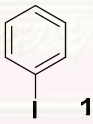
3.5 General procedure for preparation of phenyliodide (174) [51]



173 **174**

In round bottle flask was placed concentrate HCl (59.13 mmol), 30 mL of water, aniline derivatives (10.75 mmol). The mixture was stirred at 0 ^{o}C and then added aqueous solution sodium nitrite (12 mmol). Stirring was continued for ten minutes and the reaction mixture was added an aqueous solution of potassium iodide (11 mmol) at 0 ^{o}C. The reaction was monitored by TLC. The reaction was extracted with diethyl ether. The organic layer was added saturated $Na_2S_2O_8$ and washed with water. The organic phase was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography.

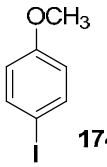
Iodobenzene (174a) [52]



174a

General procedure was followed employing 1.00 g (10.75 mmol) of aniline to give iodobenzene (2.15 g, 98 % yield) as light yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) 7.73 (d, 2H, *J* = 7.8 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.13 (d, 2H, 7.6 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 137.5×2, 130.2×2, 127.5, 94.5.

4-Iodo-phenol (174b) [53]

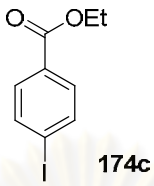


174b

General procedure was followed employing 1.00 g (8.12 mmol) of 4-methoxyaniline to give 1-iodo-4-methoxybenzene (1.81 g, 95 % yield) as light yellow oil, ^{1}H-NMR

(400 MHz, $CDCl_3$) 7.55 (d, 2H, *J* = 8.6 Hz), 6.68 (d, 2H, *J* = 8.6 Hz), 3.77 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) 159.4, 138.2, 116.4, 82.7, 55.3.

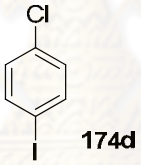
4-Iodo-benzoic acid ethyl ester (174c) [54]



174c

General procedure was followed employing 1.00 g (6.05 mmol) of ethyl 4-aminobenzoate to give ethyl 4-iodobenzoate (1.48 g, 89 % yield) as light yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) 7.69 (m, 4H), 4.30 (q, 2H, *J* = 7.2 Hz), 1.3 (t, 3H, *J* = 7.2 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 165.9, 137.6, 131.0, 129.9, 100.6, 1.2, 14.3.

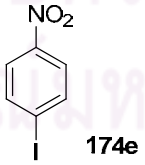
1-Chloro-4-iodo-benzene (174d) [55]



174d

General procedure was followed employing 1.00 g (7.83 mmol) of 4-chloroaniline to give 1-chloro-4-iodobenzene (1.76 g, 94 % yield) as light yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) 7.60 (d, 2H, *J* = 8.8 Hz), 7.09 (d, 2H, *J* = 8.8 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) 138.7, 130.5.

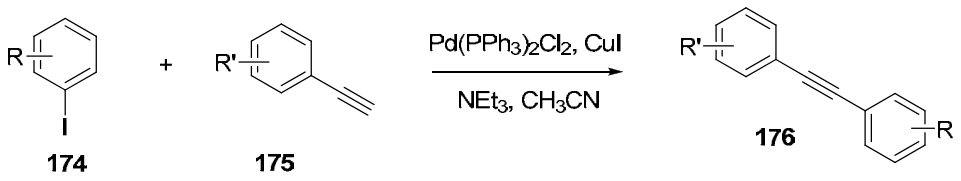
1-Iodo-4-nitro-benzene (174e) [56]



174e

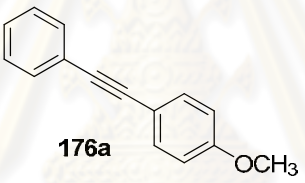
General procedure was followed employing 1.00 g (7.24 mmol) of 4-nitroaniline to give 1-iodo-4-nitrobenzene (1.73 g, 96 % yield) as light yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) 9.91 (m, 4H) ^{13}C-NMR (100 MHz, $CDCl_3$) 138.6, 124.8, 102.7.

3.6 General procedure for preparation of diarylalkyne (176) [32]



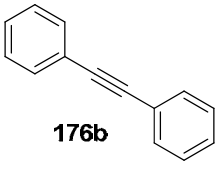
To a N_2-degassed solution of CH_3CN (2.50 mL/mmol) and triethylamine (1.0 equiv) were added phenylalkyne (1.42 equiv), phenyliodide (1.02 equiv), $Pd(PPh_3)_2Cl_2$ (2 % mol) and CuI (1.7 % mol), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, concentrated, and the residue was purified by flash chromatography on silica gel to give diphenylacethylene.

1-Methoxy-4-phenylethynyl-benzene (176a) [57]



General procedure was followed employing 4-methoxyiodobenzene **(174)** (500 mg, 2.1367 mmol). Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:9) to give 1-methoxy-4-phenylethynyl-benzene **(176a)** (436.1 mg, 98 %) as a white solid, m.p. 54-56 °C TLC, R_f 0.38 (EtOAc/hexane, 1:19); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.50 (m, 4H), 7.35 (m, 3H), 6.91-6.89 (dd, 2H, J = 8.8, 1.2 Hz), 3.82 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) 159.7, 133.1×2, 131.5×2, 128.4×2, 128.0, 123.6, 115.4, 114.0×2, 89.5, 88.1, 55.3 IR (neat) 2969, 2834, 2217, 1596, 1509, 1430, 1247 cm^{-1}.

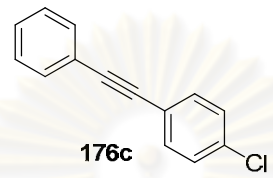
1,2-Diphenylacethylene (176b) [58]



General procedure was followed employing iodobenzene **(174a)** (372 mg, 1.8235 mmol). Purification by flash chromatography on silica gel (elution with hexane) to give 1,2-

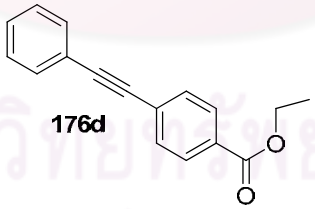
diphenylacethylene **(176b)** (321.4 mg, 99 %) as a colorless crystal, m.p. 44-46 °C TLC, R_f 0.43 (hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 4H), 7.40-7.37 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) 131.6×4, 128.4×4, 128.3×2, 123.3×2, 89.4×2 IR (neat) 3060, 1600, 1504, 1443 cm^{-1}.

1-Chloro-4-phenylethynyl-benzene (176c) [59]



General procedure was followed employing 1-chloro-4-iodo-benzene **(174d)** (1.3510 g, 5.6683 mmol). Purification by flash chromatography on silica gel (elution with hexane) to give 1-chloro-4-phenylethynyl-benzene **(176c)** (1.0151 g, 84 %) as a colorless crystal, m.p. 74-75 °C TLC, R_f 0.55 (hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.47 (dd, 2H, *J* = 8.8, 2.0 Hz), 7.37-7.33 (m, 5H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.3, 132.8×2, 131.6×2, 128.7×2, 128.5, 128.4×2, 123.0, 121.8, 90.4, 88.3 IR (neat) 3088, 2212, 1956, 1910, 1659, 1495, 835, 758 cm^{-1}.

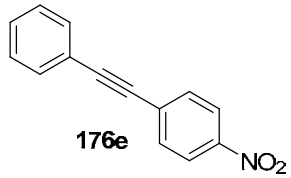
4-Phenylethynyl-benzoic acid ethyl ester (176d)



General procedure was followed employing 4-iodo-benzoic acid ethyl ester **(174c)** (612 mg, 2.6117 mmol). Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 4-phenylethynyl-benzoic acid ethyl ester **(176d)** (555.6 mg, 85 %) as a yellow solid, m.p. 77-78 °C TLC, R_f 0.58 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, *J* = 8.0 Hz), 7.60-7.54 (m, 4H), 7.36 (m, 3H), 4.38 (q, 2H, *J* = 7.2 Hz), 1.40 (t, 3H, *J* = 7.6 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 131.7×2, 131.5×2, 129.8, 129.5×2, 128.7, 128.4×2, 127.9, 122.7, 92.3, 88.7,

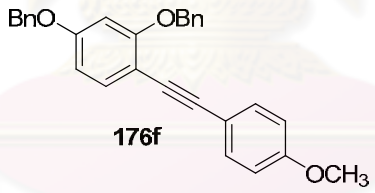
61.1, 14.3 IR (neat) 3000, 2217, 1726, 1604, 1404, 1282 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}O_2Na$ $(M+Na)^+$ m/z 273.0891 found 273.0893.

1-Nitro-4-phenylethynyl-benzene (176e) [60]



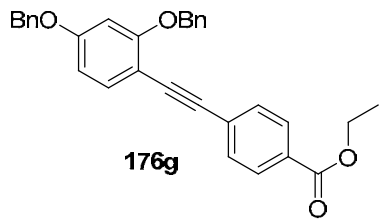
General procedure was followed employing 4-nitroiodobenzene **(174e)** (682 mg, 2.7388 mmol). Purification by flash chromatography on silica gel (elution with hexane) to give 1-nitro-4- phenylethynylbenzene **(176e)** (556.4 mg, 91 %) as a yellow crystal, m.p. 115-116 °C TLC, R_f 0.58 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, *J* = 8.8 Hz), 7.65 (d, 2H, *J* = 8.8 Hz), 7.56 (m, 2H), 7.38 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) 147.0, 132.3×2, 131.8×2, 130.2, 129.3, 128.6×2, 123.6×2, 122.1, 94.7, 87.6 IR (neat) 3104, 2204, 1586, 1508, 1343 cm^{-1}.

2,4-Bis-benzyloxy-1-(4-methoxy-phenylethynyl)-benzene (176f)



General procedure was followed employing 4-methoxyiodobenzene **(174b)** (150 mg, 2.6117 mmol). Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 2,4-bis-benzyloxy-1-(4-methoxy-phenylethynyl)-benzene **(176f)** (118.3 mg, 89 %) as a colorless crystal, m.p. 152-154 °C TLC, R_f 0.43 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2H, *J* = 7.2 Hz), 7.46-7.31 (m, 11H), 6.87 (d, 2H, *J* = 9.2 Hz), 6.60 (d, 1H, *J* = 2.4 Hz), 6.58 (dd, 1H, *J* = 8.4, 2.4 Hz), 5.16 (s, 2H), 5.05 (s, 2H), 3.83 (s, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.2, 159.9, 159.3, 137.0, 136.5, 133.8, 132.8×2, 128.6×2, 128.5×2, 128.1, 127.7, 127.6×2, 126.9×2, 116.2, 113.9×2, 106.5, 106.4, 101.3, 92.3, 84.5, 70.4, 70.2, 55.3 IR (neat) 3026, 2921, 2217, 1608, 1565, 1513, 1460 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}O_3Na$ $(M+Na)^+$ m/z 443.1623 found 443.1622.

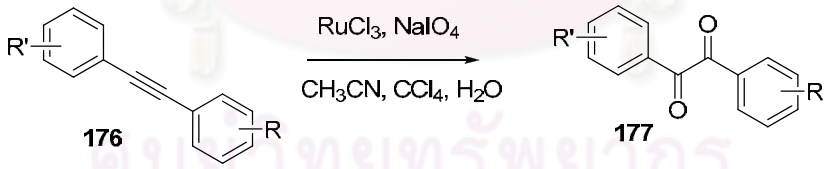
4-(2,4-Bis-benzyloxy-phenylethynyl)-benzoic acid ethyl ester (176g)



176g

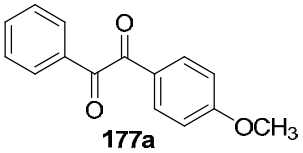
General procedure was followed employing 4-iodo-benzoic acid ethyl ester **(174c)** (400 mg, 1.4489 mmol). Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 4-(2,4-bis-benzyloxy-phenylethynyl)-benzoic acid ethyl ester **(176g)** (301 mg, 83 %) as a yellow solid, m.p. 90-92 °C TLC, R_f 0.38 (EtOAc/hexane, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, 2H, *J* = 8.0 Hz), 7.54 (t, 4H, *J* = 8.0 Hz), 7.47-7.33 (m, 9H), 6.62 (s, 1H), 6.59 (dd, 1H, *J* = 8.8, 2.0 Hz), 5.16 (s, 2H), 5.06 (s, 2H), 4.40 (q, 2H, *J* = 7.2 Hz), 1.42 (t, 3H, *J* = 7.2 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.2, 160.7, 160.6, 136.8, 136.4, 134.2, 131.2×2, 129.4×2, 129.2, 128.7, 128.6×2, 128.5×2, 128.2, 127.9, 127.6×2, 127.0×2, 106.5, 105.5, 101.1, 92.0, 89.2, 70.4, 70.3, 61.1, 14.4 IR (neat) 3043, 2986, 2208, 1713, 1600, 1513, 1274 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{26}O_4Na$ $(M+Na)^+$ m/z 485.1729 found 485.1736.

3.7 General procedure for oxidation of alkynes to 1,2-diketones 177:



The alkyne substrate (2.0 mmol), $NaHCO_3$ (13.2 mg, 0.1571 mmol), $MgSO_4$ (59 mg, 0.4937 mmol) and $NaIO_4$ (1.2833 mg, 6 mmol) in CH_3CN (3 mL), CCl_4 (3 mL) and H_2O (4 mL) was added RuCl3 stock solution (2 mL, 1 mol%, 0.01 M). The reaction mixture was stirred at room temperature until complete conversion. The reaction mixture was extracted with EtOAc (2×30 mL), washed with H_2O and dried over Na_2SO_4. After the organic solvent was removed the crude residue was purified by flash chromatography on silica gel to obtain the pure product.

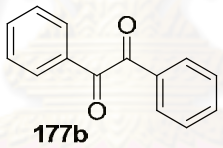
1-(4-Methoxy-phenyl)-2-phenyl-ethane-1,2-dione (177a) [34]



177a

General procedure was followed employing 416 mg (2.0 mmol) of 1-Methoxy-4-phenylethynyl-benzene **(176a)**. Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 1-(4-methoxy-phenyl)-2-phenyl-ethane-1,2-dione **(177a)** (447 mg, 93 % yield) as a light yellow crystal, m.p. 47-48 °C TLC, R_f 0.48 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 7.54-7.50 (m, 4H), 7.35 (m, 3H), 6.91-6.89 (dd, 2H, *J* = 8.8, 1.2 Hz), 3.82 (s, 3H) ^{13}C-NMR ($CDCl_3$) δ 194.9, 193.2, 165.0, 134.8, 133.1, 132.3×2, 129.9×2, 129.0×2, 126.0, 114.4×2, 55.6 IR (neat) 3061, 2834, 1674, 1695, 1513, 1260, 1169 cm^{-1}.

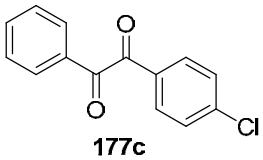
1,2-Diphenyl-ethane-1,2-dione (177b) [34]



177b

General procedure was followed employing 357 mg (2.0 mmol) of 1,2-diphenylacethylene **(176b)**. Purification by flash chromatography on silica gel (elution with EtOAc /hexane, 1:4) to give 1,2-diphenyl-ethane-1,2-dione **(177b)** (383 mg, 91 % yield) as a light yellow crystal, m.p. 76-80 °C TLC, R_f 0.50 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 7.60-7.58 (m, 4H), 7.70-7.37 (m, 6H) ^{13}C-NMR ($CDCl_3$) δ 131.6×4, 128.4×4, 128.3×2, 123.3×2, 89.4×2 IR (neat) 3060, 1600, 1504, 1443 cm^{-1}.

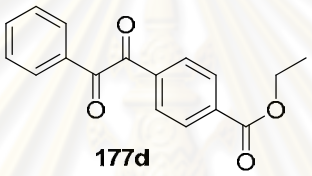
1-(4-Chloro-phenyl)-2-phenyl-ethane-1,2-dione (177c) [34]



177c

General procedure was followed employing 425 mg (2.0 mmol) of 1-Chloro-4-phenylethynyl-benzene **(176c)**. Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 1-(4-chloro-phenyl)-2-phenyl-ethane-1,2-dione **(177c)** (428 mg, 87 % yield) as a yellow crystal, m.p. 64-65 °C TLC, R_f 0.38 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 7.96 (dd, 2H, *J* = 7.6, 1.6 Hz), 7.92 (dd, 2H, *J* = 6.8, 0.8 Hz), 7.67 (t, 1H, *J* = 7.6 Hz), 7.54-7.48 (m, 4H) ^{13}C-NMR ($CDCl_3$) δ 193.9, 193.1, 141.6, 135.1, 132.8, 131.3, 131.2×2, 129.9×2, 129.4×2, 129.1×2 IR (neat) 3067, 2991, 1762, 1670, 1593, 1449, 1245, 1209 IR (neat) 2995, 1769, 1674, 1587, 1456 cm^{-1}.

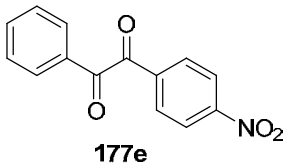
4-(2-Oxo-2-phenyl-acetyl)-benzoic acid ethyl ester (177d)



177d

General procedure was followed employing 505 mg (2.05 mmol) of 4-Phenylethynyl-benzoic acid ethyl ester **176d**. Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 1:4) to give 4-(2-oxo-2-phenyl-acetyl)-benzoic acid ethyl ester **177d** (457 mg, 79 % yield) as a light yellow crystal, m.p. 64-65 °C TLC, R_f 0.48 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 8.08 (d, 2H, *J*= 8.0 Hz), 7.95 (d, 2H, *J* = 8.4 Hz), 7.89 (d, 2H, *J* = 7.6 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.44 (t, 2H, *J* = 8.0 Hz), 4.32 (q, 2H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 7.2 Hz) ^{13}C-NMR ($CDCl_3$) δ . 193.8, 193.7, 165.4, 135.9, 135.7, 135.1, 132.7, 130.0×2, 129.9×2, 129.7×2, 129.14×2, 61.7, 14.2 IR (neat) 2922, 1717, 1674, 1600, 1452, 1278 cm-1; HRMS (ESI) calcd for $C_{17}H_{14}O_4Na$ (M+Na)+ m/z 305.0790 found 305.0793.

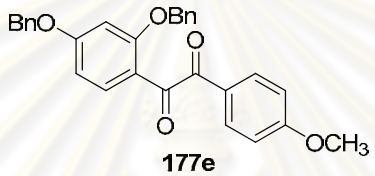
1-(4-Nitro-phenyl)-2-phenyl-ethane-1,2-dione (177e) [34]



177e

General procedure was followed employing 446 mg (2.0 mmol) of 1-Nitro-4-phenylethynyl-benzene **(176e)**. Purification by flash chromatography on silica gel (elution with EtOAc/hexane, 3:7) to give 1-(4-nitro-phenyl)-2-phenyl-ethane-1,2-dione **(177e)** (317 mg, 62 % yield) as a yellow crystal, m.p. 139-140 °C TLC, R_f 0.43 (EtOAc/hexane, 3:7); ^{1}H-NMR ($CDCl_3$) δ 8.33 (d, 2H, *J* = 1.2 Hz), 8.15 (d, 2H, *J* = 8.4 Hz), 7.97 (d, 2H, *J* = 8.4 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.54 (t, 2H, *J* = 7.6 Hz) ^{13}C-NMR ($CDCl_3$) δ 192.9, 192.1, 151.1, 137.3, 135.5, 132.3, 131.0×2, 130.0×2, 129.2×2, 124.1×2 IR (neat) 3109, 1665, 1600, 1521, 1356 cm^{-1}.

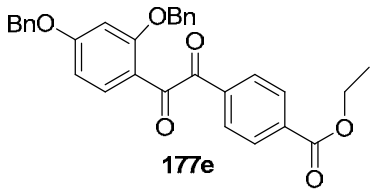
1-(2,4-Bis-benzyloxy-phenyl)-2-(4-methoxy-phenyl)-ethane-1,2-dione (177f)



177e

General procedure was followed employing 530 mg (1.5 mmol) of 2,4-Bis-benzyloxy-1-(4-methoxy-phenylethynyl)-benzene **(176f)**. Purification by flash chromato-graphy on silica gel (elution with EtOAc/hexane, 1:4) to give 1-(2,4-bis-benzyloxy-phenyl)-2-(4-methoxy-phenyl)-ethane-1,2-dione **(177f)** (645 mg, 95 % yield) as a colorless crystal, m.p. 97-98 °C TLC, R_f 0.18 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 8.05 (d, 1H, *J* = 9.2 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 7.40-7.35 (m, 5H), 7.26-7.16 (m, 3H), 7.00 (d, 2H, *J* = 6.8 Hz), 6.77 (d, 2H, *J* = 8.8 Hz), 6.71 (dd, 1H, *J* = 8.8, 1.6 Hz), 6.52 (d, 1H, J = 1.6 Hz), 5.10 (s, 2H), 4.82 (s, 2H), 3.84 (s, 3H) ^{13}C-NMR ($CDCl_3$) δ 193.6, 192.6, 165.6, 163.8, 161.4, 135.8, 134.7, 132.8, 131.7×2, 128.8×2, 128.4, 128.3×2, 128.0, 127.9×2, 127.5×2, 126.1, 117.5, 113.8×2, 107.7, 99.9, 71.0, 70.5, 55.5 IR (neat) 3030, 2926, 1665, 1596, 1517, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}O_5Na$ (M+Na)+ m/z 475.1521 found 475.1524.

4-[2-(2,4-Bis-benzyloxy-phenyl)-2-oxo-acetyl]-benzoic acid ethyl ester (176g)



177e

General procedure was followed employing 694 mg (1.5 mmol) of 4-(2,4-Bis-benzyloxy-phenylethynyl)-benzoic acid ethyl ester **(176g)**. Purification by flash chromato-graphy on silica gel (elution with EtOAc/hexane, 1:4) to give 4-[2-(2,4-bis-benzyloxy-phenyl)-2-oxo-acetyl]-benzoic acid ethyl ester **(177g)** (550 mg, 74 % yield) as a light yellow oil. TLC, R_f 0.25 (EtOAc/hexane, 1:4); ^{1}H-NMR ($CDCl_3$) δ 7.96 (d, 1H, *J* = 8.4 Hz), 7.82 (d, 2H, *J* = 8.4 Hz), 7.56 (d, 2H, *J* = 8.0 Hz), 7.31-7.25 (m, 5H), 7.16-7.11 (m, 1H), 7.05 (t, 2H, *J* = 7.6 Hz), 6.85 (d, 2H, *J* = 7.2 Hz), 6.65 (dd, 1H, *J* = 9.2, 2 Hz), 6.43 (d, 1H, *J* = 1.6 Hz), 5.02 (s, 2H), 4.68 (s, 2H), 4.31 (q, 2H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz) ^{13}C-NMR ($CDCl_3$) δ 192.9×2, 166.0, 165.7, 161.5, 136.1, 135.7, 134.3, 134.1, 132.7, 129.5×2, 129.1×2, 128.8×2, 128.4×3, 128.3, 128.1×2, 127.5×2, 117.0, 108.0, 99.7, 71.1, 70.5, 61.4, 14.3 IR (neat) 3052, 2934, 2874, 1721, 1683, 1643, 1591, 1439, 1269 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{26}O_6Na$ (M+Na)+ m/z 517.1627 found 517.1626.

3.8 Synthesis of Dichloribis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$) [61]

Triphenylphosphine (PPh_3) (622 mg, 2.37 mmol) was add to a solution of 100 mg (2.37 mmol) lithium chloride and 200 g (1.13 mol) palladium(II)chloride $PdCl_2$ dissolved in 20 mL of methanol. The mixture was warmed under nitrogen and stirred in a hot water bath until all the triphenylphosphine and the yellow, nearly insoluble product forms (~1h). The reaction mixture was cooled and the product was separated by filtration washed with 20 mL of fresh methanol, and air dried. The yield of yellow product was 753 mg (95%) and the mp is >250 °C.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

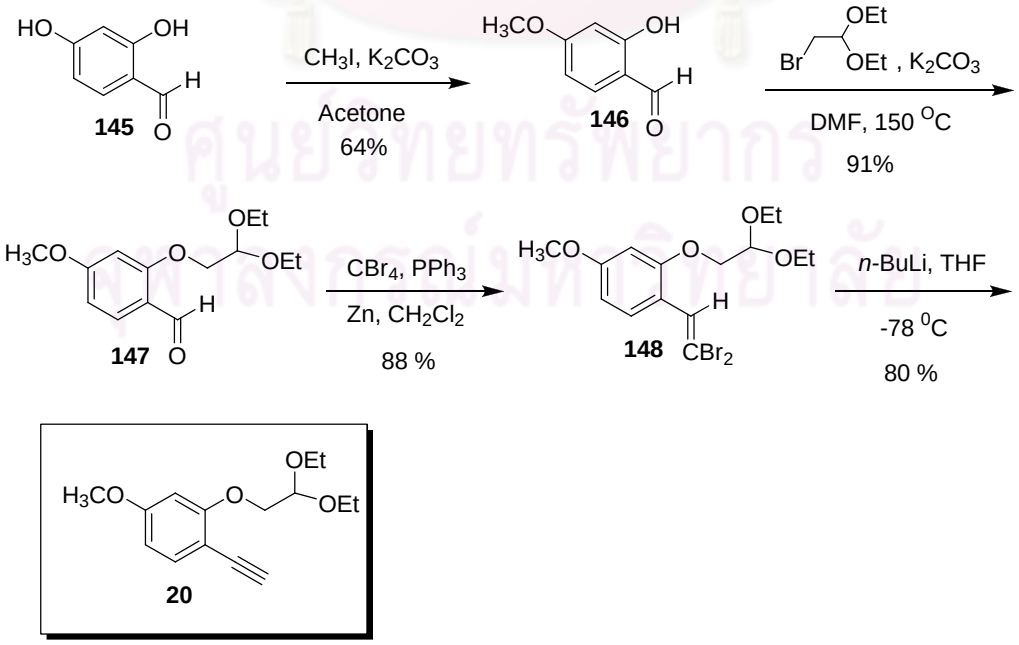
CHAPTER IV

RESULTS AND DISCUSSION

4.1 Synthesis of Dehydrorotenoid (1)

4.1.1 Synthetic approach to monoaryl substituted acetylene (20)

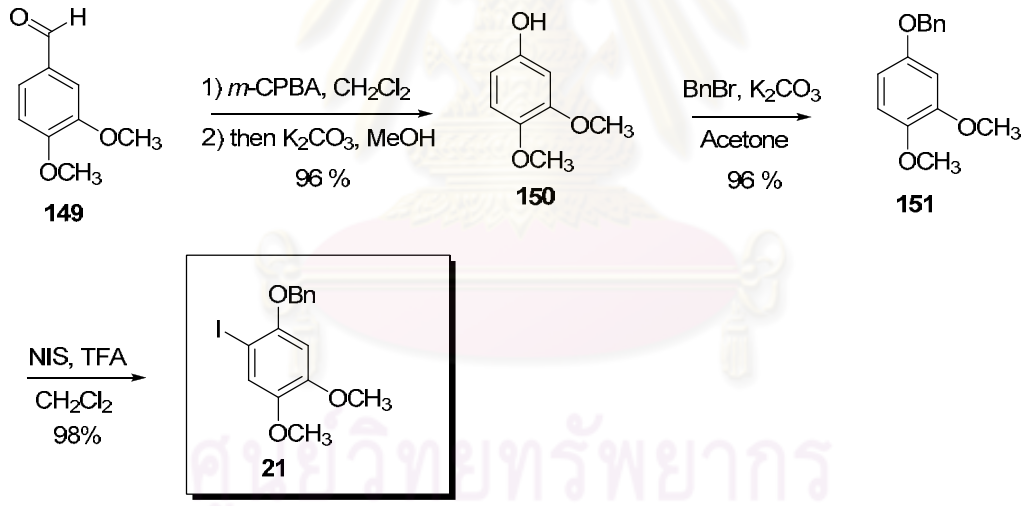
The synthesis of arylacetylene **20** is presented in Scheme 58. To realize this approach, compound **146** was prepared by treatment of the commercially available 2,4-dihydroxybenzaldehyde **(145)** with 1 equiv. of methyl iodide under basic condition. This reaction could not avoid the double methylation product. However product yields was governed by the concentration of reaction mixture. Compound **146** was achieved in 64 % yield when the concentration of reaction was 0.25 M, whereas the product yield was decreased to 35 % yield when the reaction was carried out on 0.5 M. Moreover the selectivity of methylation at 4-hydroxy position was controlled by the hydrogen bonding between carbonyl of aldehyde and 2-hydroxy position. Therefore, 4-hydroxy group of compound **145** was easier to deprotronate and methylate. Treatment of **146** with bromoacetaldehyde diethylacetal in the presence of potassium carbonate in DMF at 150 °C gave ether **147** in 91% yield.[44] Conversion of **147** to **20** was accomplished by the Corey-Fuchs alkynylation via dibromide **148**.[28]



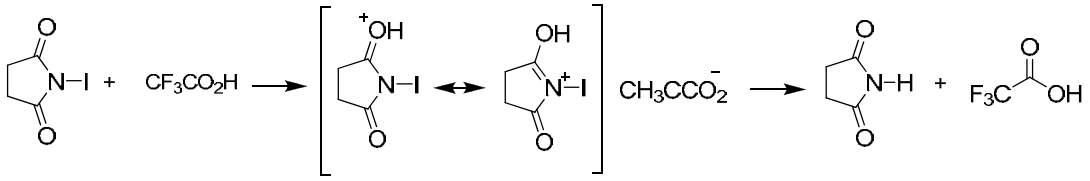
Scheme 58 Synthesis of compound **20**

4.1.2 Synthesis approach to compound 21

The preparation of **21** is outlined in Scheme 21. 3,4-Dimethoxybenzadehyde **(149)** was converted to 3,4-dimethoxyphenol **(150)** in 96 % yield using an *m*-CPBA-mediated Baeyer-Villiger oxidation [32] followed by hydrolysis under basic conditions. The phenolic hydroxyl moiety of compound **150** was protected as its benzyl derivative (96%),[45] and then iodinated with NIS in the presence of trifluoroacetic acid to give compound **21** in 98% yield.[46] A variety of methods for the iodination of aromatic compound have been reported. However, I selected NIS for this experiment since NIS is an excellent reagent for the regioselective iodination of activated aromatic compounds. It offered product **21** with high yield at room temperature and short reaction times. The mechanism of this iodination reaction has been proposed as shown in Scheme 60. The active species for the iodination is the "in situ formed" iodine trifluoroacetate which can act as a very reactive electrophlie, allowing iodination in short reaction times at room temperature.



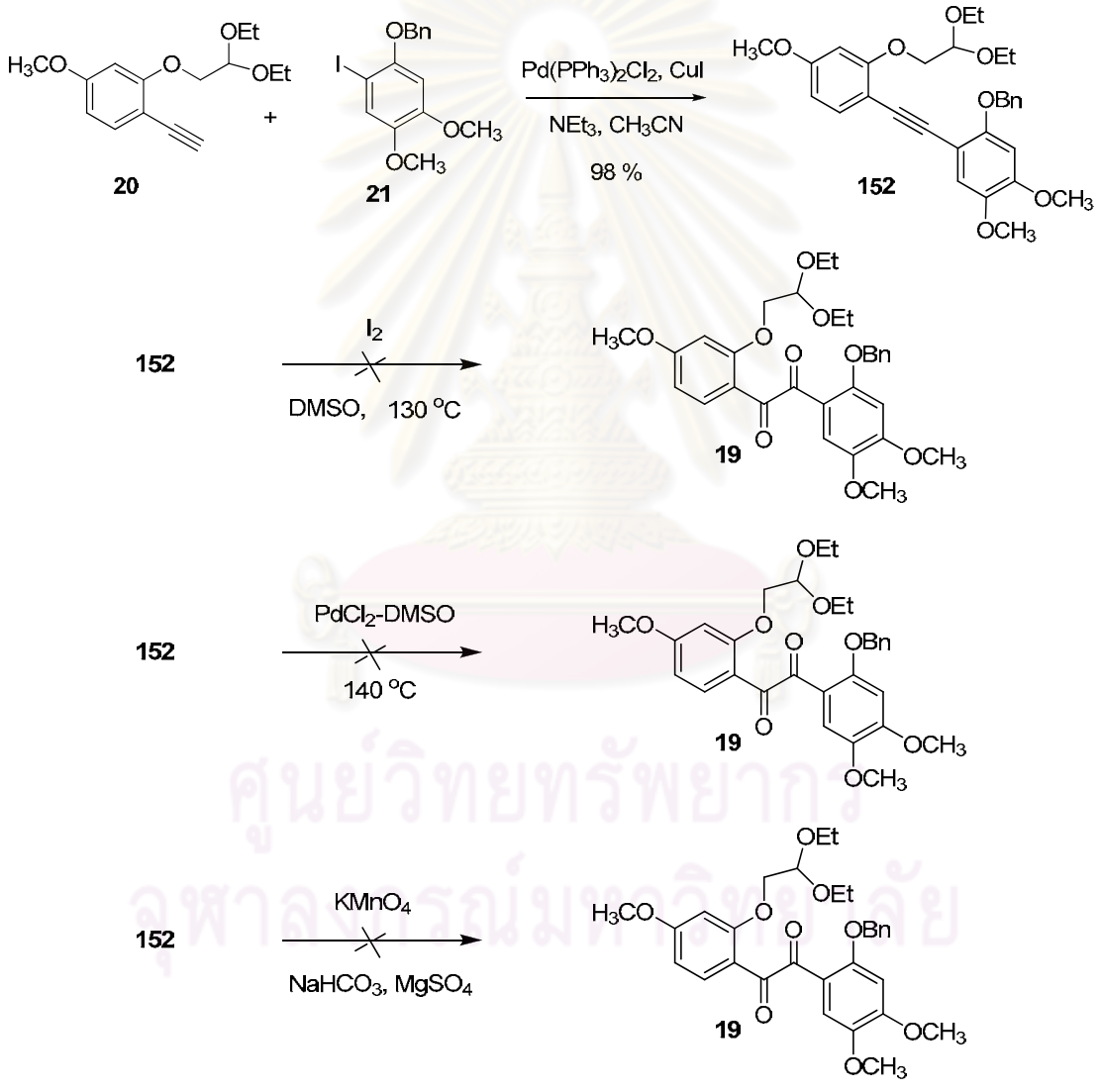
Scheme 59 Synthesis of compound **21**



Scheme 60 Mecahnism of iodination using NIS

4.1.3 Synthesis approach to compound 19

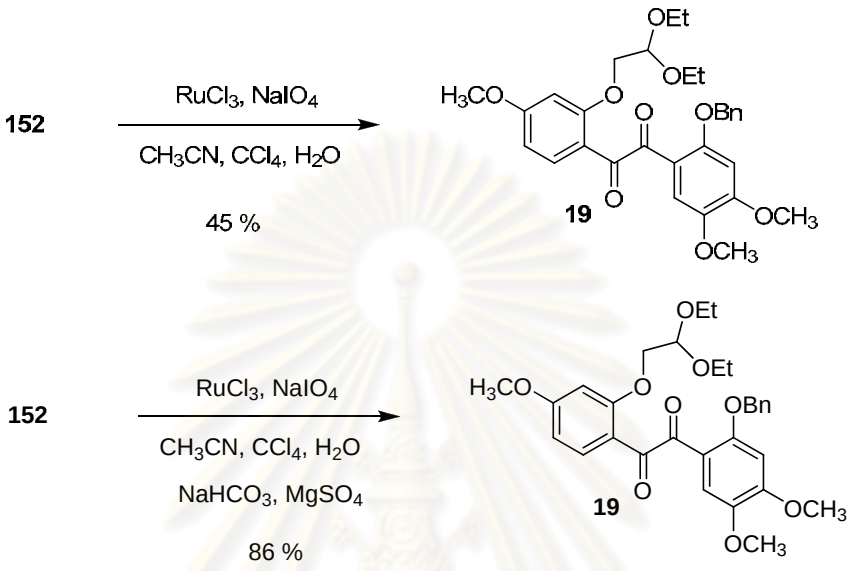
Sonogashira coupling reaction of monoaryl substituted acetylene **(20)** and aryl iodide **(21)** afforded the substituted diarylacetylene **(152)** in excellent yield (98 %). [32] With a reliable route to diaryl-substituted acetylene **152** in hand, I set out to examine the key oxidation reaction. Initially, compound **152** was oxidized with I_2/DMSO at 140 °C. This condition was no reaction. The oxidation procedures using $KMnO_4$ and $PdCl_2$/DMSO were then investigated carefully. Unfortunately, both procedures gave the complex mixture of products.



Scheme 61 Synthesis of 1,2-diketone **19**

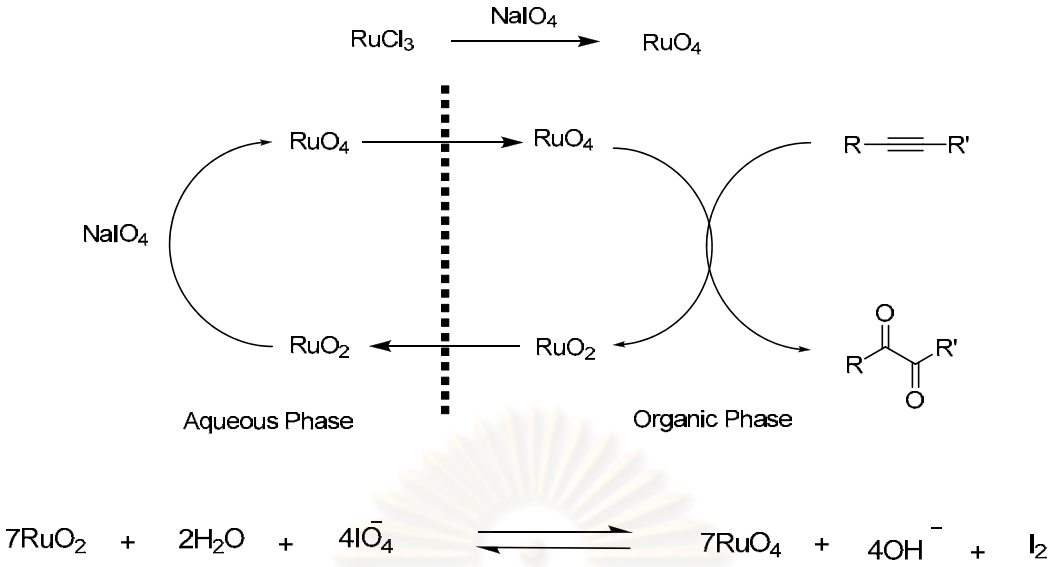
Then, compound **152** was attempted to oxidize with $RuCl_3$ (1 mol %), $NaIO_4$, $H_2O/CH_3CN/CCl_4$ according to a reported procedure[37]. The crude product of this

method had difficulty to purify by using column chromatography and also gave the deserted product **19** in low yield (45 %). To improve the yield of diketone **19**, this oxidation reaction was buffered with $NaHCO_3$ and $MgSO_4$.[39] Under this optimized condition, the desired diketone **19** was obtained in 86 % yield (Scheme 62).



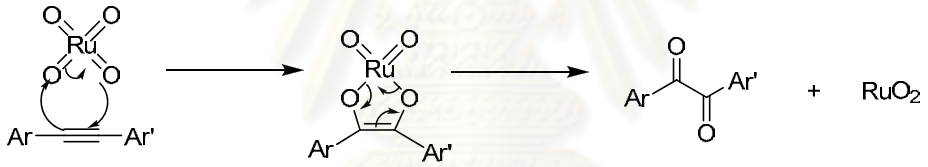
Scheme 62 Synthesis of 1,2-diketone using ruthenium catalyst

The reaction mechanism has been explained in Scheme 63. RuO_4 was generated *in situ* from a catalytic amount of $RuCl_3$ and a stiochiometric amount of $NaIO_4$ in aqueous layer. The RuO_4 was extracted into Carbontetrachloride (CCl_4) where it is most soluble [62]. The diaryl acetylenes were oxidized by RuO_4 in the organic phase to give the 1,2-diketone product. The ruthenium dioxide produced when oxidation occurs is insoluble in all solvents and migrated to the interface where it contacted the co-oxidant (in the aqueous layer) and was reoxidized. Thus best result was obtained when the mixture was shaken or stirred vigorously throughout the course of the reaction to achieve good contact between all components. In the reoxidized step, the hydroxide ions were produced during the reduction of RuO_4. Therefore, the added salts ($NaHCO_3$ and $MgSO_4$) serve as buffer and neutralize the hydroxide ions which effected to a decreasing of the cleavage products. Since the diketones are more polar than the parent alkynes, would be more soluble in aqueous solutions and thus experience greater contact with $NaIO_4$. Therefore diketones underwent cleaves more easily. So the addition of acetronitrile to the system greatly improves yields.



Scheme 63 Mechanism of ruthenium catalyzed oxidation reaction

The reaction mechanism of the oxidation of diaryl acetylenes is proposed in Scheme 64.



Scheme 64 Mechanism of the synthesis of 1,2-diketone

The scope of this oxidation procedure for the conversions of various substituted diarylacetylenes into the corresponding diketones was examined (Table 4). Therefore, the diarylactylenes was prepared via Sonogashira reaction. The results have been presented in Table 3.

Arylalkynes substituted with an electron-donating group have been transformed into the corresponding diketone in good yield and with shorter reaction time (entry 1 and 6). On the other hand, the presence of a nitro group on the aryl moiety entry 3) resulted in a significantly lower yield of diketone product.

Table 3. The preparation of diaryl acetylenes by Sonogashira coupling reaction.

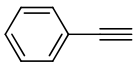
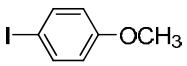
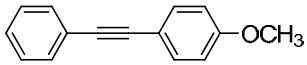
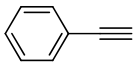
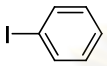
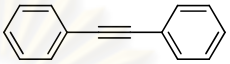
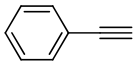
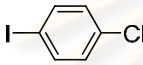
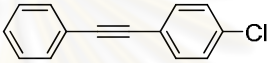
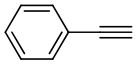
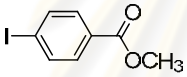
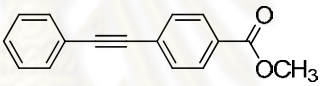
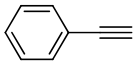
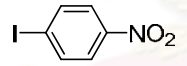
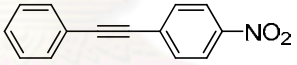
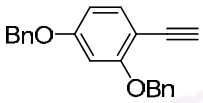
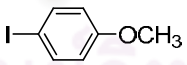
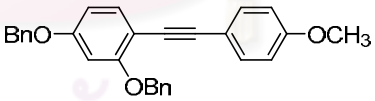
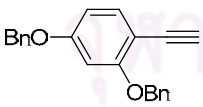
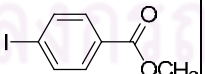
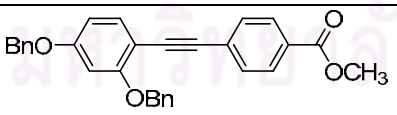
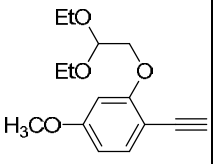
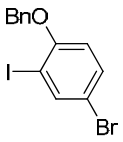
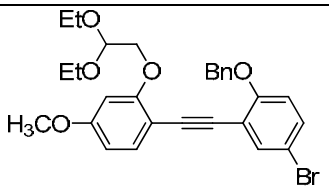
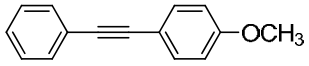
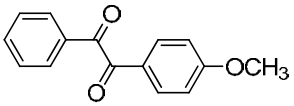
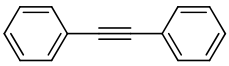
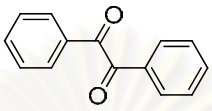
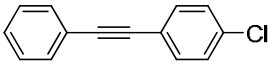
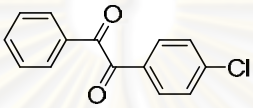
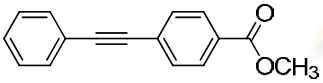
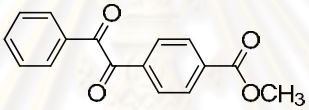
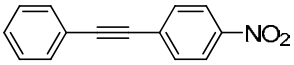
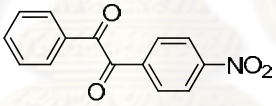
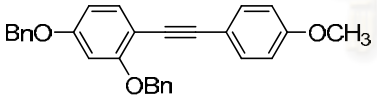
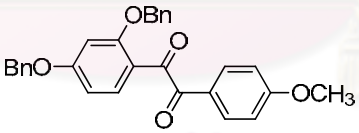
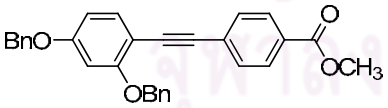
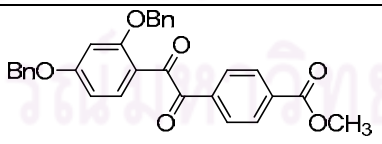
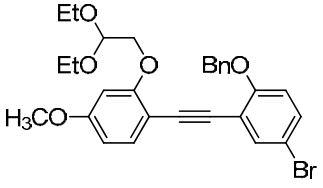
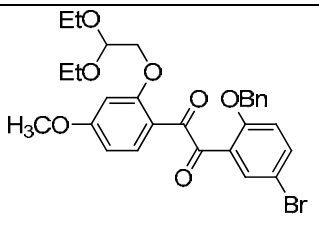
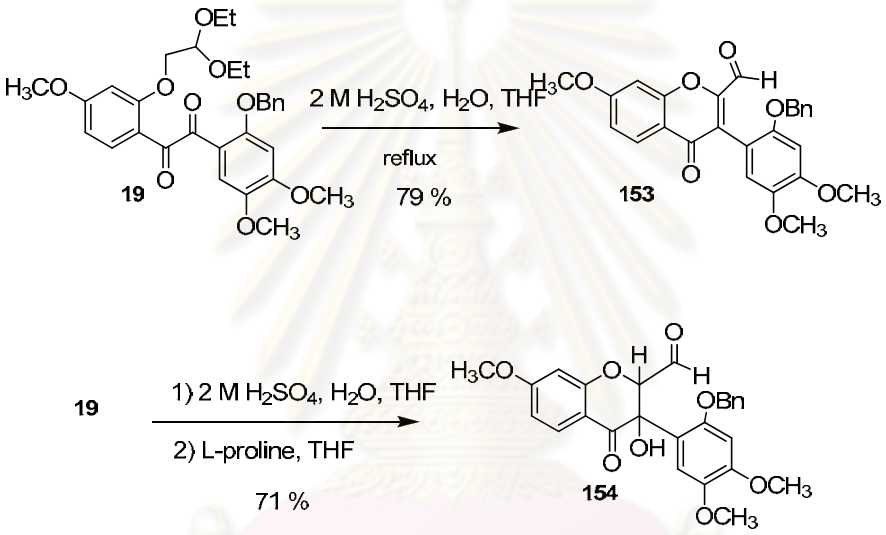
Diaryl Acetylenes	Aryl halide	1,2-Diketone	Yield (%)
		 **176a**	98
		 **176b**	99
		 **176c**	84
		 **176d**	85
		 **176e**	91
		 **176f**	89
		 **176g**	83
		 **159**	89

Table 4. Oxidation of various substituted diaryl acetylenes by $RuCl_3/NaIO_4$, H_2O/CH_3CN /CCl_4 buffered with $NaHCO_3$, $MgSO_4$

Diaryl Acetylenes	1,2-Diketone	Time (h)	Yield (%)
	 **177a**	3	93
	 **177b**	1	91
	 **177c**	2	87
	 **177d**	1	79
	 **177e**	4	62
	 **177f**	3	95
	 **177g**	1	74
	 **160**	3	83

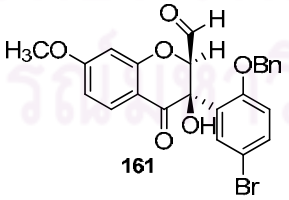
4.1.4 Synthesis of target dehydrorotenoid (1)

Aldol cyclization of **19** under acidic conditions afforded benzopyranone **153** through cyclization onto the distal ketone and dehydration. Notably, none of the corresponding 5-membered ring (benzofuran) was observed. In order to avoid potential conflictions in the removal of the benzyl ether, a stepwise aldol sequence was then employed. Compound **19** was treated with 2 M H_2SO_4, H_2O/THF to transform the diethyl acetal moiety into an aldehyde intermediate, which was followed by treatment with L-proline in THF to initiate an intramolecular aldol condensation leading to **154** in 71 % yield.



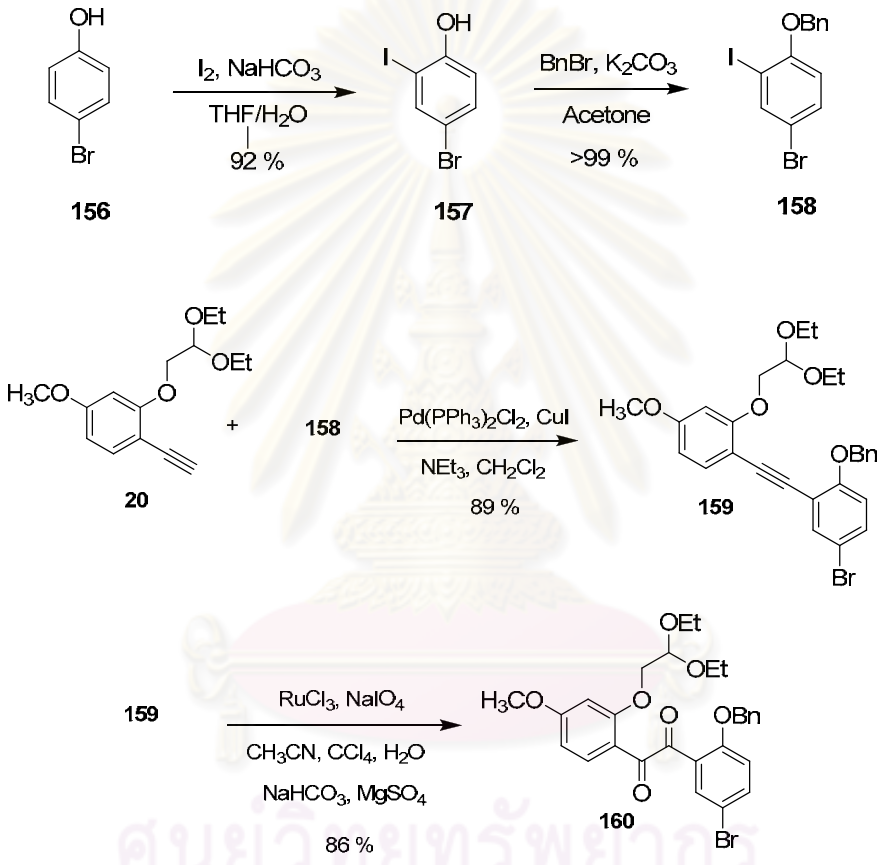
Scheme 65 Synthesis of compound **154**

4.1.5 Attempts to establish the stereochemistry



Attempts to establish the stereochemistry of **154** by X-ray analysis were unsuccessful due to the non-crystalline, unstable nature of compound **154**. Thus, a bromo analog **(160)** was prepared and subjected to identical L-proline catalyzed-intramolecular aldol reaction.

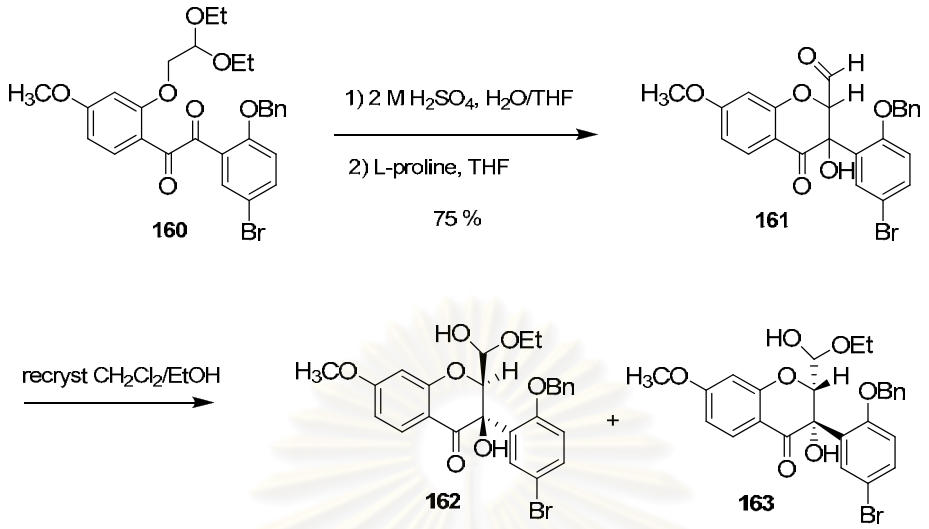
The bromophenol **(156)** was iodinated using I_2 and $NaHCO_3$ to generate compound **157** in 92 % yields. The hydroxyl group of compound **157** was then protected with benzyl group to furnish compound **158**. When I have compound **20** and **15**8 in hand, Compound **158** was coupled with compound **20**, under standard Sonogashira coupling condition to provide the desired disubstituted acetylene **159** in 89 % yield. The Ruthenium catalyzed-oxidation optimized conditions, the diketone **160** was obtained concisely in 86 % yields as shown in Scheme 66.



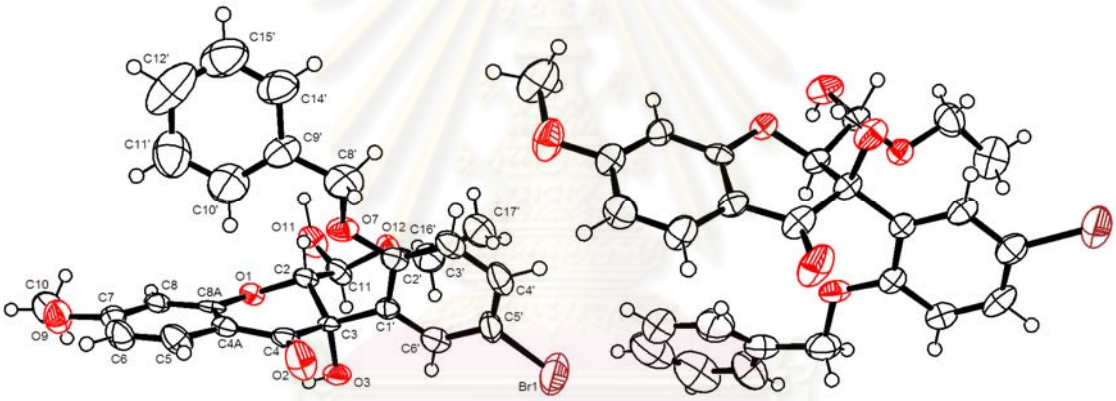
Scheme 66 Synthesis of compound **160**

The acetal moiety of 1,2-Diketone **160** was converted to aldehyde by treatment with 2 M H_2SO_4 at room temperature. This crude aldehyde was reacted with L-proline through the aldol reaction to generate compound **160** in 75 % yields as a white amorphous solid. Compound **161** was recrystallized from dichloromethane and ethanol (1:4) to give single crystals. The syn stereochemistry of compound **161** (carbonyl at C2 and OH-C3) was ascertained from the correlation of X-ray diffraction data of **162** and **163** (Figure 6). Thus, the stereochemistry of compound **153** (carbonyl

at C2 and OH-C3) was assigned to be syn by analogy. However, the stereogenic centers of compound **154** will be destroyed in the final step.



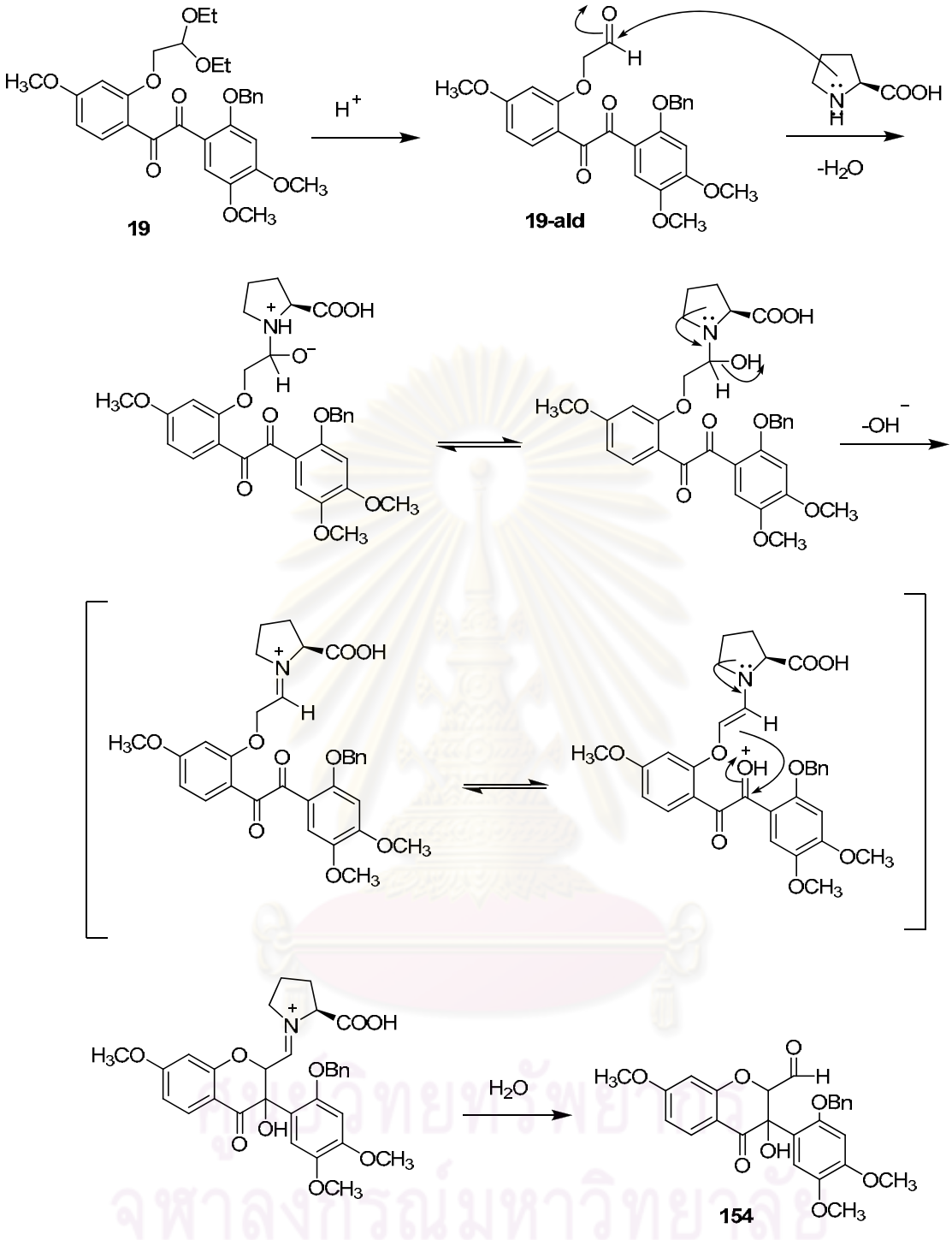
Scheme 67 Synthesis of compound **161**



162 **163**

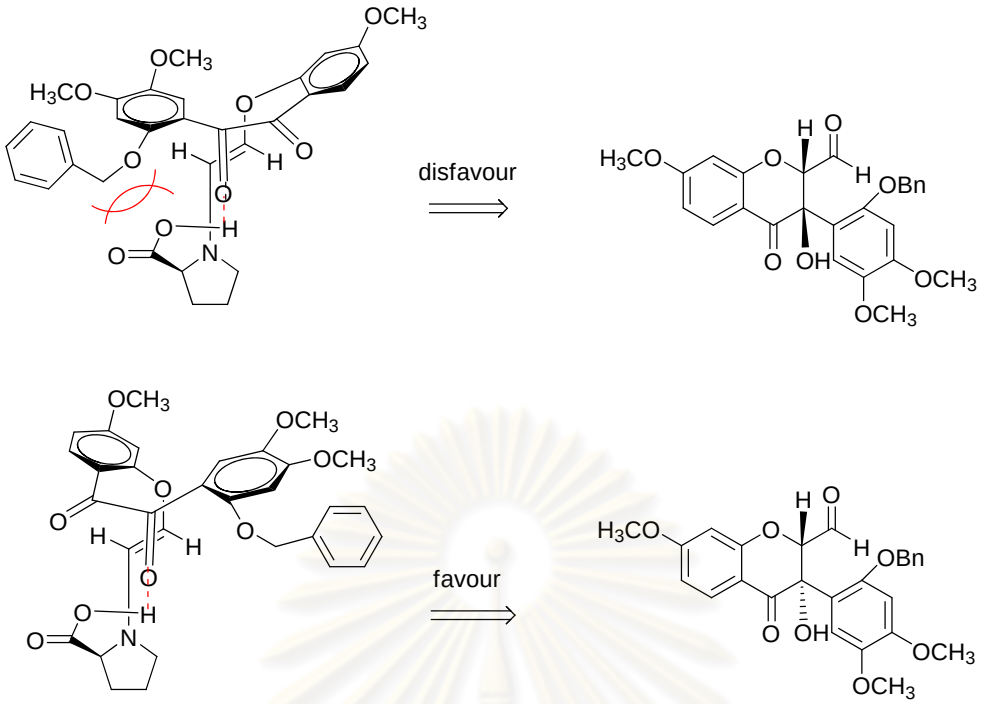
Figure 6. ORTEP diagram for compounds **162** and **163.**

The mechanism of L-proline catalyzed Aldol condensation is illustrated in Scheme 68. L-Proline effects reaction through enamine catalysis that generate from reaction between L-proline nitrogen and carbonyl group. The enamine attaches on the *re*-face of the carbonyl ketone and subsequently hydrolyzed to afford chiral β-hydroxyketone.



Scheme 68 Mechanism of L-proline catalyzed Aldol condensation

Proposed transition state demonstrates in scheme 69. Enamine attack occurs on the *re*-face of the aldehyde. This facial selectivity of attack by enamine is dictated by minimizing steric interaction between the benzyl group and enamine moiety.



Scheme 69 Proposed transition state of L-proline catalyzed Aldol condensation

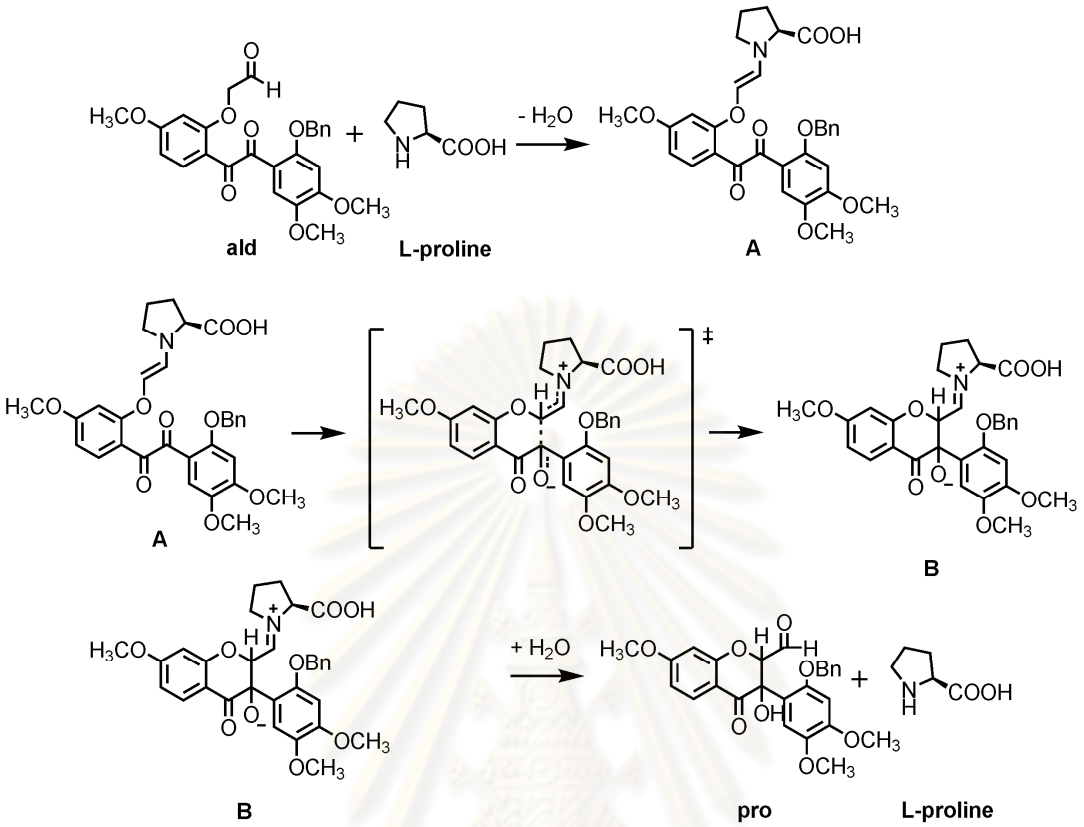
4.1.6 Theoretical study of the stereoselective L-proline-catalyzed intramolecular Aldol reaction.

The stereoselective intramolecular Aldol cyclization of **19-ald** conversion to compound **154** diastereoisomeric products using L-proline catalyst has been investigated. Understanding of these stereoselective reaction mechanisms lead to achieve in syntheses of stereoisomers of isoflavanone carbaldehyde derivatives for the purpose of drugs discovery.

All the calculations were carried out with Gaussian 03. The geometry optimizations of structures of reactant ald, intermediate reactants, transition states, intermediate products, diastereoisomeric product and other involved species were carried out using density functional theory (B3LYP/6-31G(d)).

Eight catalytic reaction pathways of reactant ald conversion to diastereoisomeric products were found and there are four paths (paths 1, 2, 3 and 4) for cis-isomeric and another four paths (paths 1', 2', 3' and 4') for trans-isomeric reactants. Mechanism of each reaction path is consisted of three reaction steps. The first reaction step is the reaction between reactant **19-ald** and L-proline catalyst to afford intermediate reactant A and a released water molecule. The second step is a rate-determining step which an intermediate is converted to intermediate product B via TS transition state. The last step, B reacts with a water molecule to afford a molecule of diastereoisomeric product

pro with L-proline catalyst. The reaction mechanism is graphically presented as shown in Scheme 70.



Scheme 70. Reaction mechanism of ald reactant conversion to stereoisomeric product

Energy profiles of four pathways for cis-isomeric intermediate reactants and another four pathways for trans-ones are shown in Figures 7-14.

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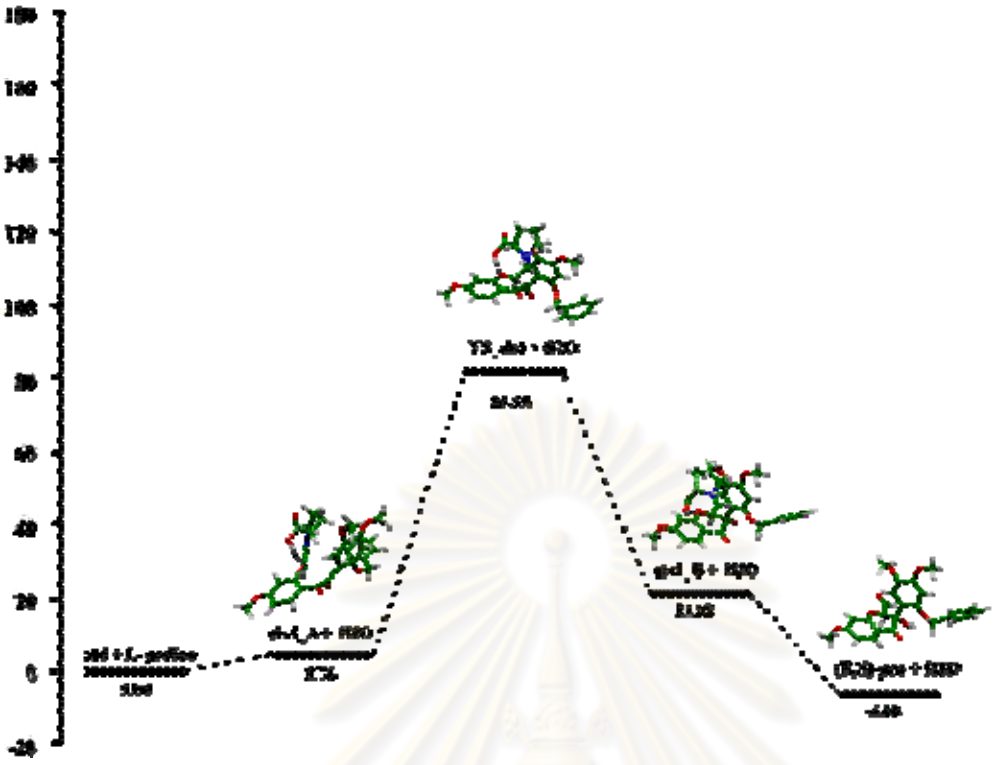

Figure 7 Energy profile of cis1_A

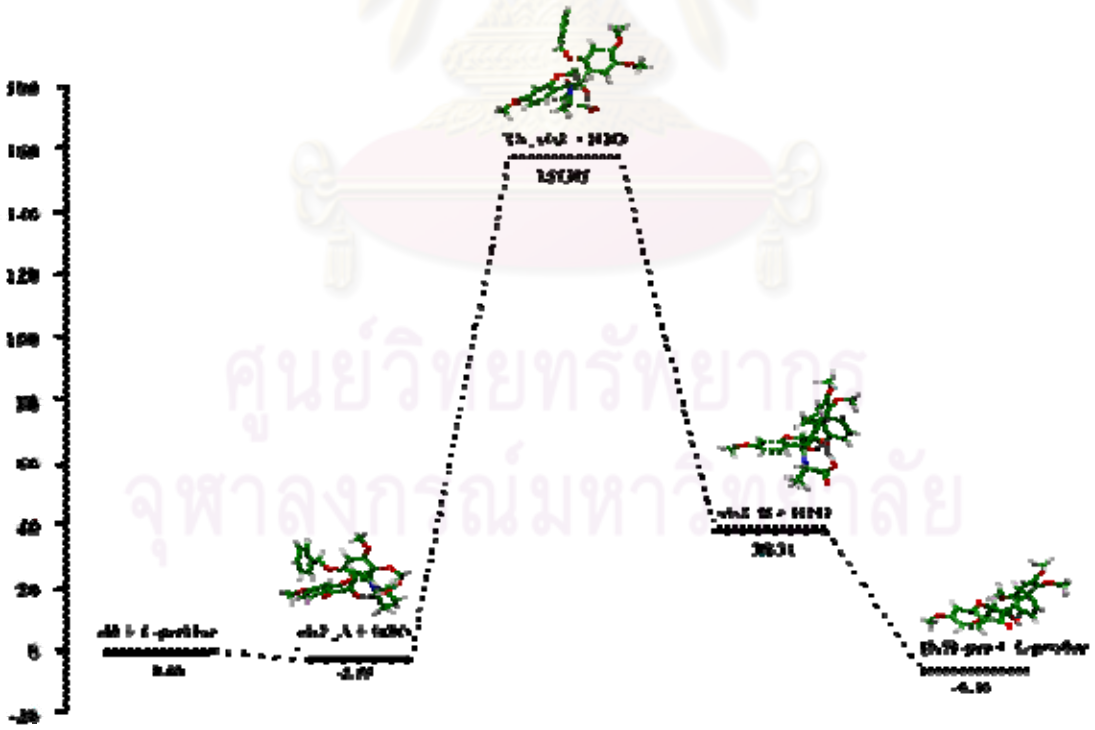

Figure 8 Energy profile of cis2_A

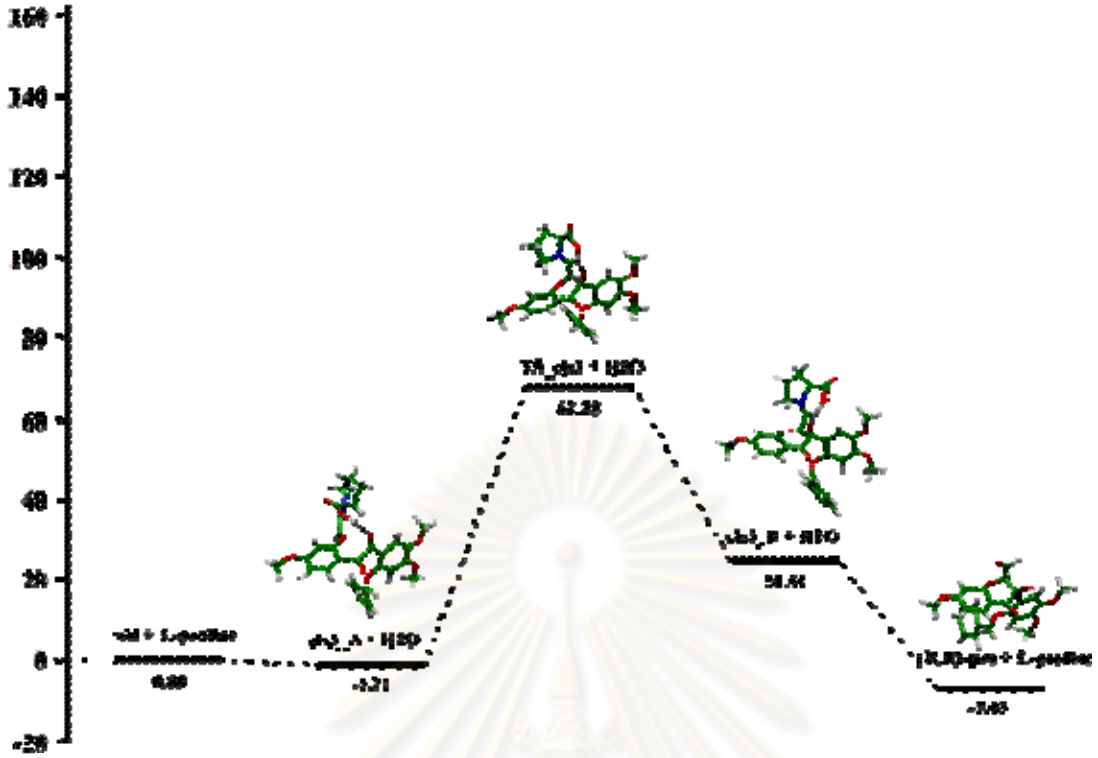

Figure 9 Energy profile of cis3_A

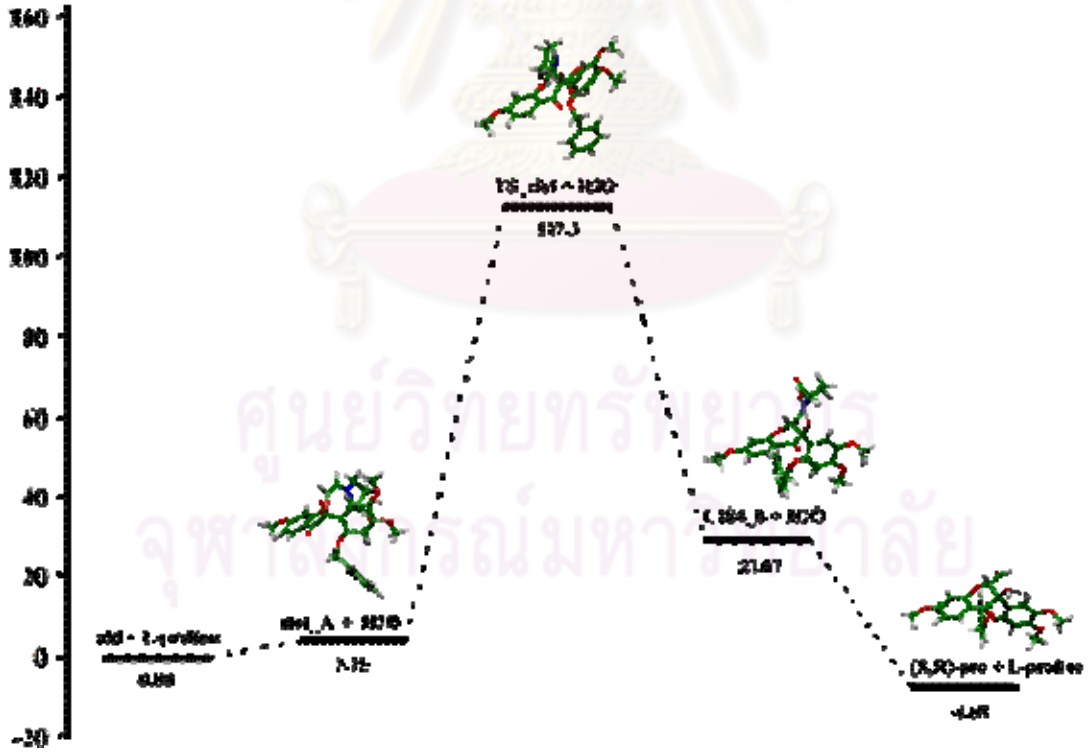

Figure 10 Energy profile of cis4_A

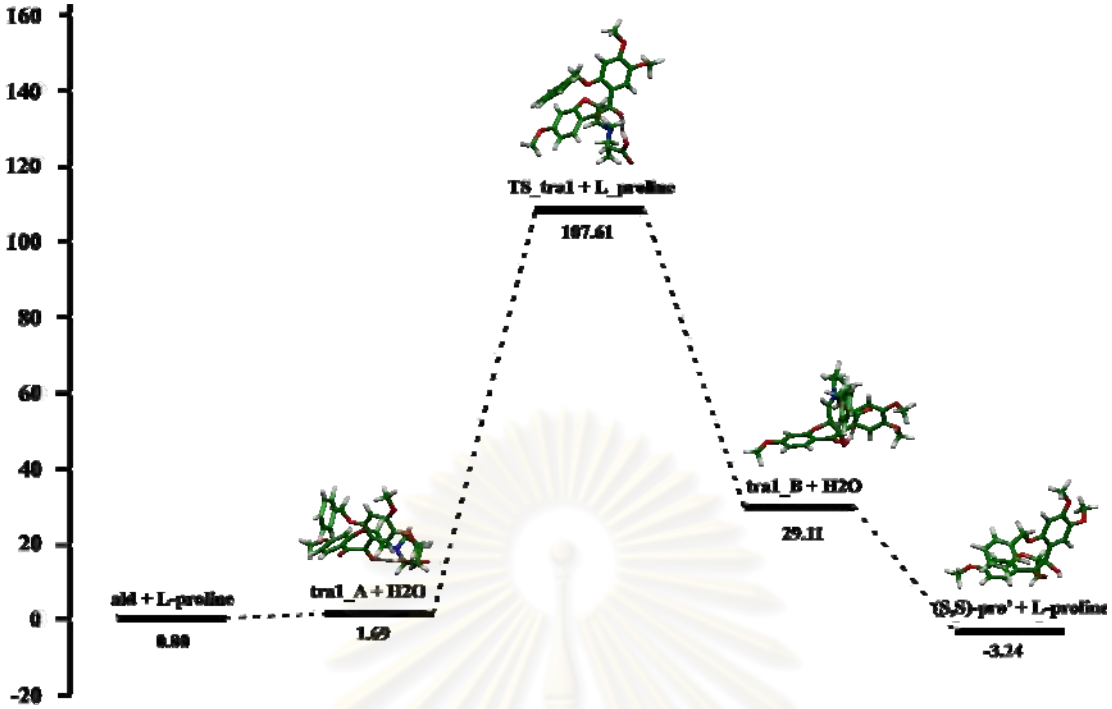

Figure 11 Energy profile of tra1_A

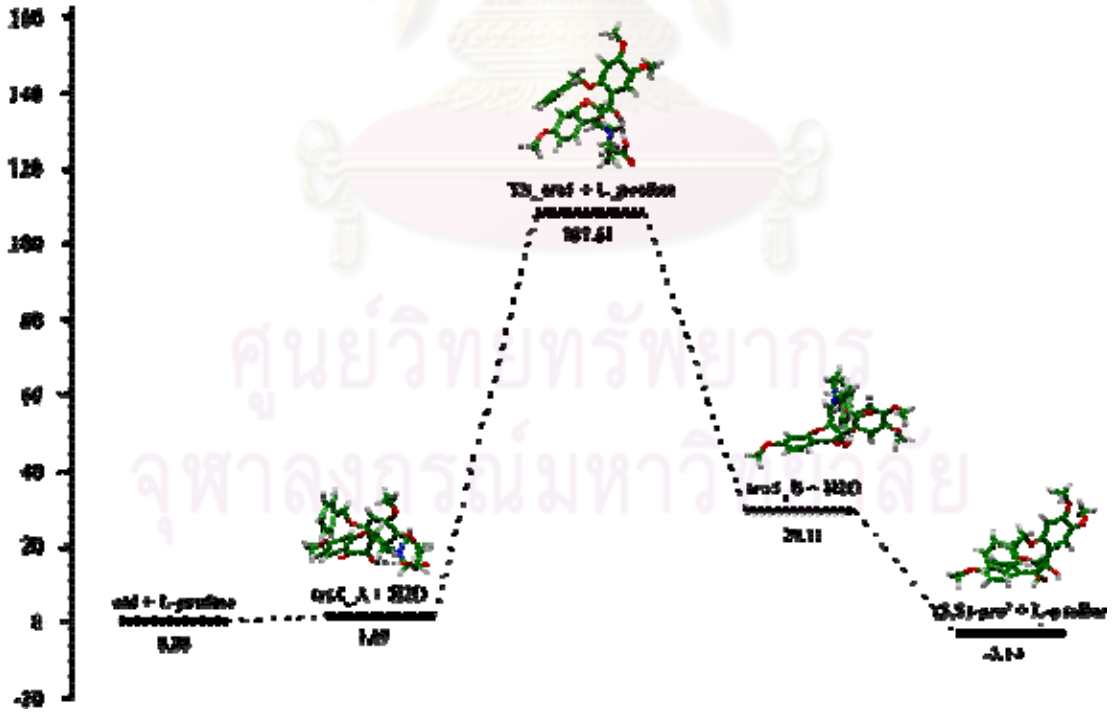

Figure 12 Energy profile of tra2_A

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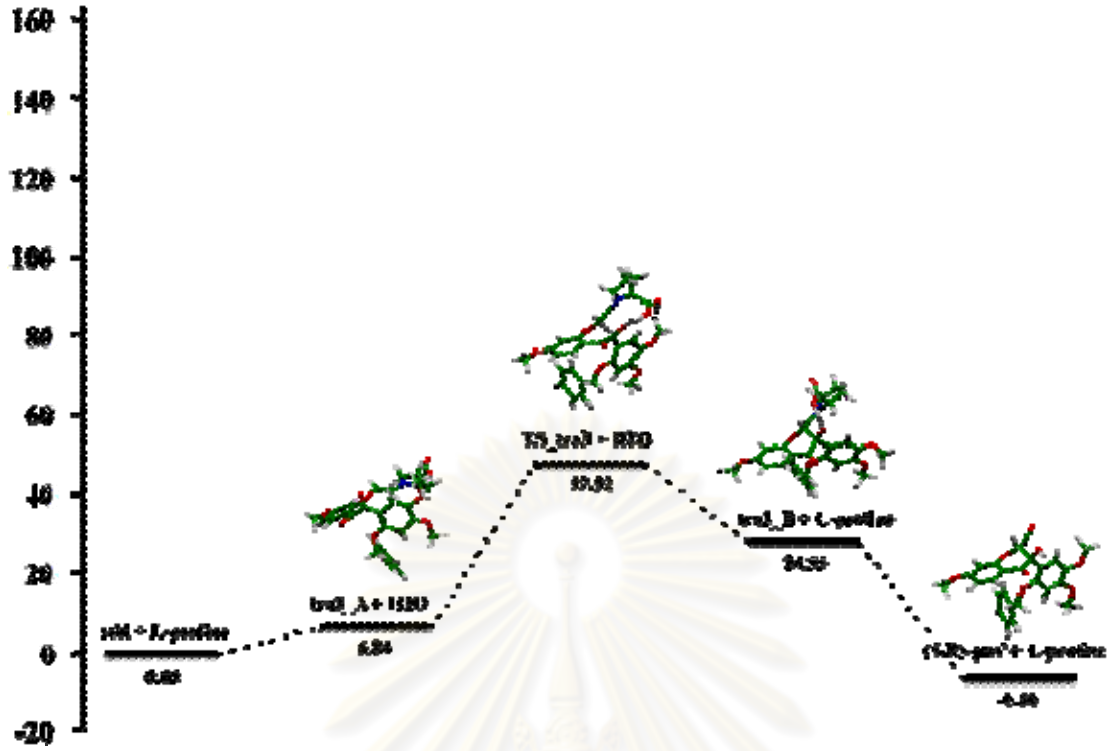


Figure 13 Energy profile of tra3_A

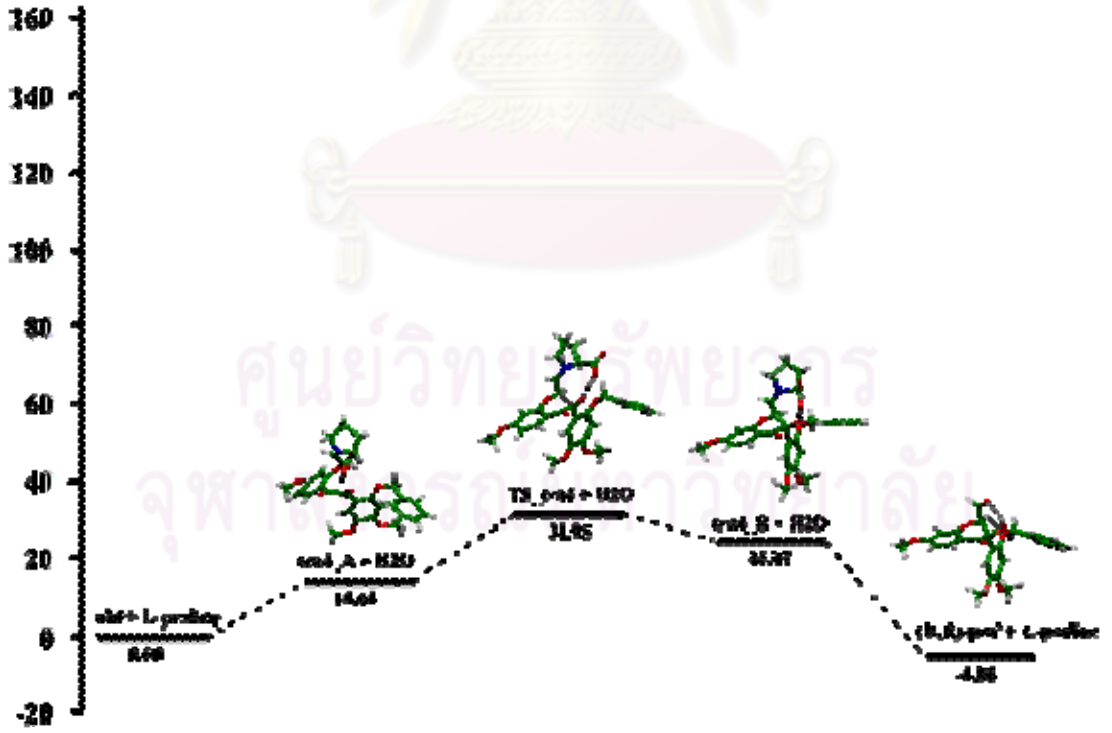


Figure 14 Energy profile of tra4_A

Activation barriers and reaction energies of eight possible pathways based on cis- and trans-isomeric intermediate reactants are separated into two groups (groups of paths 1, 2, 3and 4 and paths 1', 2', 3' and 4') of reaction pathways as shown in Table 5. Relative stabilities of intermediate reactants are in orders: cis3_A ~ cis2_A > cis4_A > cis1_A and tra1_A > tra3_A > tra2_A > tra4_A for cis- and trans-isomeric pathways, respective-ly. The last step for all pathways is energetically exothermic reaction.

Table 5. Activation Barriers and Reaction Energies of All Reaction Pathways of the Aldehyde ald Conversion to Diastereoisomeric Products

Path	Reactions	$E^{\ddagger\,a}$ (kcal/mol)	$\Delta_r E^a$ (kcal/mol)
Pathways for *cis*-isomeric intermediate reactants			
1	ald + L-proline → cis1_A + H_2O	–	8.76
	cis1_A → TS_cis1 → cis1_B	76.79	14.32
	cis1_B + H_2O → L-proline + (R,S)-pro	–	-29.76
2	ald + L-proline → cis2_A + H_2O	–	-2.55
	cis2_A → TS_cis2 → cis2_B	160.42	40.87
	cis2_B + H_2O → L-proline + (S,S)-pro	–	-44.67
3 [a]	ald + L-proline → cis3_A + H_2O	–	-2.72
	cis3_A → TS_cis3 → cis3_B	69.97	27.2
	cis3_B + H_2O → L-proline + (R,R)-pro	–	-31.53
4	ald + L-proline → cis4_A + H_2O	–	3.75
	cis4_A → TS_cis4 → cis4_B	103.59	23.92
	cis4_B + H_2O → L-proline + (S,R)-pro	–	-34.35
Pathways for *trans*-isomeric intermediate reactants			
1'	ald + L-proline → tra1_A + H_2O	–	1.69
	tra1_A → TS_tra1 → tra1_B	105.92	27.42
	tra1_B + H_2O → L-proline + (S,S)-pro'	–	-32.35
2'	ald + L-proline → tra2_A + H_2O	–	9.26
	tra2_A → TS_tra2 → tra2_B	66.85	42.49
	tra1_B + H_2O → L-proline + (R,S)-pro'	–	-52.65
3'	ald + L-proline → tra3_A + H_2O	–	6.84
	tra3_A → TS_tra3 → tra3_B	41.08	21.71
	tra3_B + H_2O → L-proline + (S,R)-pro'	–	-35.41
4' [c]	ald + L-proline → tra4_A + H_2O	–	14.64
	tra4_A → TS_tra4 → tra4_B	17.31	10.43
	tra4_B + H_2O → L-proline + (R,R)-pro'	–	-30.04

The Mulliken electronegativity (χ), chemical hardness (η) and electronic chemical potential (μ) for all involved species were derived from B3LYP/6-31G(d)-orbital energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in terms of the first ionization potential (I) and electron affinity (A) of the N-electron molecular system with a total energy (E) and external potential. The first ionization potential and electron affinity are obtained by formulae I = E(N–1) –E(N) and A = E(N) – E(N+1), respectively. According to the Koopmans, theorem, I and A were computed from the HOMO and LUMO energies using the relations: $I = -E_{HOMO}$ and $A = -E_{LUMO}$. Relative reactivities of intermediate reactants based on the energy gaps ($\Delta E_{HOMO-LUMO}$) are in decreasing orders: cis4_A > cis2_A ~ cis1_A > cis3_A and tra2_A > tra3_A > tra1_A >> tra4_A, for cis- and trans-isomeric pathways, respectively. Four typical diastereoisomers of products pro were found as isomers (2R,3S)-pro, (2S,3S)-pro, (2R,3R)-pro and (2S,3R)-pro as shown in Figure 15.

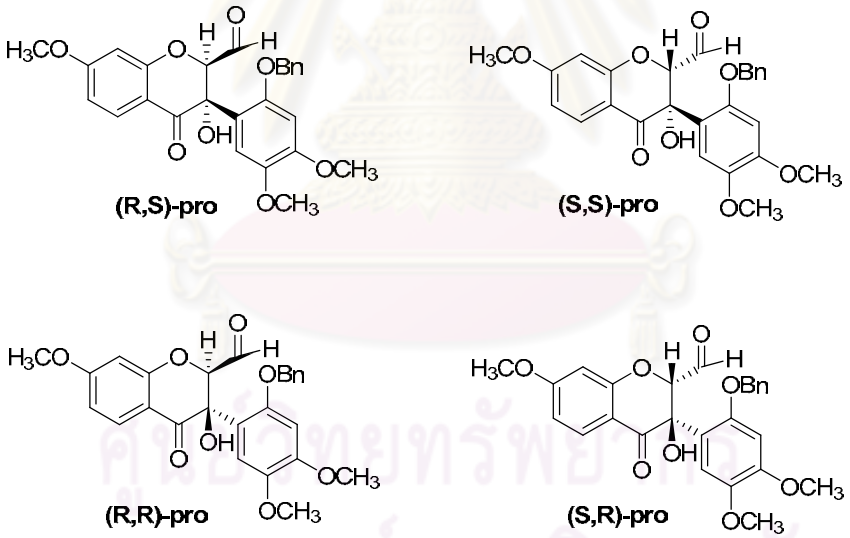
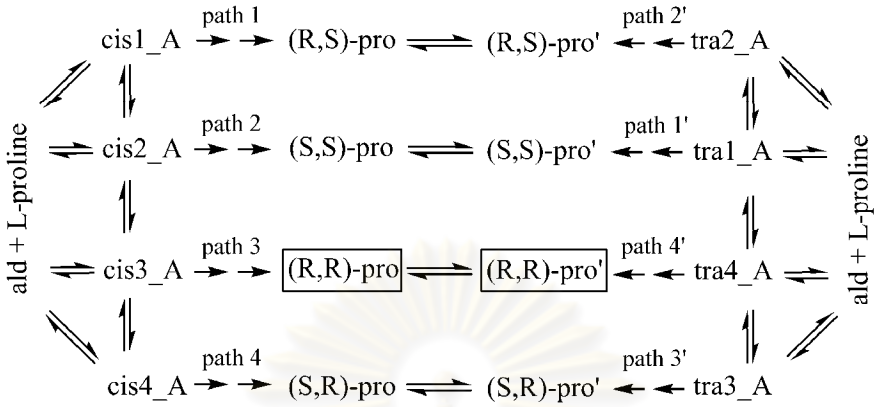


Figure 15. Structures of four typical diastereoisomer of products

As path 4' is the lowest energy barrier of reaction compared to all pathways (see Scheme 71 and Figure 16 and 17), its product (R,R)-pro' is therefore predicted as a major of diastereoisomeric product. The lowest activation barrier path 4' is lower than the next higher-barrier pathway by approximation 23.8 kcal/mol. The structure of

transition-state TS_tra4 (see Figure 16) shows its strong intra-molecular interaction between O3 and H3 atoms of which energy is 29 kcal/mol by approximation.



Scheme 71. The Overall Reaction Pathways of ald Conversion to Four Typical Diastereoisomeric products pro

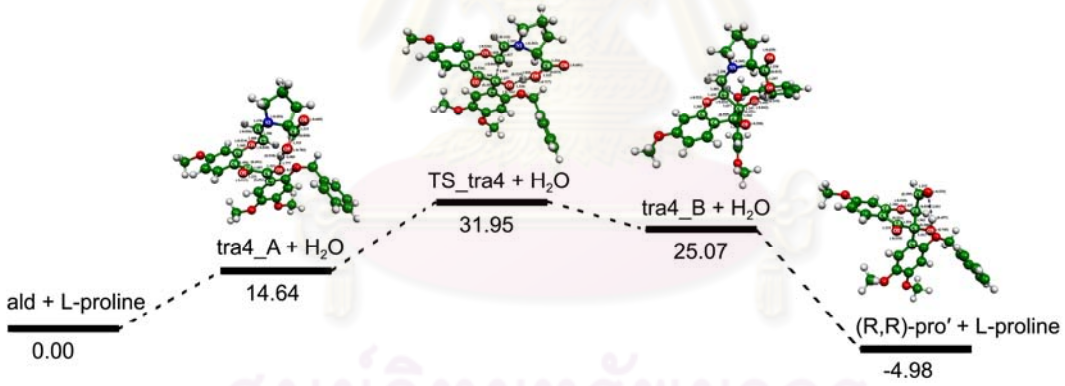


Figure 16 Energy profile of (R,R')-pro'

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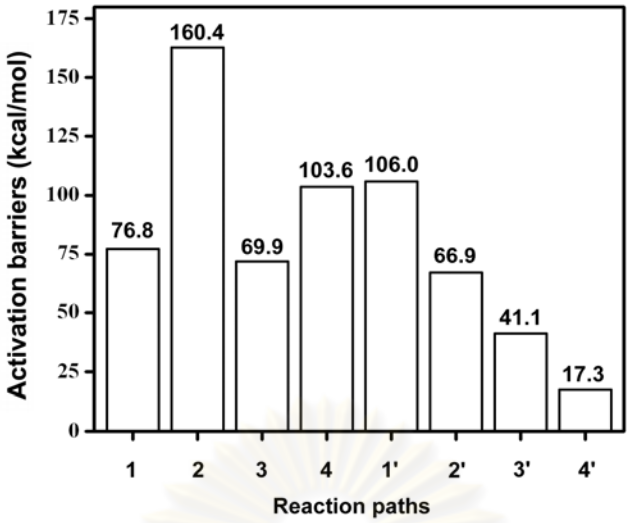


Figure 17 Activation barriers of overall pathways

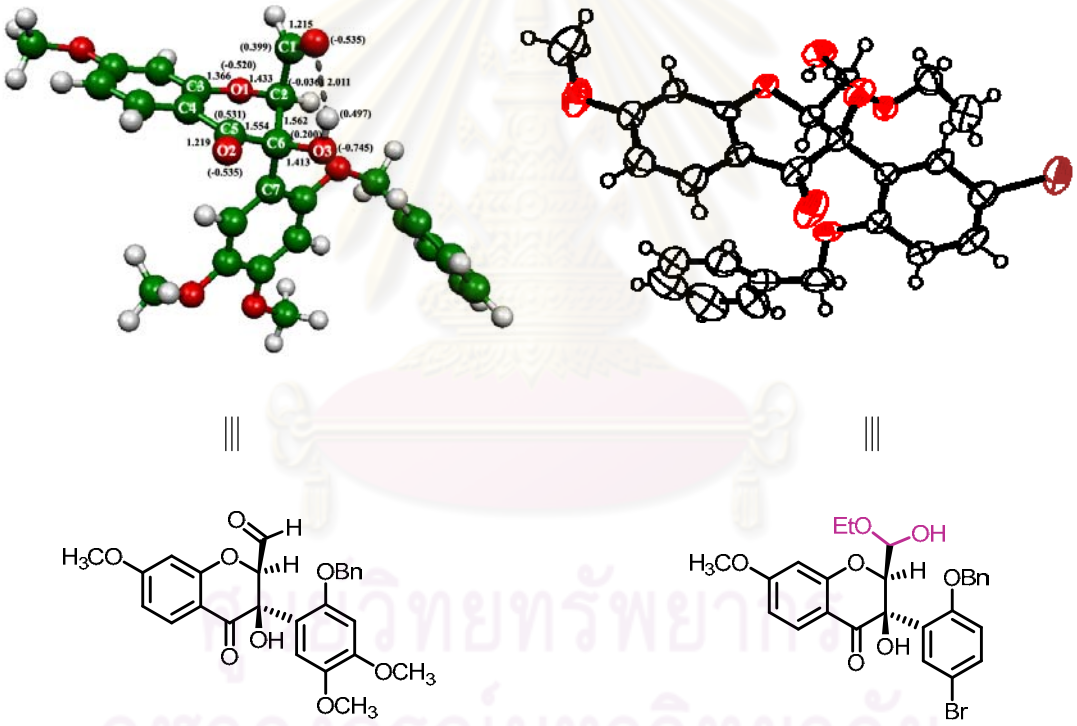
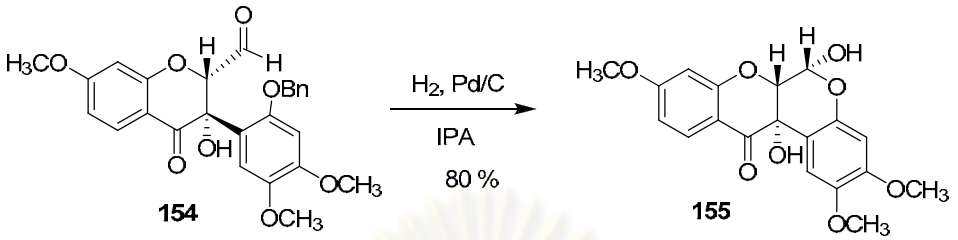


Figure 18 The comparison of structures from the calculation and X-ray data

The stereochemistry of transition-state TS_tra4 product was consistent with the X-ray data of compound **163.** From these results supported that the stereoisomer of product from L-proline catalyzed-Aldol reaction should be anti-isomer between H-6a and OH-12a.

Preparation of the rotenoid hemiacetal **155** was accomplished in 80 % yield by removing the benzyl group from compound **154** using 10 % Pd/C under H_2

atmosphere. The sterochemistry indicated for compound **155** was confirmed by the NOESY correlations; the hemiacetal at C-6 was formed almost exclusively with only small amount of epimer being observed in the NMR spectrum.



Scheme 72 Synthesis of compound **155**

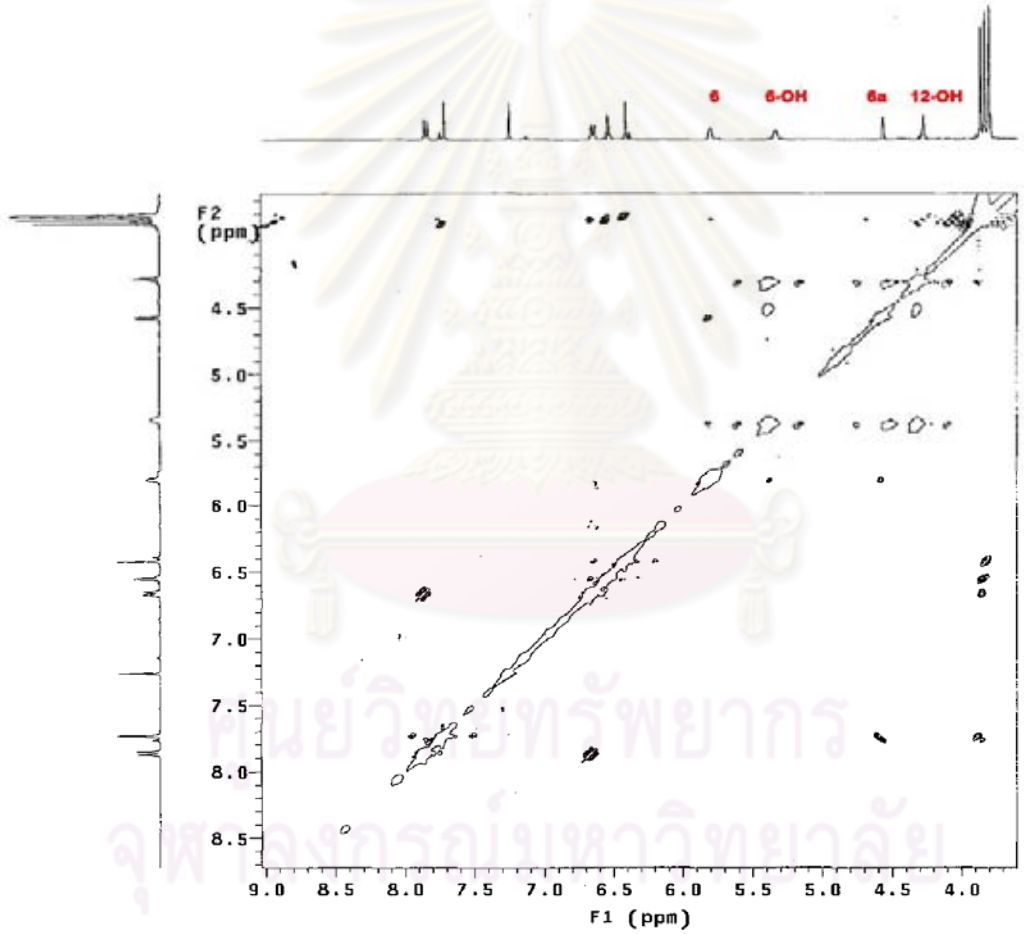


Figure 19 NOESY correlations of compound **155**

To explain this stereochemical outcome, we invoke an intramolecular H-bond between the hydroxyl at position C3 and the aldehyde carbonyl (Figure 19), which locked the carbonyl and exposed it to be attacked by phenolic-OH leading to 6β-OH

of a hemiacetal moiety. This new hydroxyl can engage in a similar intramolecular hydrogen bond (not shown) to stabilize the product **154.**

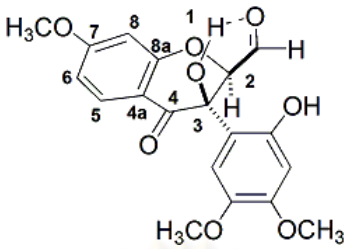
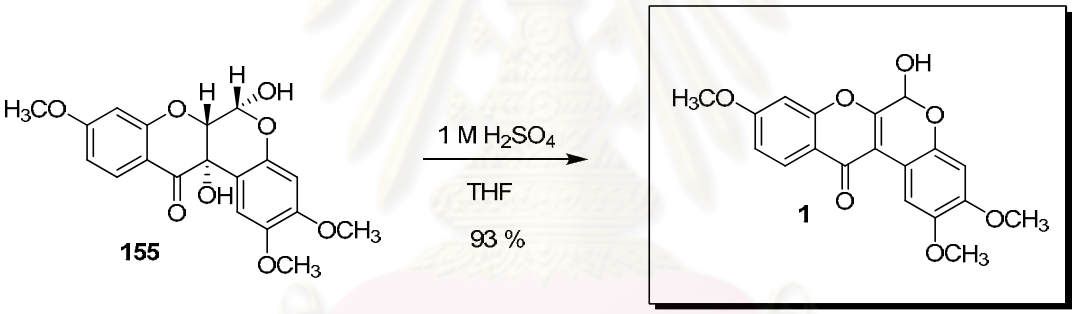


Figure 20 Probable transition-state model.

Finally, dehydration of **155** was performed in 0.5 M H_2SO_4 in THF to provide the target molecule 1 in 93 % yields. Synthetic **1** exhibited ^{1}H and ^{13}C-NMR spectral data in agreement with those of the natural product.



Scheme 73 Synthesis of dehydrorotenoid **1**

The ^{1}H and ^{13}NMR spectra of synthetic desired product **1** are chosely mathing with those published for the related natural product as shown in Table 6.

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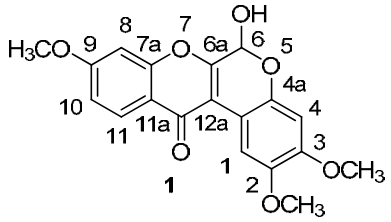
Table 6 Comparison of ^{1}H and 13C-NMR spectra for the synthetic and isolated compound **1**.



position	Natural product		Synthesis	
	^{1}H	^{13}C	^{1}H	^{13}C
1	8.18 (s)	115.4	8.48 (s)	114.7
1a		111.2		109.5
2		150.3		149.0
3		144.9		143.2
4	6.16 (s)	100.9	6.53 (s)	100.2
4a		145.1		143.8
6	6.46 (br s)	90.2	6.04 (s)	88.9
6a		156.6		155.1
7a		157.4		156.8
8	6.19 (d, 3.0)	103.0	6.77 (d, 2)	101.2
9		164.6		164.0
10	6.12 (dd, 3.0, 10.0)	111.7	6.87 (dd, 2, 8.8)	110.5
11	7.52 (d, 10.0)	127.9	8.03 (d, 8.8)	127.2
11a		118.9		118.1
12		175.7		175.4
12a		110.2		108.8
2-OCH3	3.85 (s)	56.0	3.74 (s)	55.8
3-OCH3	3.89 (s)	56.2	3.78 (s)	55.8
9-OCH3	4.00 (s)	56.8	3.81 (s)	56.2
6-OH	5.85 (br s)		2.45 (s)	

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4.2 Synthesis of Isoflavonoid derivative 172

The benzopyran-4-one and chroman-4-one ring system are the core structure found in a number of natural products such as isoflavonoids and isoflavanoids. These compounds represent a relatively large group of naturally occurring secondary metabolites, displaying a wide array of physiological activities. Many isoflavonoids and isoflavanoids possess a variety of potent biological activities including insecticidal[63], anticancer[64], antiplasmodial[65], antibacterial[66], antifungal[67], and inhibition of HMG-CoA reductase activities[68]. Regardless of functional group composition, most benzopyran-4-ones and chroman-4-ones bear basic core structure (Figure 20). Considering the bioactivity of these compounds, I applied the L-proline catalyzed Aldol condensation reaction of 1,2-diaryldiketone to synthesize the the isoflavonoid core structure which also exhibits a potent pharmacological activity.

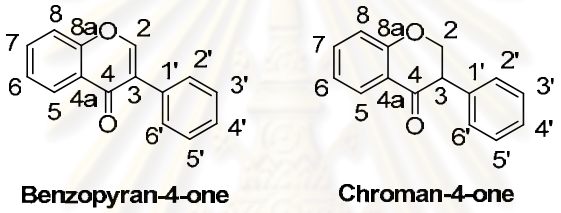
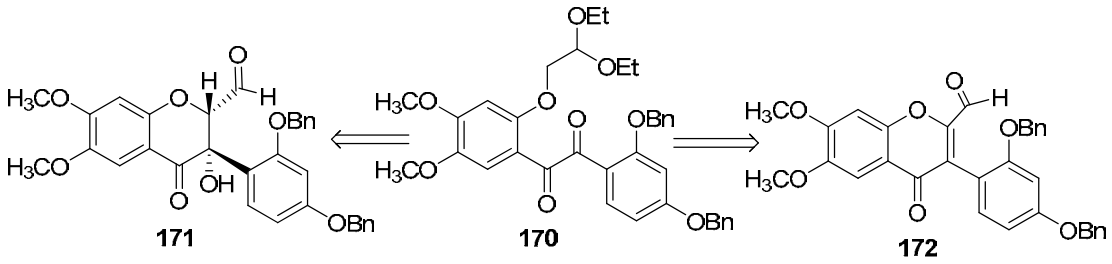


Figure 21 Structure of benzopyranone and chroman-4-one

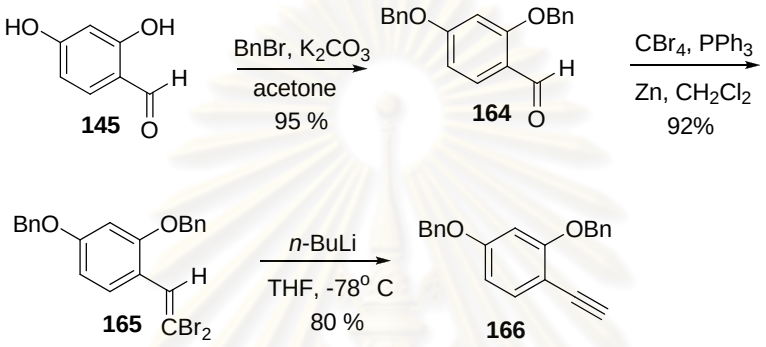
A new methodology for synthesis of 2,3-disubstituted benzopyranone and chroman-4-one core structure are achieved within one step using the corresponding 1,2-diaryl diketone as a key intermediate has been developed.

The synthesis pathway was adopted for compound **171** and **172** outlined in Scheme 74. The synthetic strategy is based on one key successive intramolecular cyclization step of 1,2-diaryl diketone **170** which was obtained from the corresponding substituted diaryl acetylene. The preparation of the desired substituted diaryl acetylene was accomplished by Sonogashira coupling reaction between monoaryl substituted acetylene and aryl iodide.



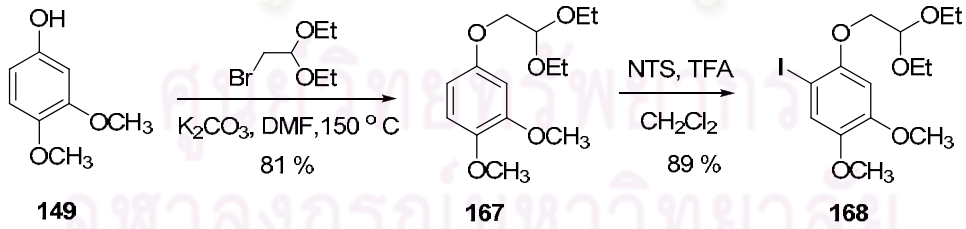
Scheme 74 Synthesis pathway of compound **171** and **172**

The synthesis of monoaryl substituted acetylene **166** is presented in Scheme 75. To realize this approach, commercially available **145** were treated with benzyl bromide under basic condition to obtain compound **164** with a quantitative yield. Conversion of this compound to the corresponding dibromide **165** was accomplished by the Corey-Fuchs alkynylation in 92 % yield. Then compound **165** was treated with 2 equiv of *n*-BuLi at -78 °C to afford the desired compound **166** in 80 % yields.



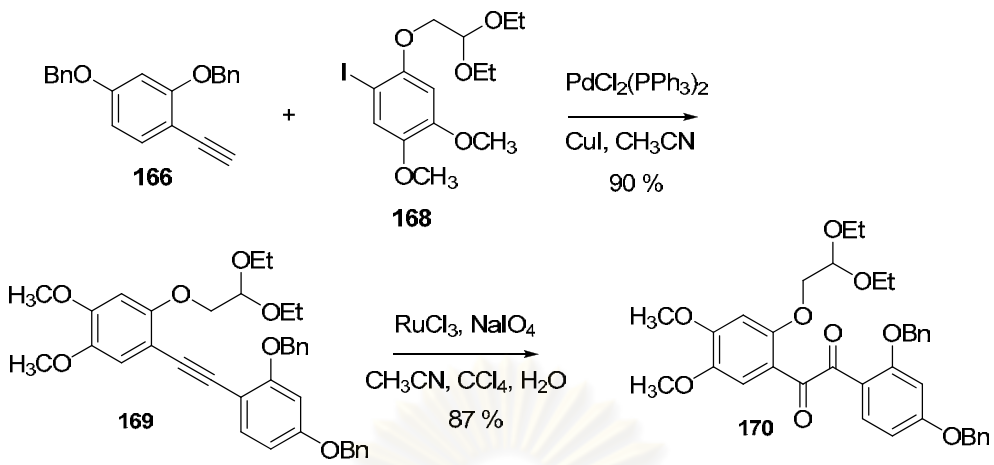
Scheme 75 Synthesis of compound **166**

Treatment of **149** with bromoacetaldehyde diethylacetal in the presence of potassium carbonate in DMF at 150 °C gave the required compound **167** in 81 % yield and then iodinated with NIS in the presence of trifluoroacetic acid to give compound **168** in 89% yield (Scheme 76).



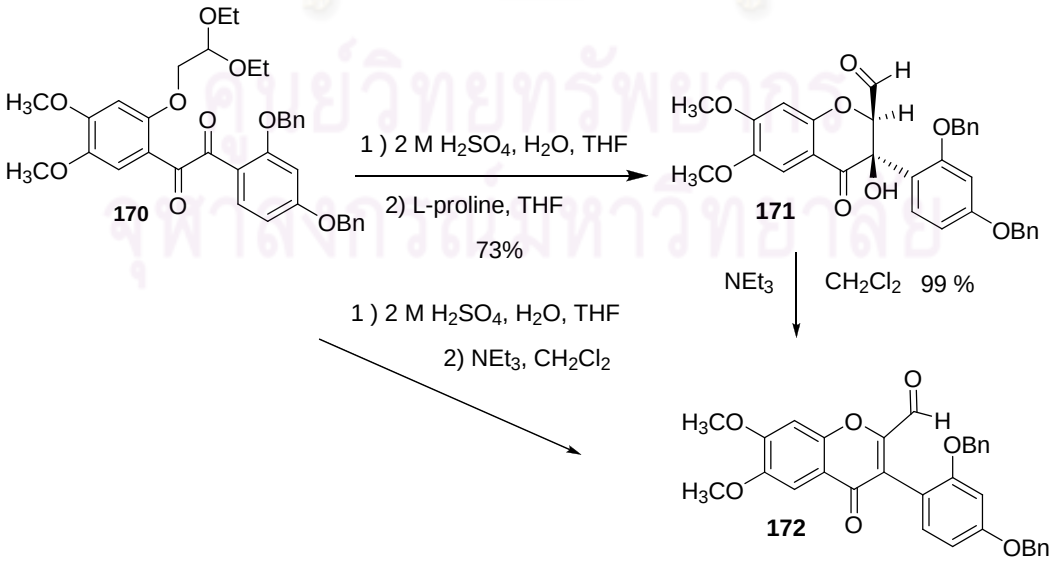
Scheme 76 Synthesis of compound **168**

With compound **166** and **168** in hand, the substituted diaryl acetylene **(169)** was achieved by Sonogashira coupling reaction of monoaryl substituted acetylene and aryl iodide in excellent yield (90 %). Compound **169** was oxidized with $RuCl_3$ (catalyst), $NaIO_4$, $H_2O/CH_3CN/CCl_4$ in the presence of $NaHCO_3$ and $MgSO_4$ to obtain the 1,2-diaryl diketone **170** in moderate yield (87 %) as shown in scheme 77.



Scheme 77 Synthesis of compound **170**

The 2,3-disubstituted chroman-4-one (**171)** was synthesized as outline in Scheme 78. The diketone intermediate **170** was converted to the target molecule by treatment with H_2SO_4, H_2O/THF to transform diethyl acetal moiety into aldehyde intermediate and followed by treatment with L-proline in THF to initiate an intramolecular enantioselective aldol condensation resulting in 2,3-disubstituted chroman-4-one **(171)** with a 73 % yield ($[\alpha]_D$+6). Structure of compound **171** was confirmed using X-ray crystallography and its structure has been related with natural occurring isoflavanoid compounds.



Scheme 78 Synthesis of compound **172**

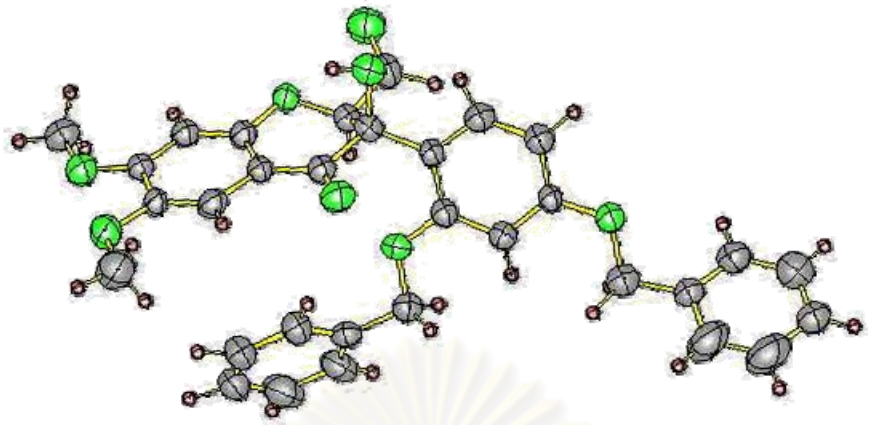


Figure 22 ORTEP drawing of **171**

2,3-disubstituted benzopyran-4-one **(172)** has been directly synthesized via intramolecular aldol condensation of 1,2-diketone. The acetal group of **170** was converted to aldehyde moiety by treatment with H_2SO_4 in H_2O/THF, and followed by treatment NEt_3 in CH_2Cl_2 which product of this reaction was immediately dehydrated to provide target isoflavonoid **172** in 99 % yield.

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4.3 Biological activity of synthesized compounds

The synthesized compounds were investigated the biological activity in inhibition of cancer cell line. Therefore, all diarylacetylene and 1,2-diaryl-diketone analogues were investigated the biological activity on cancer cell lines. The results were illustrated in table 7. Compounds **169**, **176a**, **176d**, **177b**, and **177e** demonstrated inhibitory activity on cancer cell lines. These results showed that the electron density of substituted on the aromatic ring of diarylacetylene and 1,2-diaryl-diketone derivatives did not effect to inhibitory activity. (The results obtained from The Institute of Biotechnology and Genetic Engineering, Chulalongkorn University Institute Bldg.3, Phayathai Rd., Pathumwan, Bangkok 10330, Thailand.)

Table 7 Inhibitory Activity of synthesized compounds on cancer cell lines.

compound	%Inhibition Activity					
	SW620	BT474	KATO-III	Hep-G2	CHAGO	CH-LIVER
176a	74	64	46	50	87	19
176b	98	82	92	93	94	76
176d	39	71	57	67	92	20
176e	75	85	80	67	98	45
176f	97	89	93	87	95	78
176g	90	113	89	83	95	63
177a	91	79	75	67	97	45
177b	47	63	35	19	87	17
177d	93	68	77	72	95	35
177e	74	61	58	30	98	29
177f	100	120	88	100	95	95
177g	97	108	91	81	96	71
169	25	48	32	24	57	15
170	94	83	86	65	92	34

Therefore, compound **169**, **176a**, **176d**, **177b**, and **177e** were explored the IC_{50} in inhibition of cancer cell lines. These results were presented in table 8.

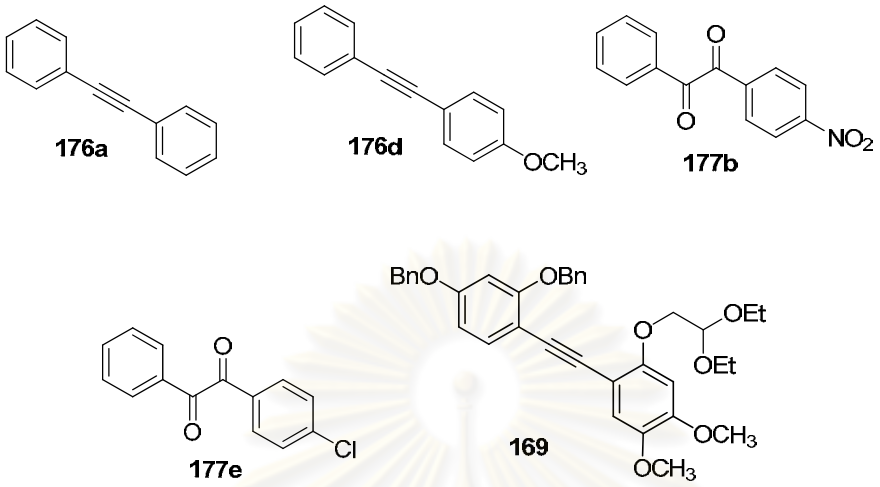


Figure 23 Structure of compounds **169**, **176a**, **176d**, **177b**, and **177e**

Table 8 IC_{50} of compounds **169**, **176a**, **176d**, **177b**, and **177e** in inhibition of cancer cell lines

compound	IC_{50} (μg/ mL)					
	SW620	BT474	KATO-III	Hep-G2	CHAGO	CH-LIVER
176a	8.84	>10	0.10	<0.001	3.32	0.10
176d	1.00	>10	1.00	<0.001	1.07	<0.001
177b	3.45	>10	0.01	<0.001	1.00	1.00
177e	0.01	>10	<0.001	<0.001	0.01	<0.001
169	0.10	6.35	0.01	<0.001	0.66	0.10
Doxorubicin	0.76	0.53	0.07	0.08	0.10	0.09

The IC_{50} value of the synthesized-compounds and doxorubicin (standard control) were compared as shown in table 8. The results indicated that compounds **177e** and **169** showed the efficient inhibition of SW620 cancer cell lines, while KATO-III cancer cell lines were inhibited by compound **176a**, **177b**, **177e** and **169**. Moreover the results indicated that all of five synthesized-compounds in Figure 23

displayed significant in inhibitory activity against Hep-G2 cancer cell lines. The anticancer activities for CHAGO and CH-LIVER were evaluated. As summarized in table 8, compound **177e** could inhibit both cancer cell lines whereas compound **176d** provided a good activity only inhibition of CH-LIVER. All the results designated that the 1,2-diaryldiketone containing chlorine as substituent provided a broad range of biological activities and this compound resulted in highly potent inhibitor of SW620 and KATO-III cancer cell lines.

Moreover, compound **154**, **155** and **1** were evaluated for cytotoxicity against Vero cells of African green monkey kidney, Anti-NCI-H187 (Human, small cell line cancer) and Anti-cancer (Oral human epidermal carcinoma: KB and human breast adenocarcinoma: MCF7) as shown in Table 9, 10 and 11, respectively. The structures of these compounds have the same nucleus that is isoflavanoid core structure. (These results obtained from Bioassay laboratory, National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), 113 Paholyotin Road, Klong 1, Klong Luang, Pathumthani)

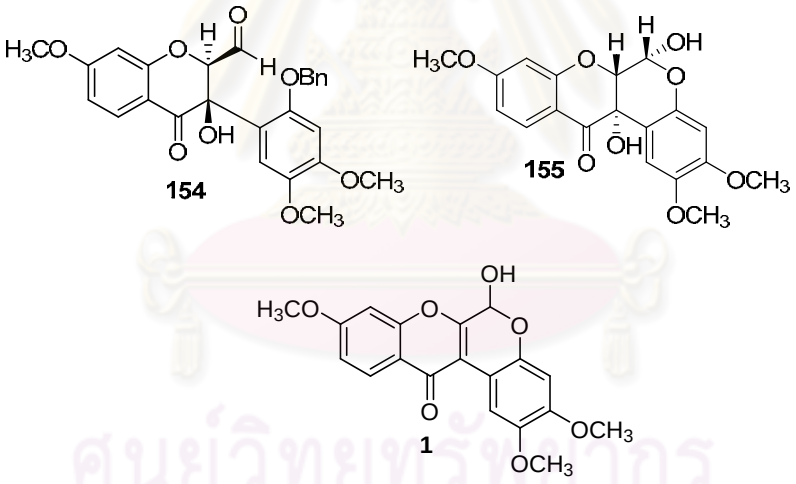


Figure 24 Structure of compounds **154, 155,** and **1**

Table 9 Testing: Cytotoxicity against Vero cells (African green monkey kidney)
Method: Sulforhodamine B (SRB) assay

compound	Cytotoxicity activity	IC50 (μg/ mL)
154	Cytotoxic	19.97
155	Inactive	-
1	Inactive	-

Table 10 Testing: Anti-NCI-H187 (Human, small cell line cancer)
Method: Colorimetric Method; 3-(4,5-dimethylthiazol 2-yl)-2.5-diphenyltetrazo- lium bromide (MIT) Assay

entry	Cytotoxicity activity	IC_{50} (μg/ mL)
154	Weakly active	17.97
155	Inactive	-
1	Inactive	-

Table 11 Testing: Anti-cancer (Oral human epidermal carcinoma: KB and human breast adenocarcinoma: MCF7)
Method: Colorimetric method: Sulforodamine B assay (SRB)

entry	KB		MCF7	
	Activity	IC_{50}(μg/ mL)	Activity	IC_{50}(μg/ mL)
154	Inactive	-	Weakly active	13.46
155	Inactive	-	Inactive	-
1	Inactive	-	Inactive	-

The results indicated that compound **155** and **1** has no biological activity in inhibition of three cancer cell lines, whereas compound **154** show weakly active in inhibition of cancer cell line oral human epidermal carcinoma (KB) and human breast adenocarcinoma (MCF7). The relationship among the structures of the tested compounds, the cyclization of ring B position affect to the disappearance of bioactivity in inhibition of cancer cell line as product **155** and dehydration product **1.**

From literature review[9], compound **1** was reported as the anti-inflammatory. The pharmacological property was evaluated for using the capillary permeability assay. Compound **1** showed inhibition of increase in vascular permeability caused by acetic acid, which is a typical model of first stage inflammatory reaction. In this research, the anti-inflammatory activity of the synthesized dehydrorotenoid **1**, **154**, and **155** were examined using radioimmunoassay (RIA) as illustrated in Table 12. (These results obtained from Bioassay laboratory, National Center for Genetic

Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), 113 Paholyotin Road, Klong 1, Klong Luang, Pathumthani)

Table 12 Testing: Anti-inflammation

Method: Radioimmunoassay (RIA)

entry	**Anti-COX-2**		**Anti-COX-1**	
	Activity	**IC_{50}(μg/ mL)**	**Activity**	**IC_{50}(μg/ mL)**
154	Inactive	-	Inactive	-
155	Inactive	-	Inactive	-
1	Inactive	-	Inactive	-

Evaluation of anti-inflammatory activity of the synthesized compound **1, 154,** and **155** were observed that they had inactive activity. In this testing, anti-inflammatory was evaluated using radioimmunoassay in inhibition of Cyclooxygenases 1 and 2 (COX-1, COX-2)[69]. They were enzymes involving in the conversion of arichidonate to prostaglandins. COX-1 and COX-2 are very similar in structure and function, though they vary in expression. COX-1 is normally expressed in most cell types, whereas COX-2 expression is at low levels unless induced by hormonal stimuli. From the literature, compound **1** showed anti-inflammatory activity which was evaluated by measuring acetic acid induced vascular permeability. The results in this study did not conform to the literature review. The possible reasons of inconsistent results were the difference of evaluation method and the difference ratio of α/β epimer position at ring-B between natural products and synthesize dehydrorotenoid **1**. However the ratio of α/β epimer of natural product compound was not reported. Even the synthesized dehydrorotenoid **(1)**, target molecule, does not show the expected biological activity but this synthetic methodology provides a very useful procedure for synthesis of the most isoflavanoid, rotenoid and dehydrorotenoid core structure. Therefore, this methodology is valuable for the further study of structure-activity relationship.

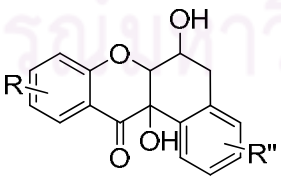
CHAPTER V

CONCLUSION

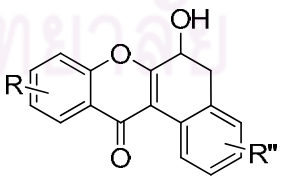
The total synthesis of dehydrorotenoid **(1)**, anti-inflammatory, was successfully achieved in three steps through an intramolecular aldol reaction of the corresponding 1,2-diaryl diketone **(19)** as a key intermediate. The corresponding 1,2-diaryl diketone was easily accessed via the ruthenium-catalyzed oxidation of diarylacetylene which was obtained from Sonogashira coupling between monoaryl substituted acetylene and aryl iodide. Treatment of 1,2-diaryl diketone with L-proline induced a selective intramolecular aldol reaction, forming the desired benzopyranone over the alternative benzofuran. Finally, the target dehydrorotenoid was accomplished in good overall yield by deprotection and dehydration reactions, respectively.

The synthesized dehydrorotenoid **(1)** and intermediate compounds were evaluated for their biological activities. Compound **154** shows activity inhibition of NCI-H187, KB and MCF7 cancer cell lines, whereas this compound is toxicant to normal cells. Moreover, compound **169**, **176a**, **176d**, **177b**, and **177e** have been found to potently inhibit the SW620, BT474, KATO-III, Hep-G2, CHAGA, and CH-LIVER cancer cell lines. However, the synthesized dehydrorotenoid **(1)**, target molecule with anti-inflammatory, does not show the expected the anti-inflammatory activity but this synthetic methodology provides a very useful procedure for synthesis of the most isoflavanoid, rotenoid and dehydrorotenoid core structure. Therefore, this methodology is valuable for the further study of structure-activity relationship.

Isoflavanoid



Rotenoid



Dehydrorotenoid

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ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

APPENDIX

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

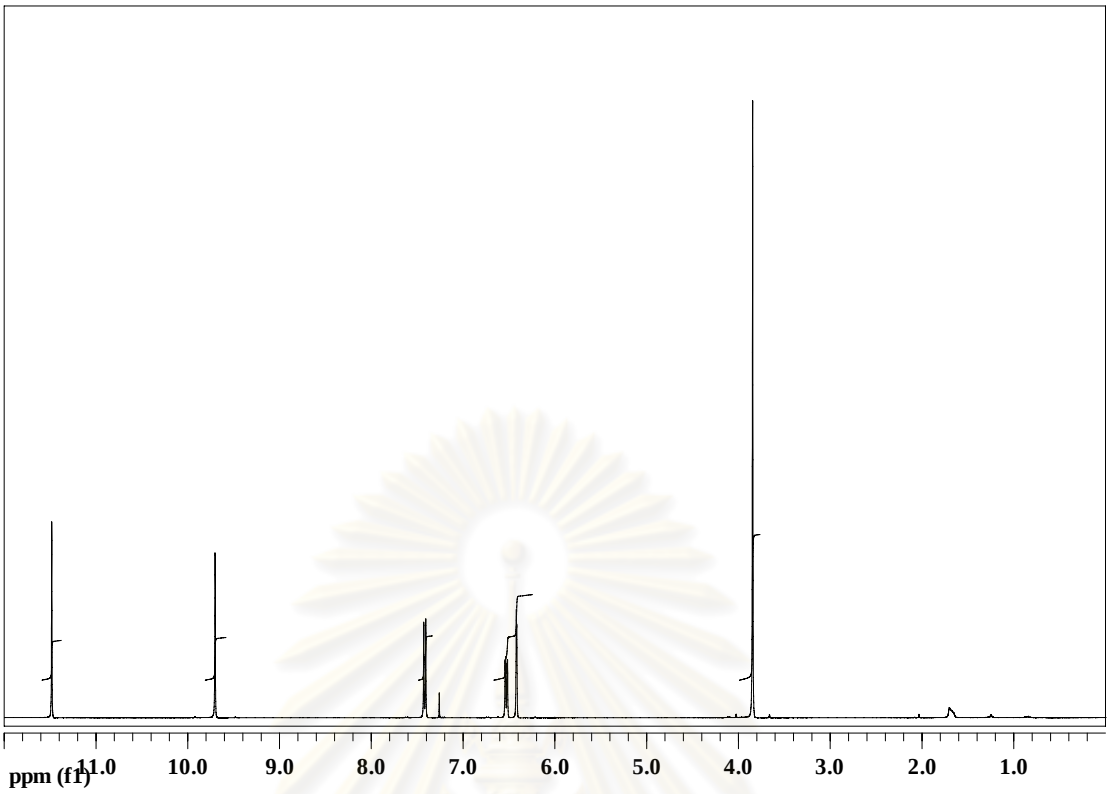

Figure 28 ^{1}H-NMR spectra of compound **146**

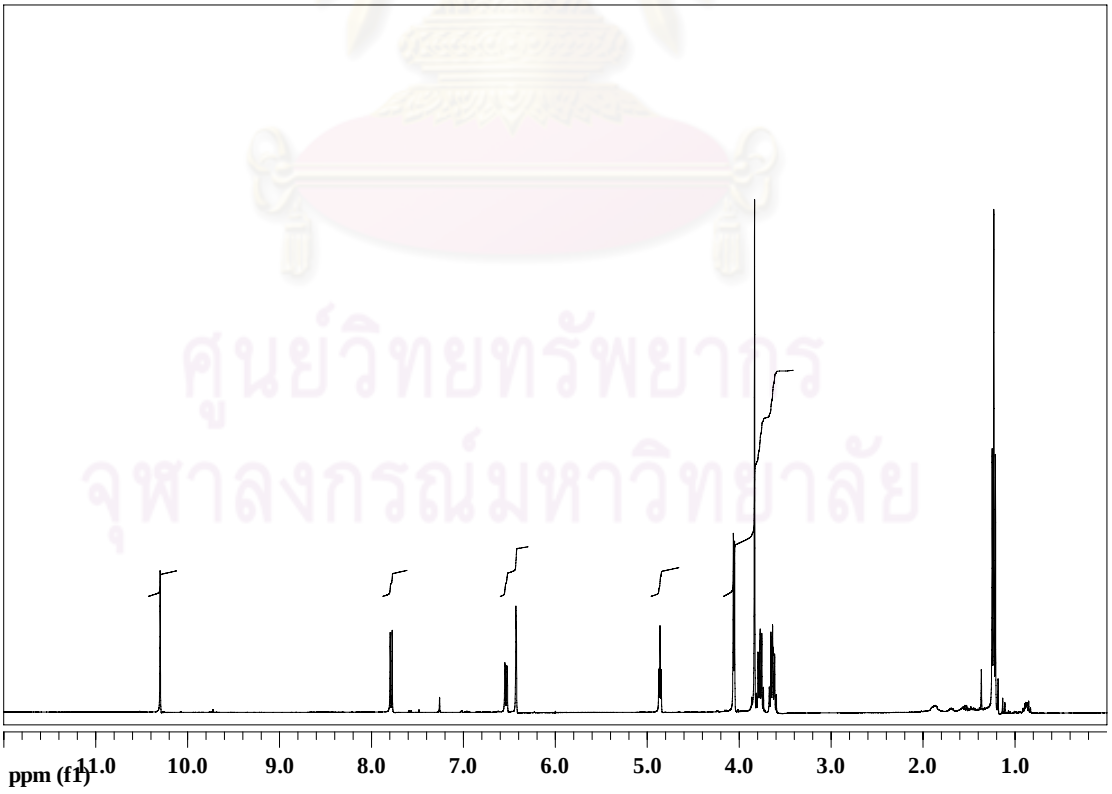

Figure 29 ^{1}H-NMR spectra of compound **147**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

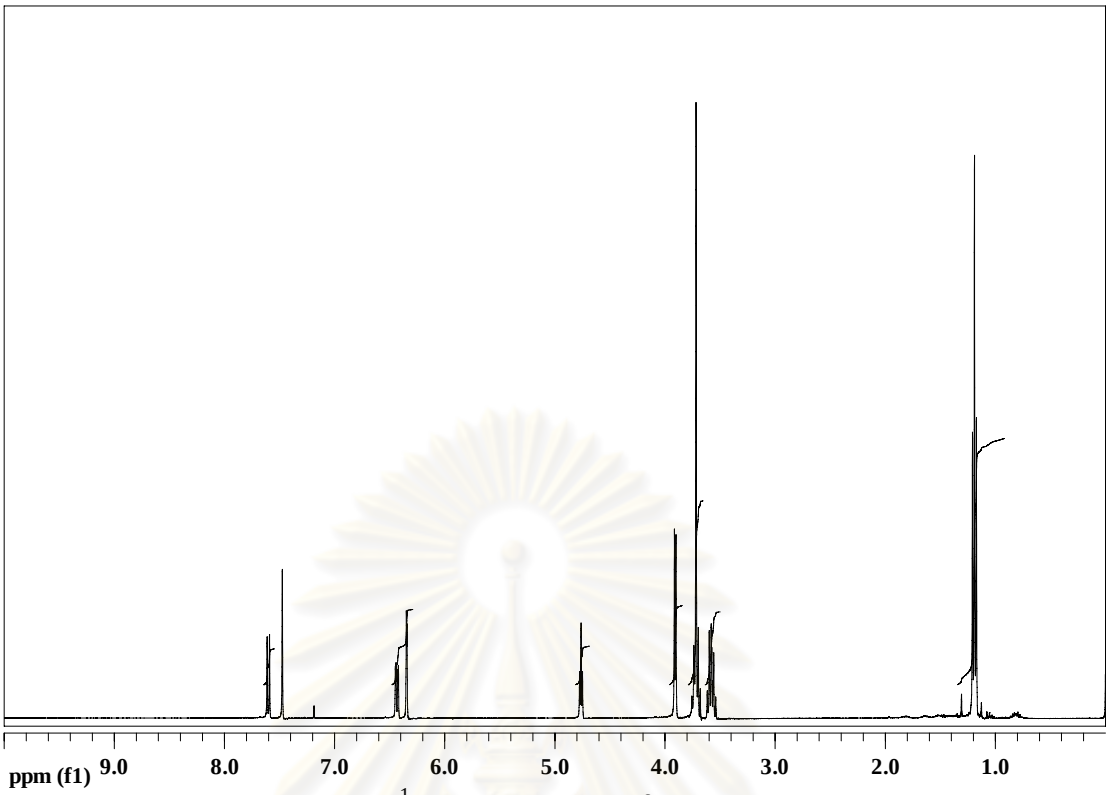

Figure 30 ^{1}H-NMR spectra of compound **148**

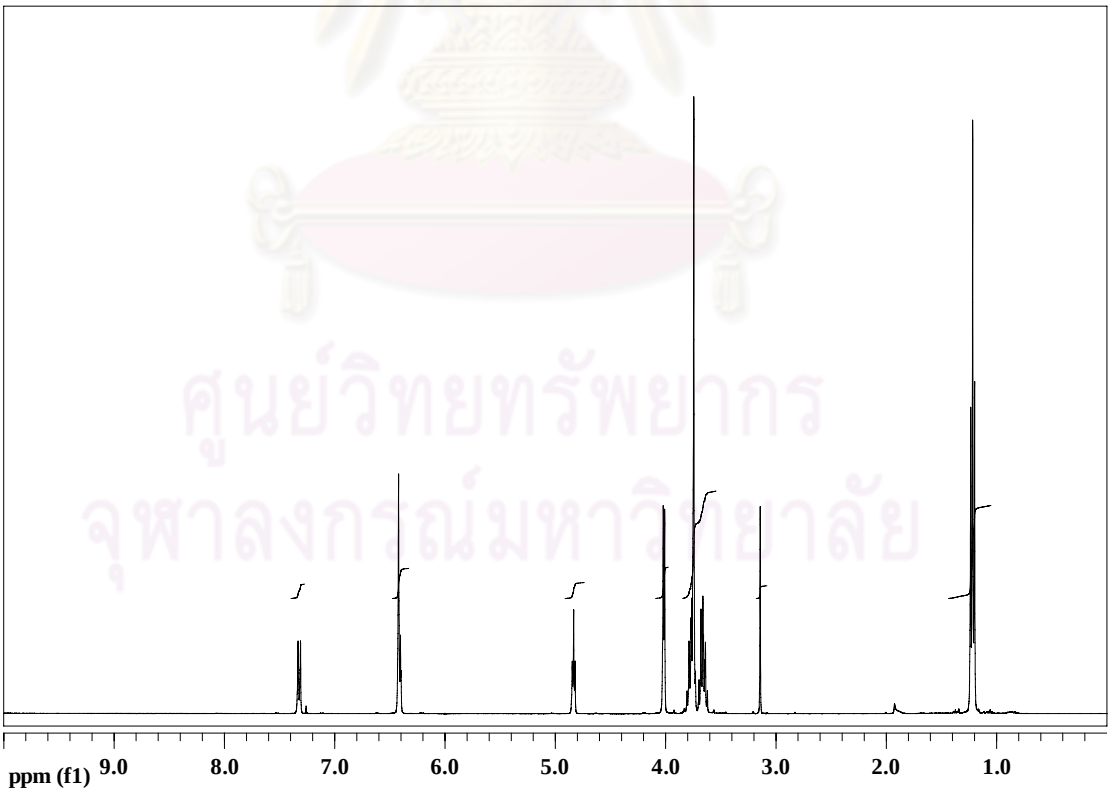

Figure 31 ^{1}H-NMR spectra of compound **20**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

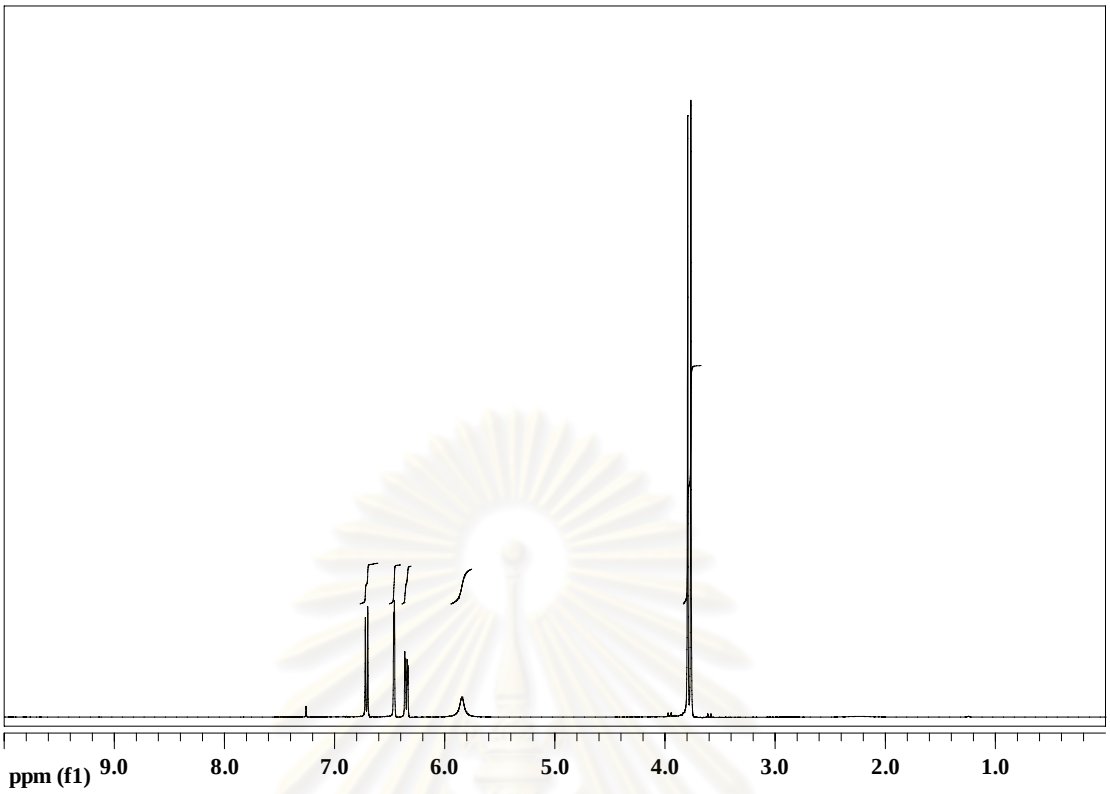

Figure 32 ^{1}H-NMR spectra of compound **150**

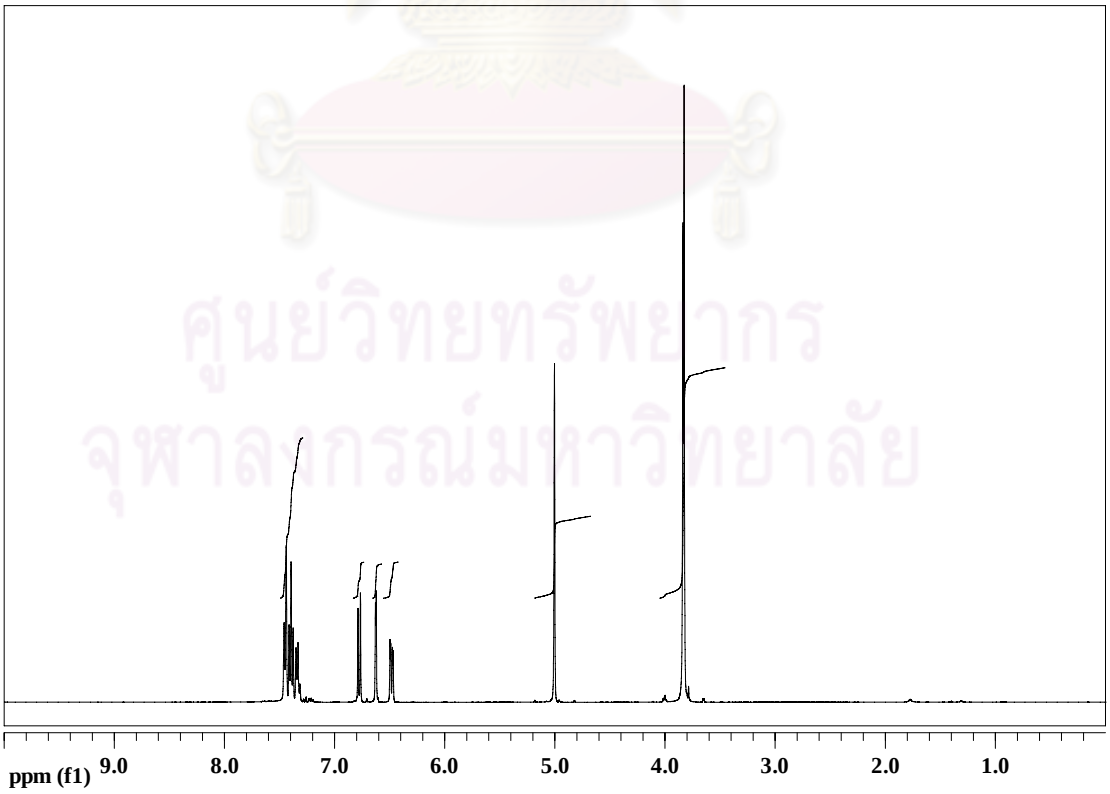

Figure 33 ^{1}H-NMR spectra of compound **151**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

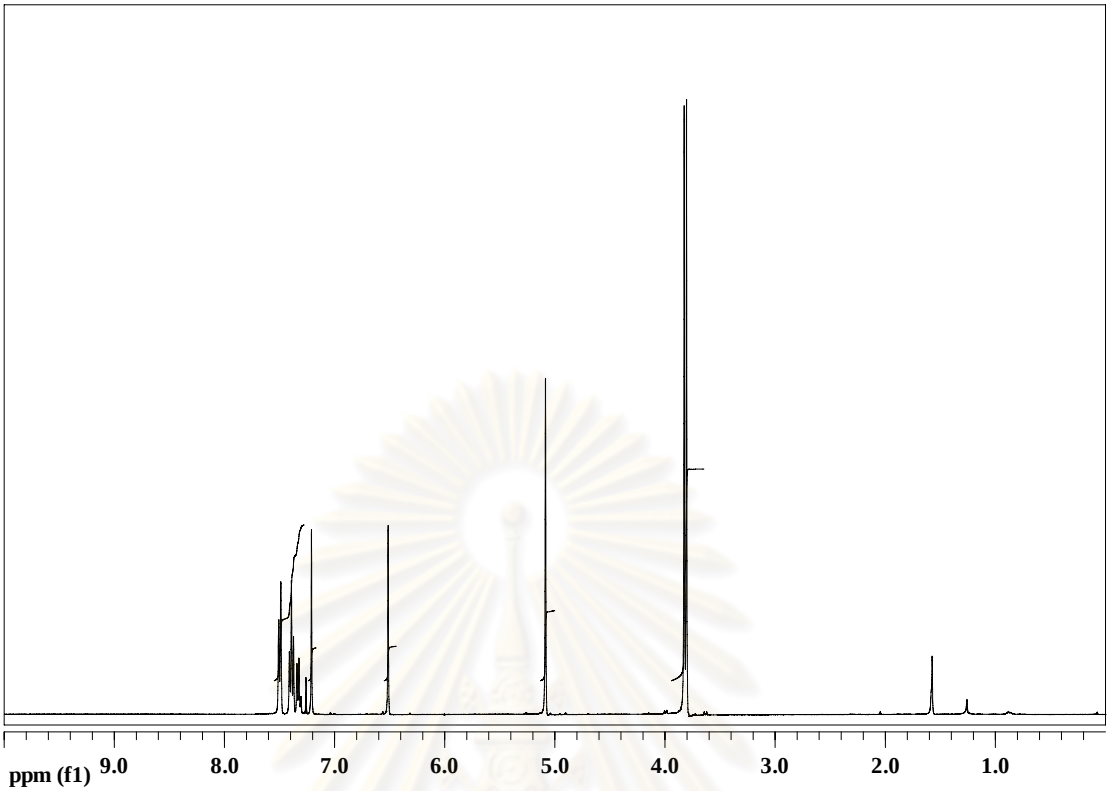

Figure 34 ^{1}H-NMR spectra of compound **21**

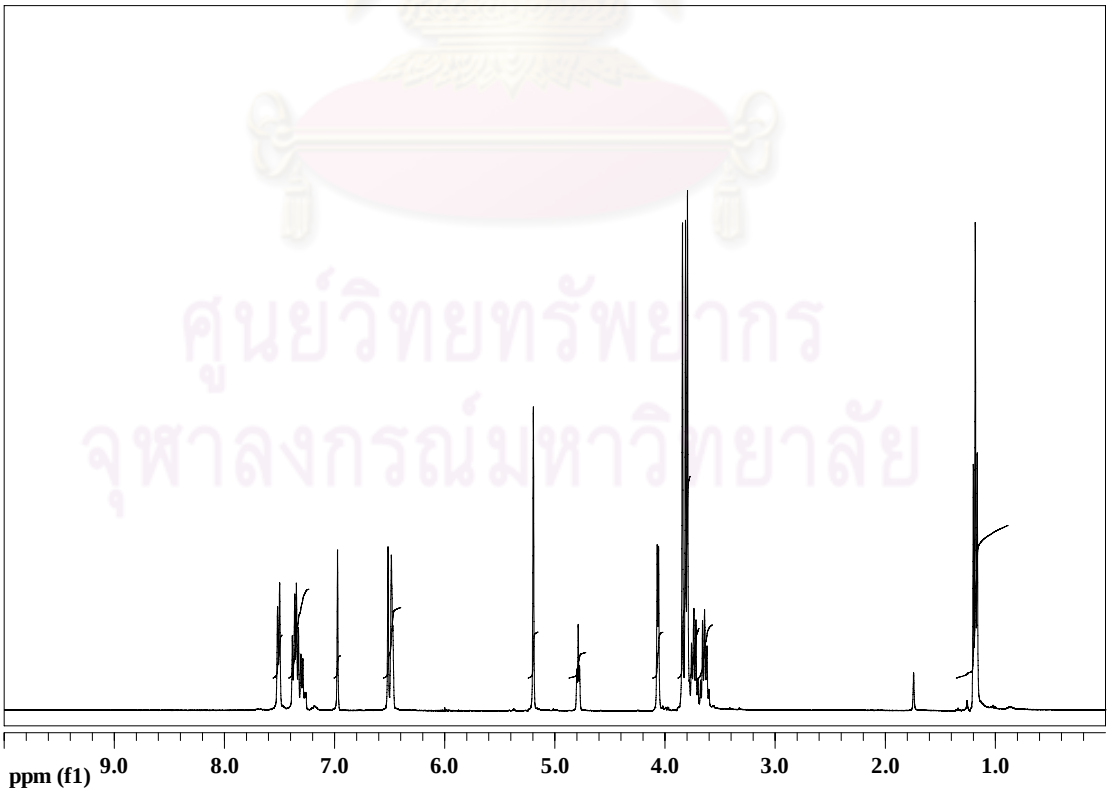

Figure 35 ^{1}H-NMR spectra of compound **152**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

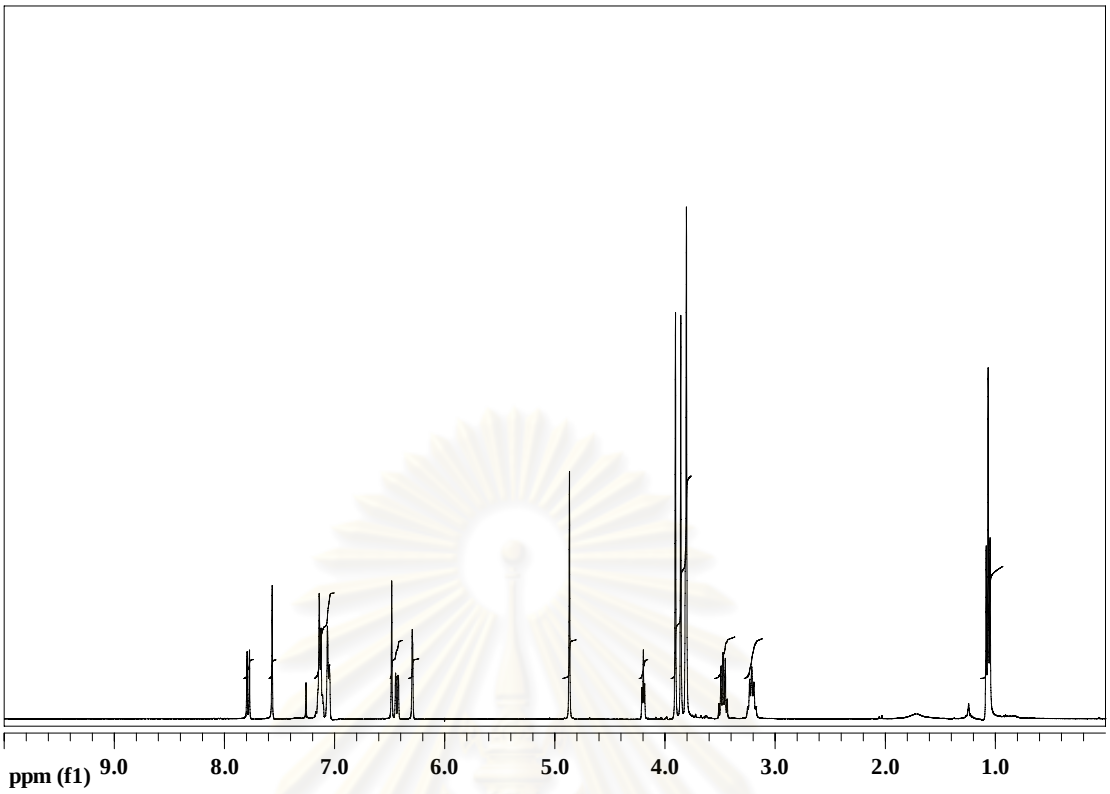

Figure 36 ^{1}H-NMR spectra of compound **19**

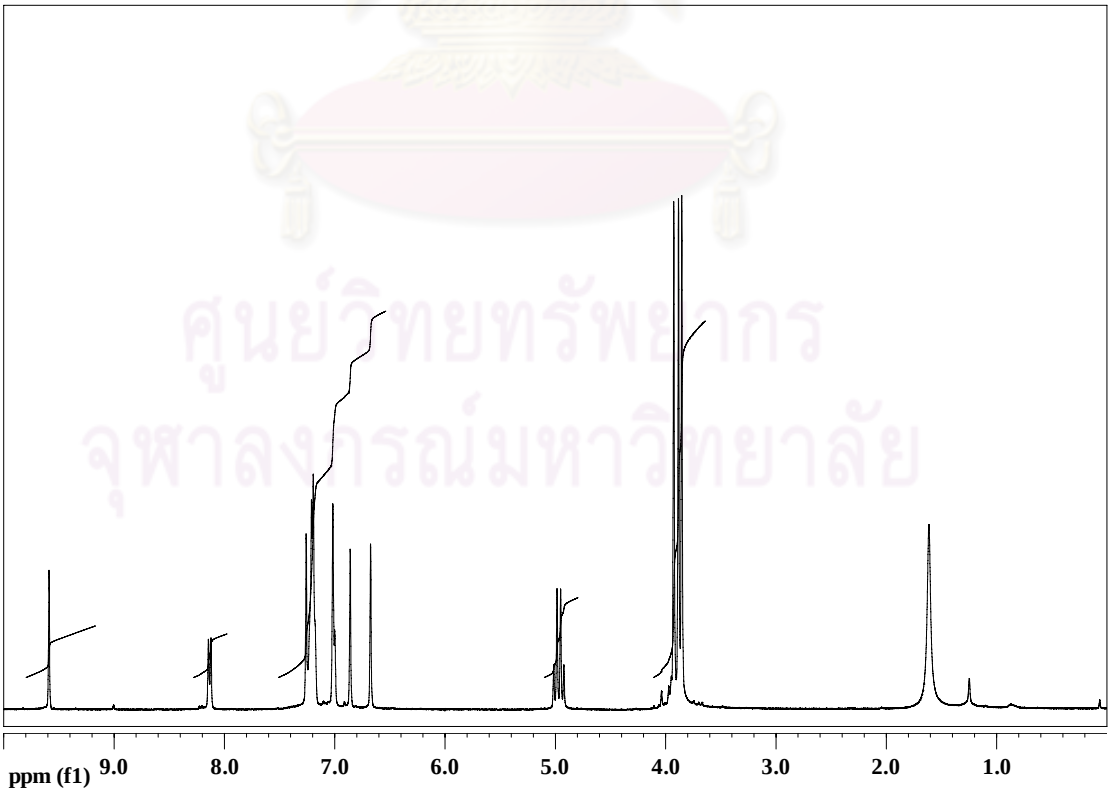

Figure 37 ^{1}H-NMR spectra of compound **153**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

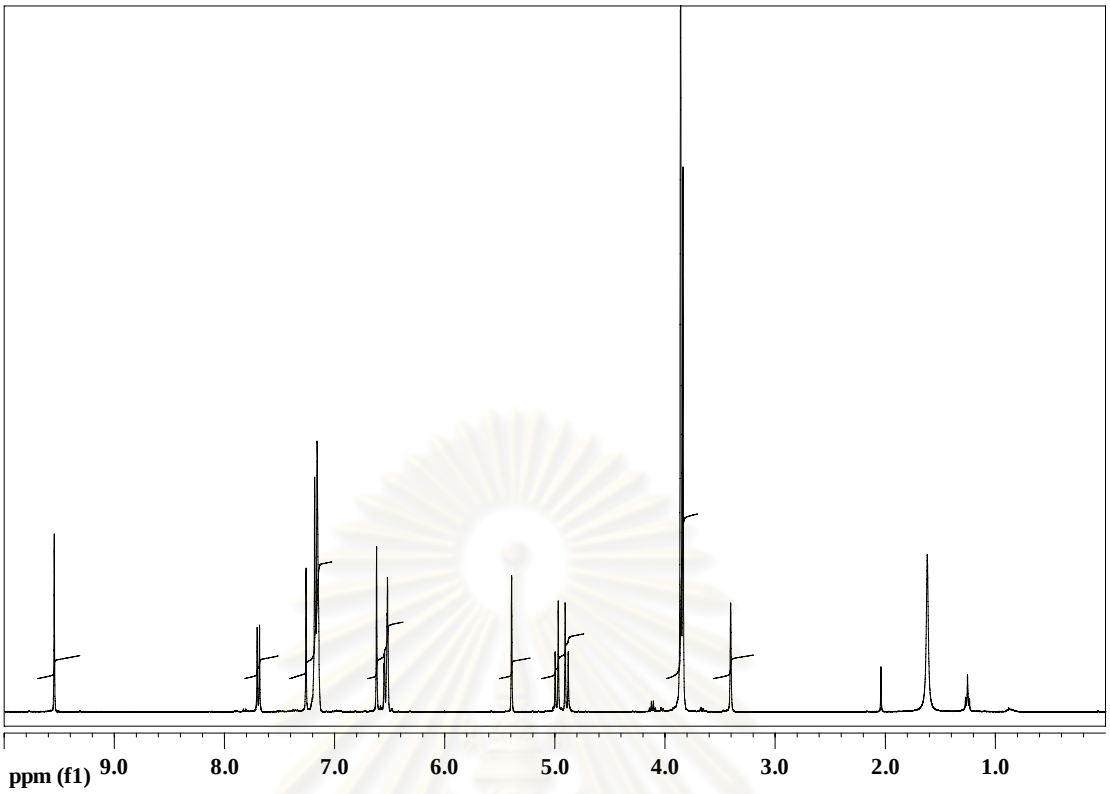

Figure 38 ^{1}H-NMR spectra of compound **154**

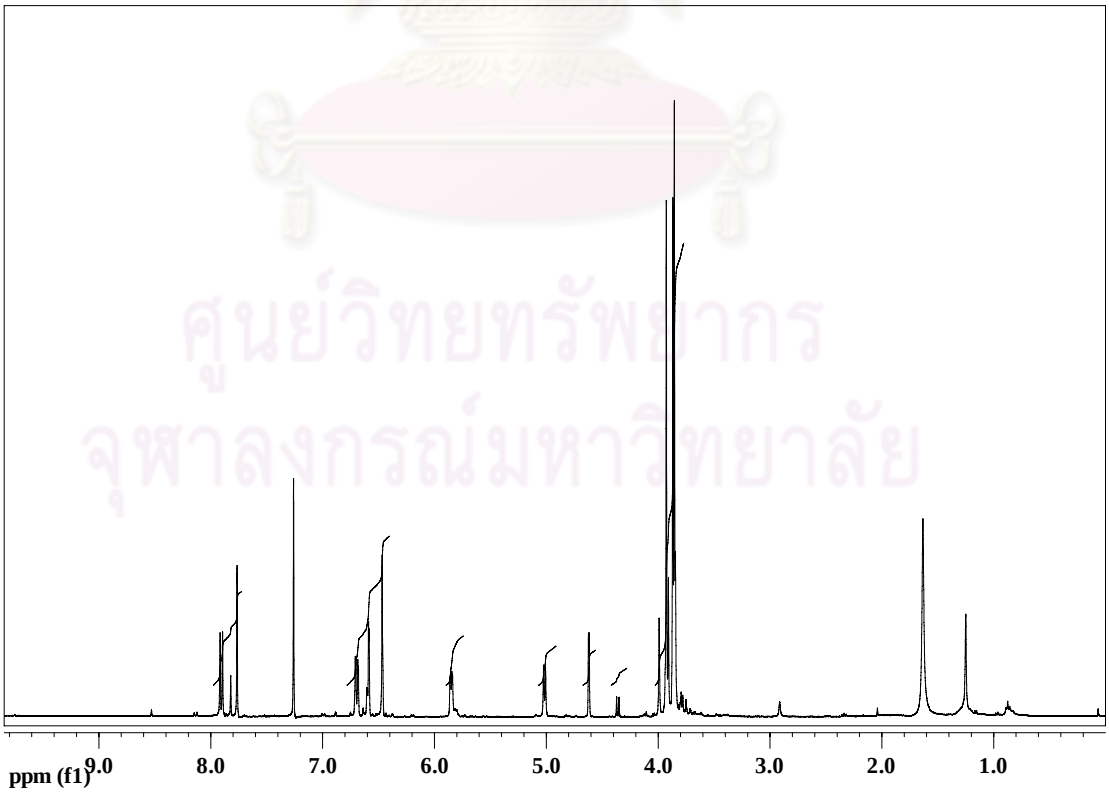

Figure 39 ^{1}H-NMR spectra of compound **155**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

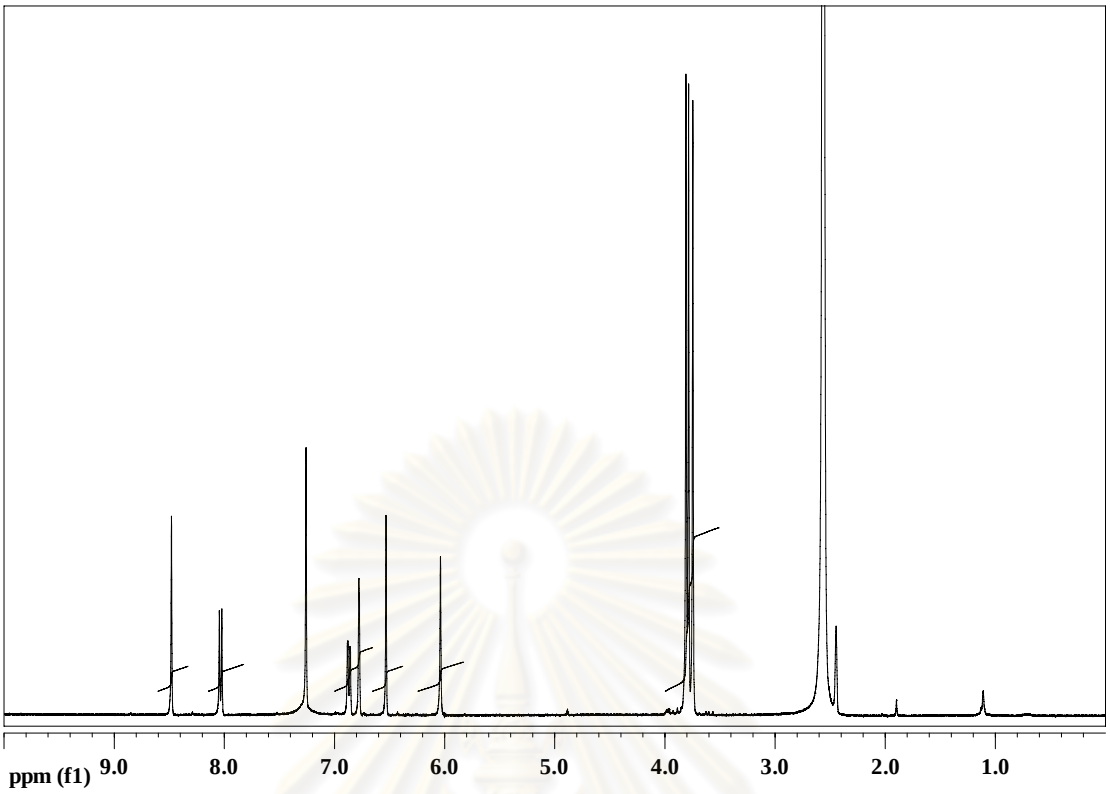

Figure 40 ^{1}H-NMR spectra of compound **1**

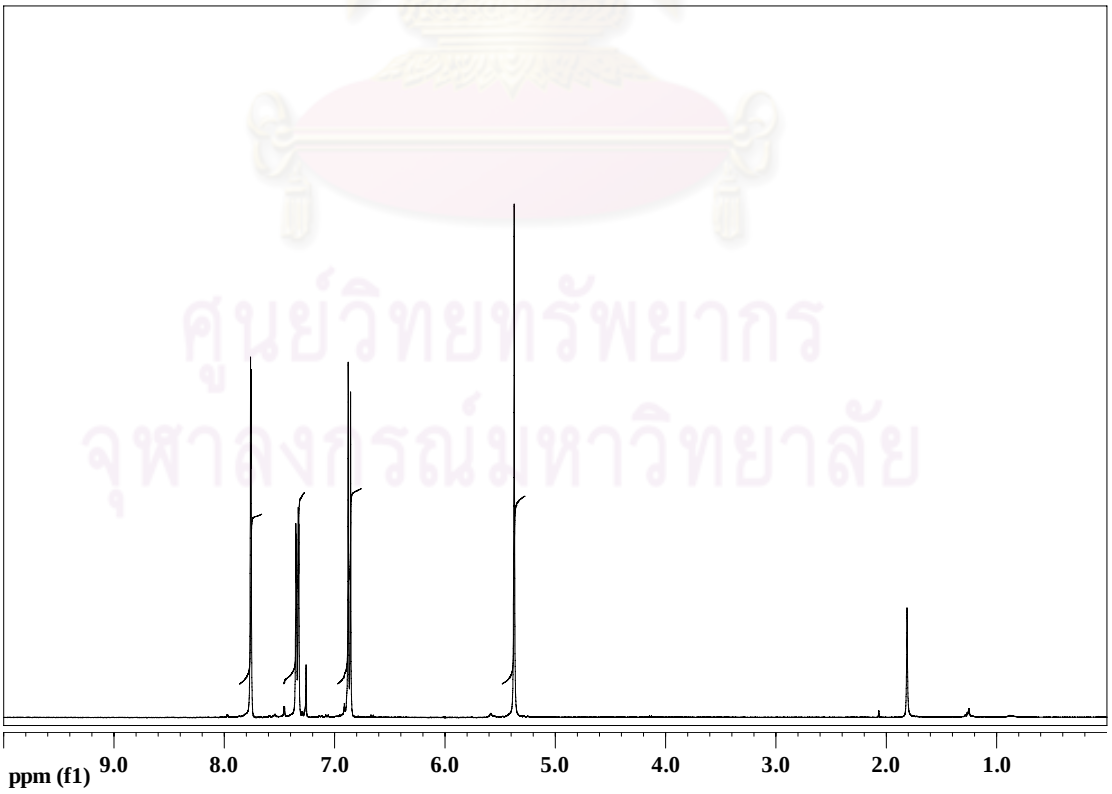

Figure 41 ^{1}H-NMR spectra of compound **157**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

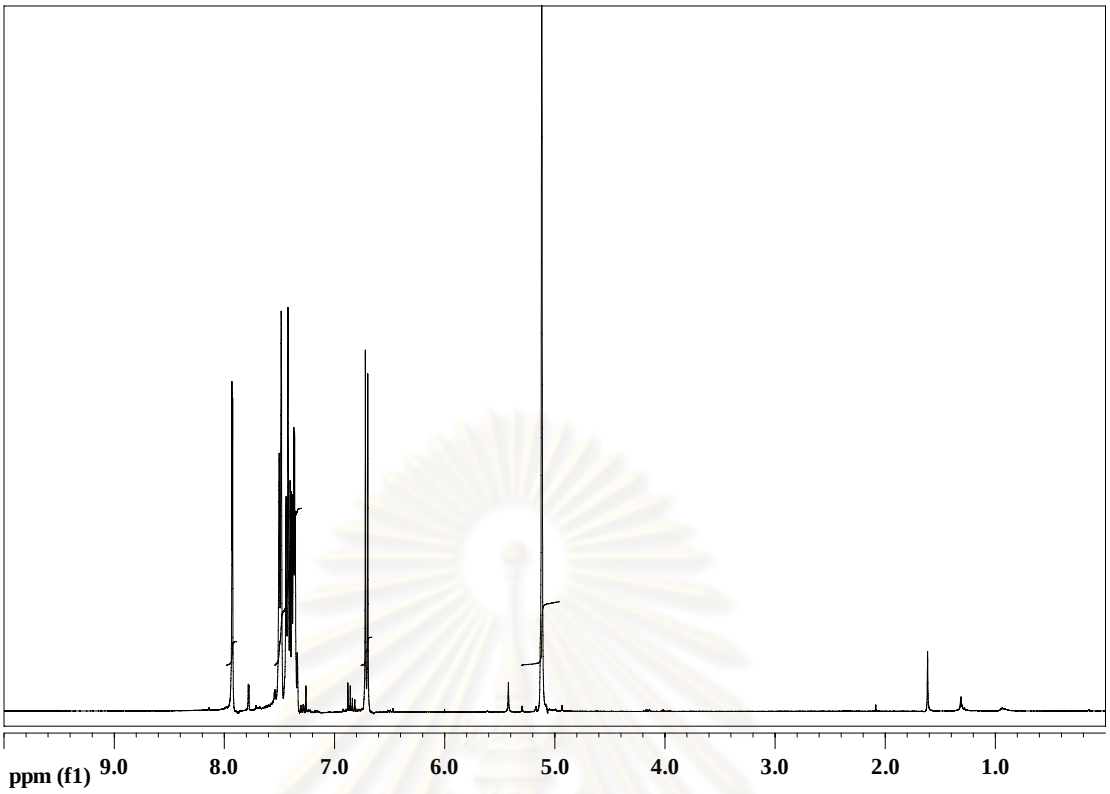

Figure 42 ^{1}H-NMR spectra of compound **158**

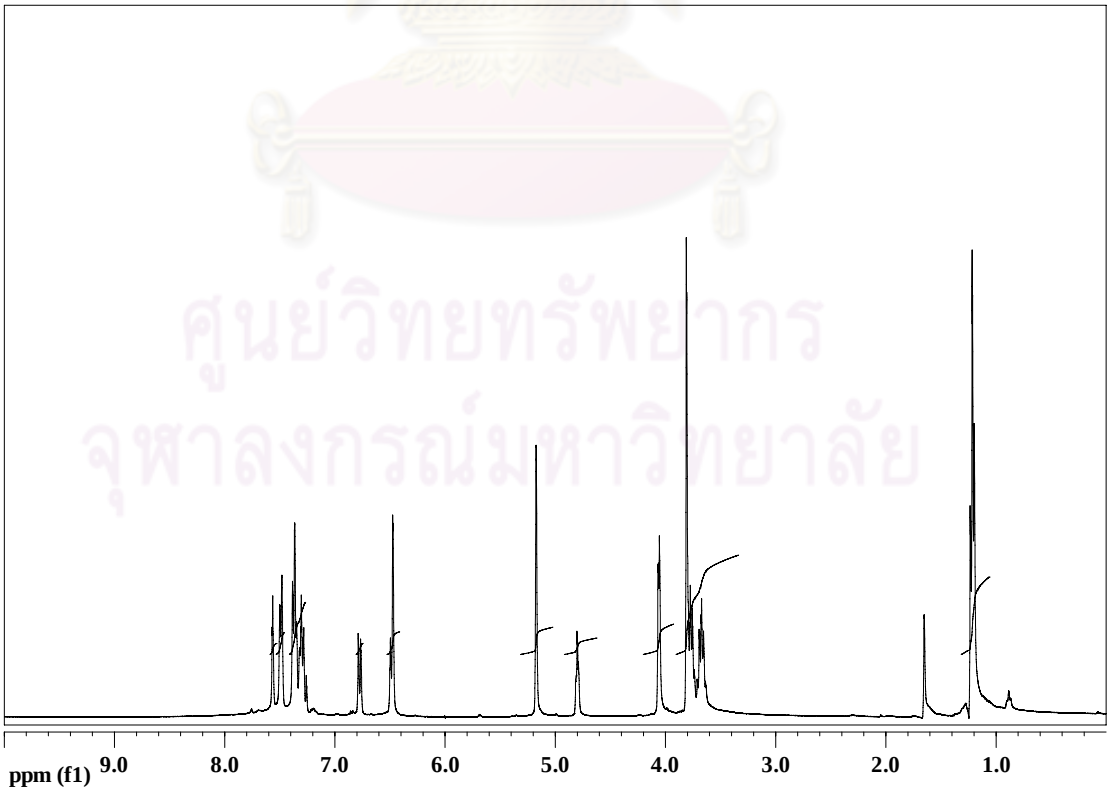

Figure 43 ^{1}H-NMR spectra of compound **159**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

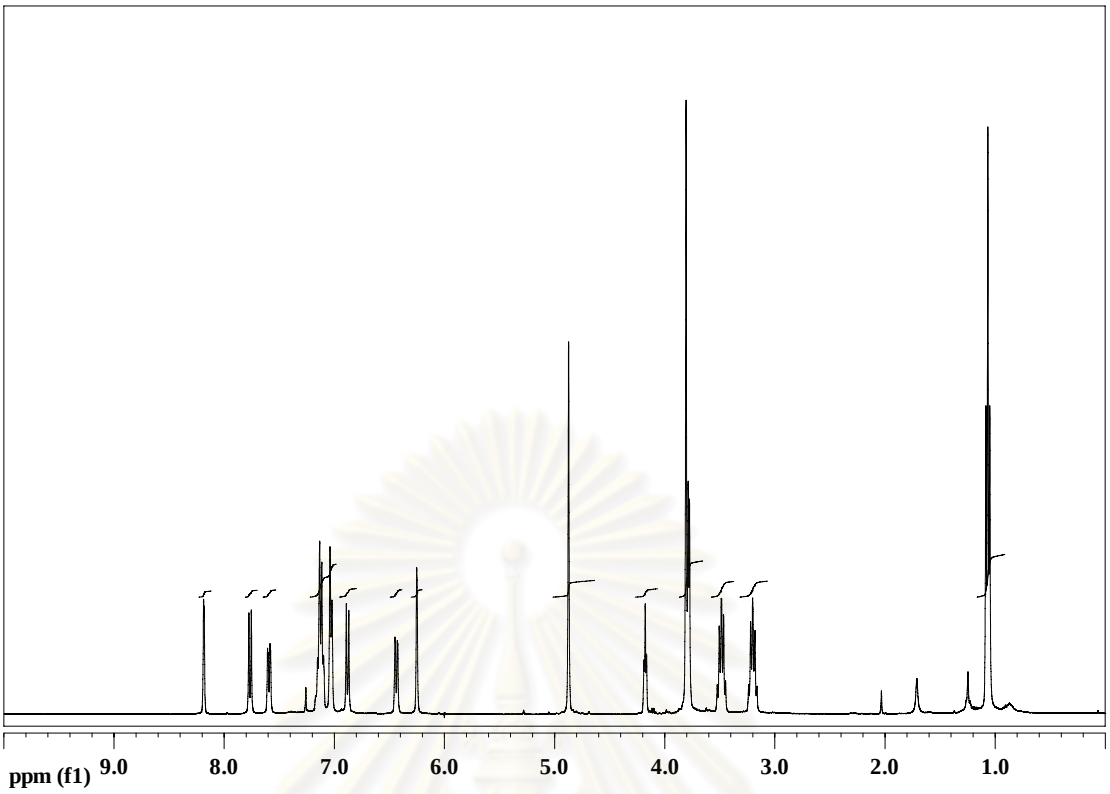

Figure 44 ^{1}H-NMR spectra of compound **160**

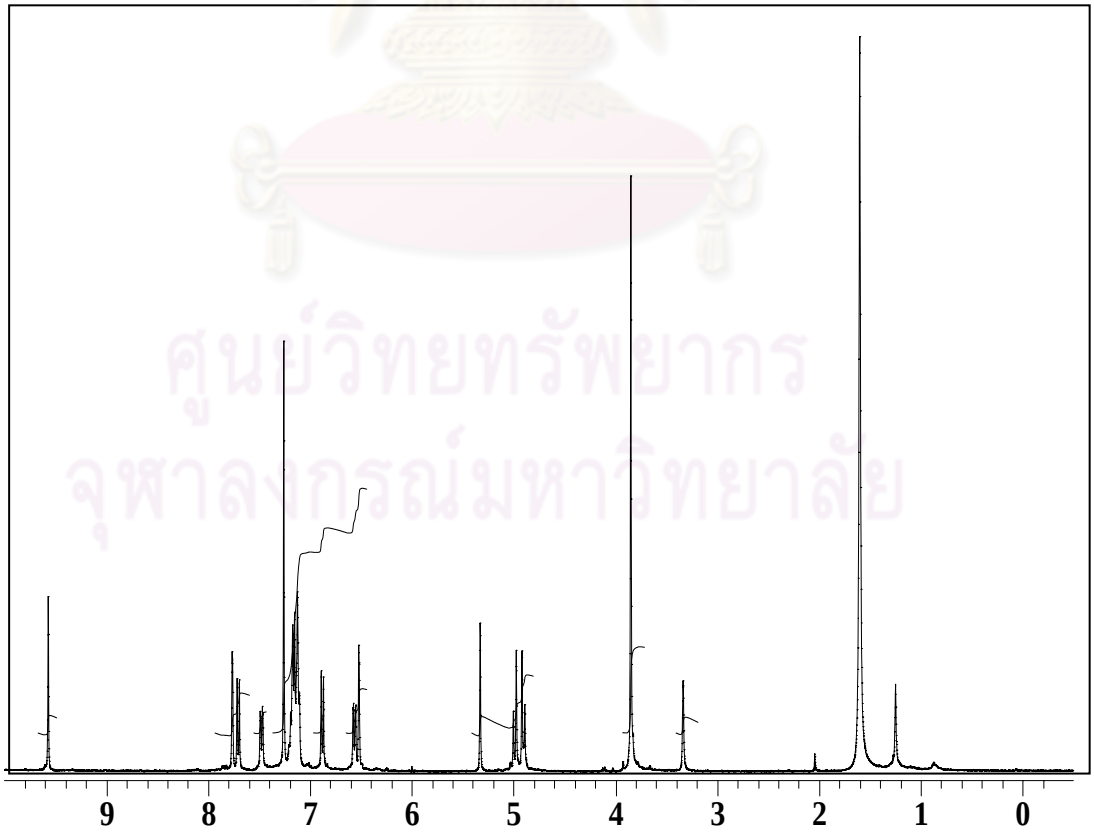

Figure 45 ^{1}H-NMR spectra of compound **161**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

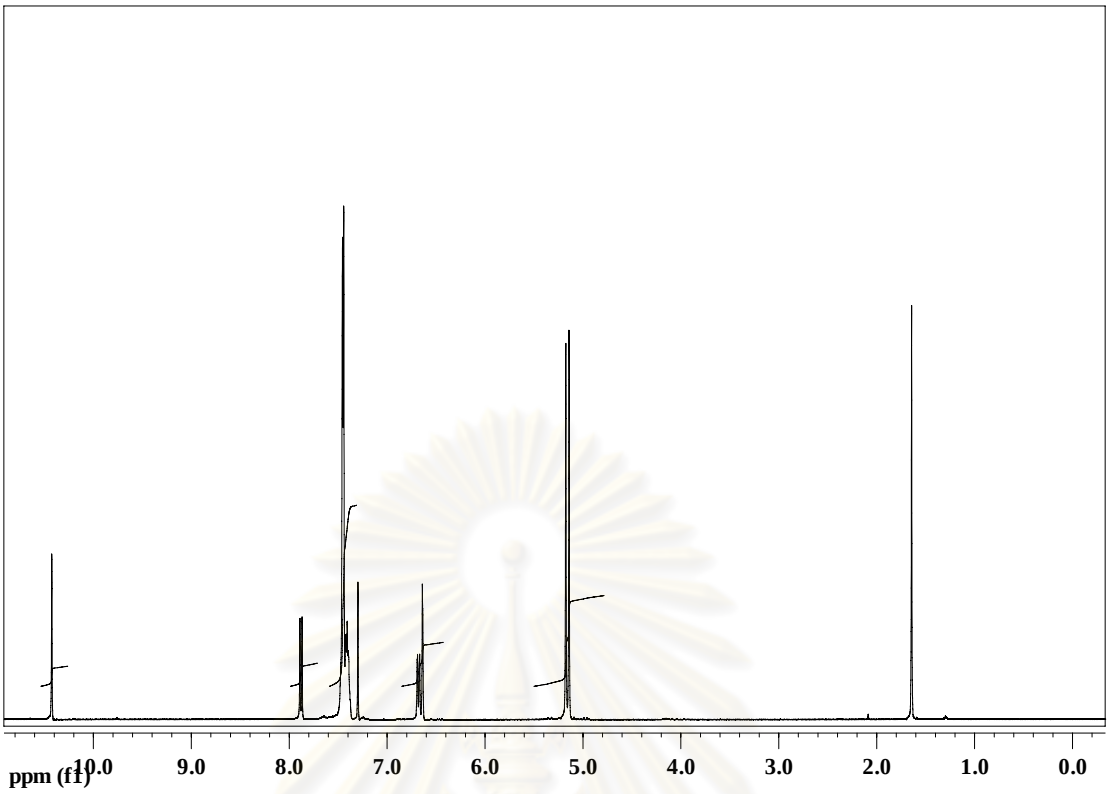

Figure 46 ^{1}H-NMR spectra of compound **164**

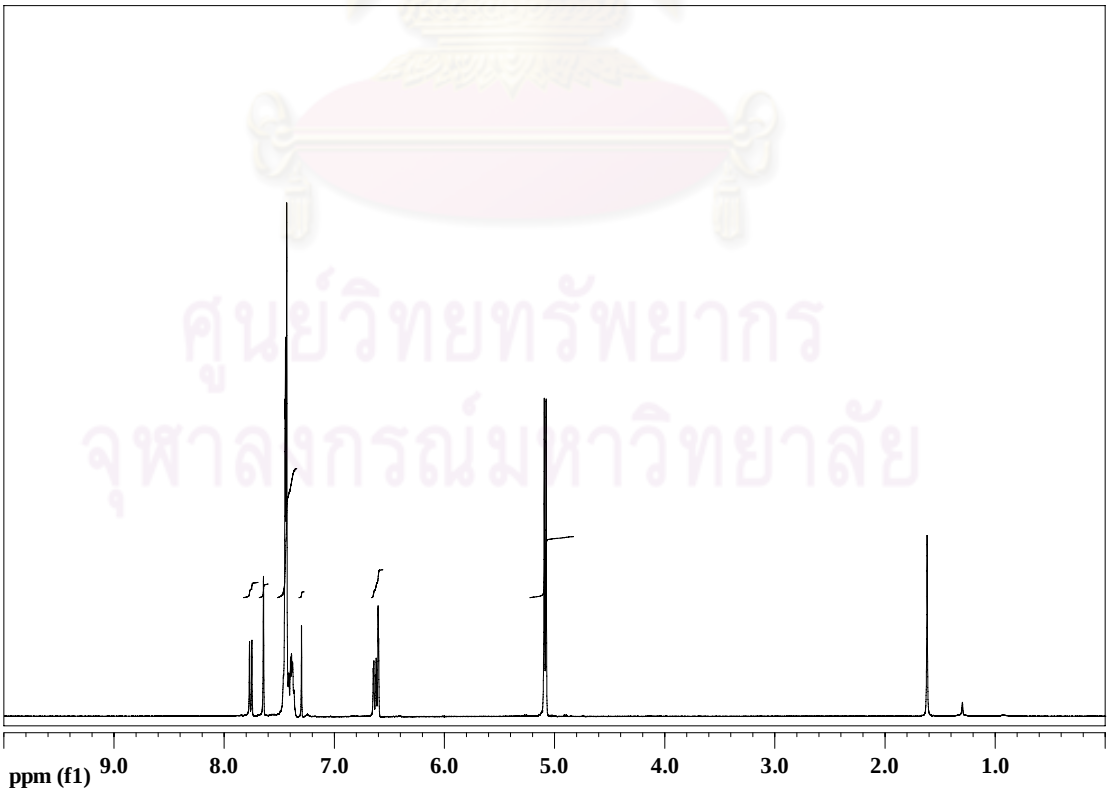

Figure 47 ^{1}H-NMR spectra of compound **165**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

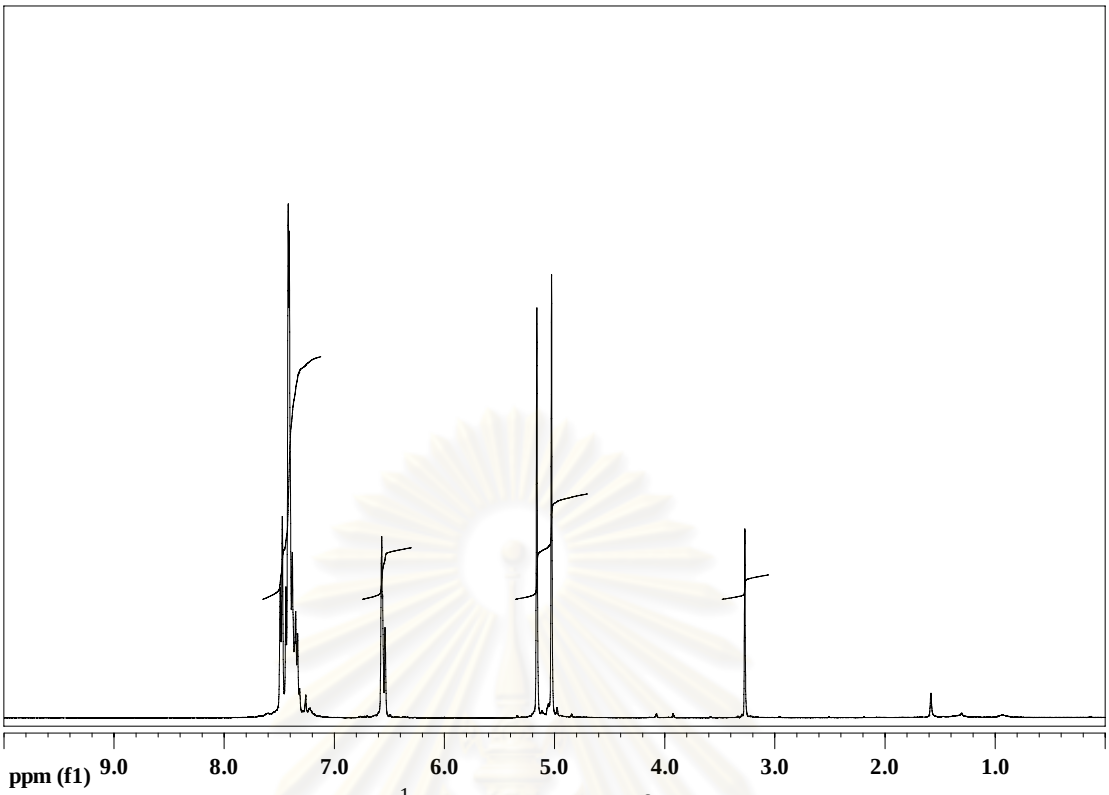

Figure 48 ^{1}H-NMR spectra of compound **166**

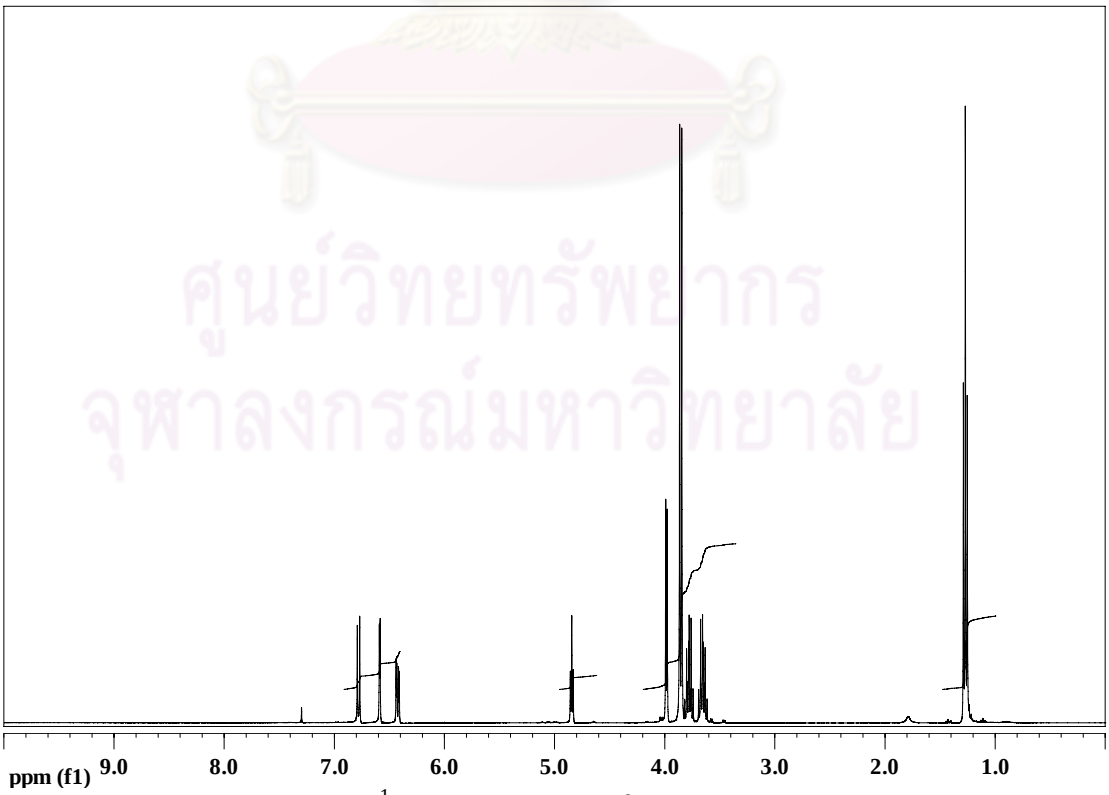

Figure ^{1}H-NMR spectra of compound **167**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

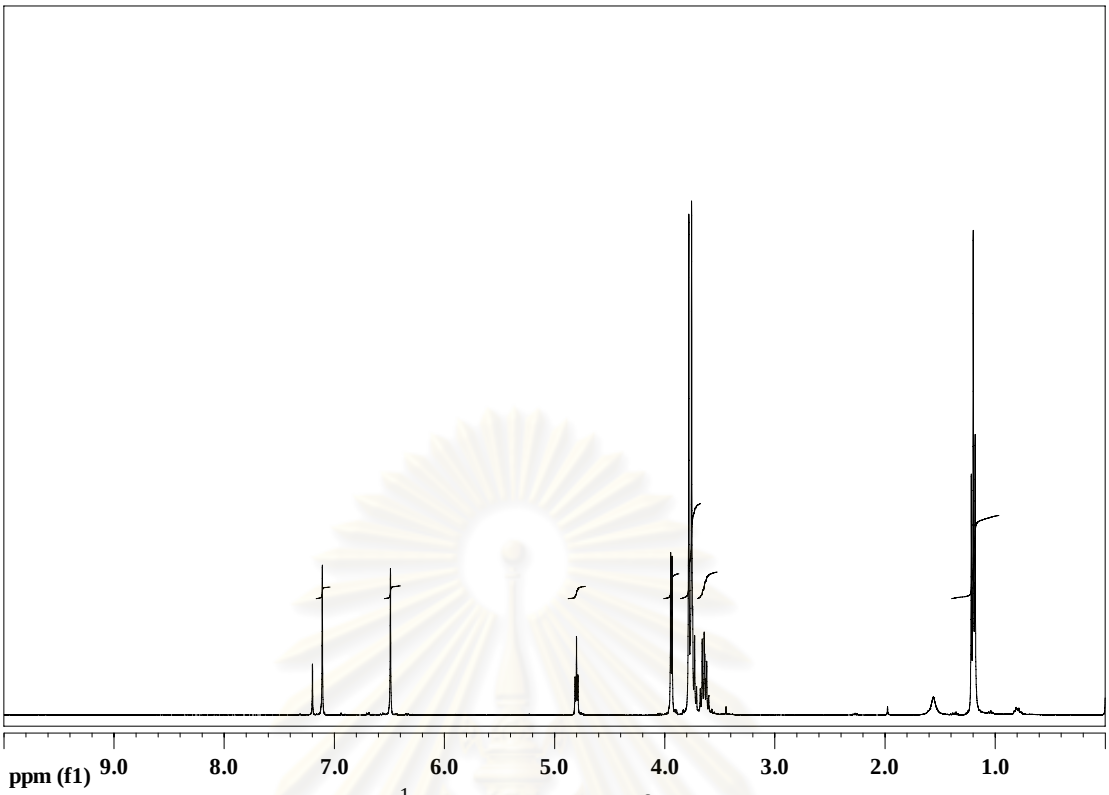

Figure 50 ^{1}H-NMR spectra of compound **168**

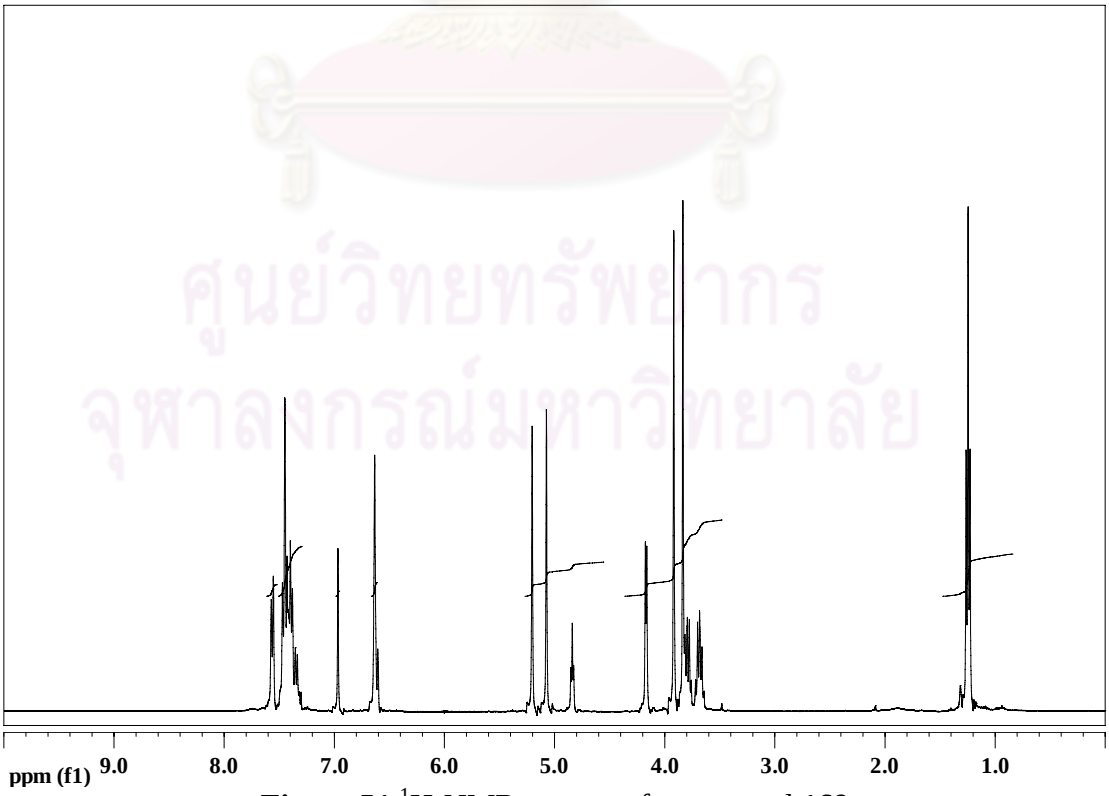

Figure 51 ^{1}H-NMR spectra of compound **169**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

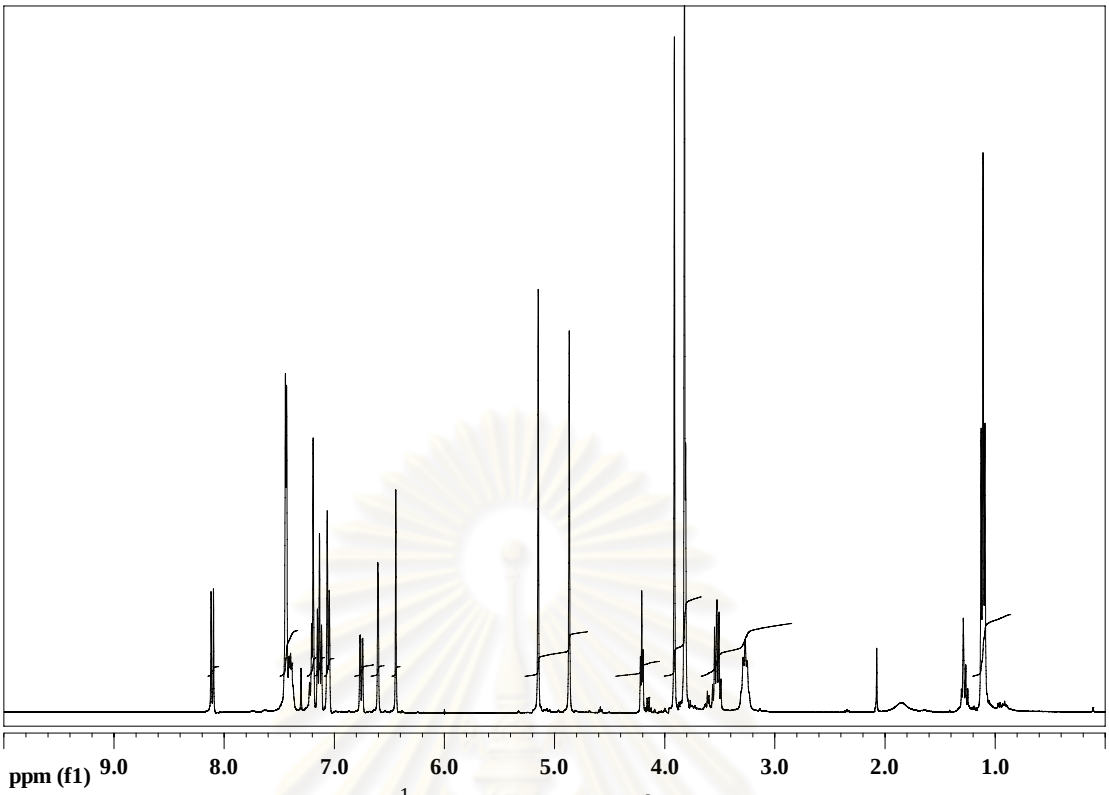

Figure 52 ^{1}H-NMR spectra of compound **170**

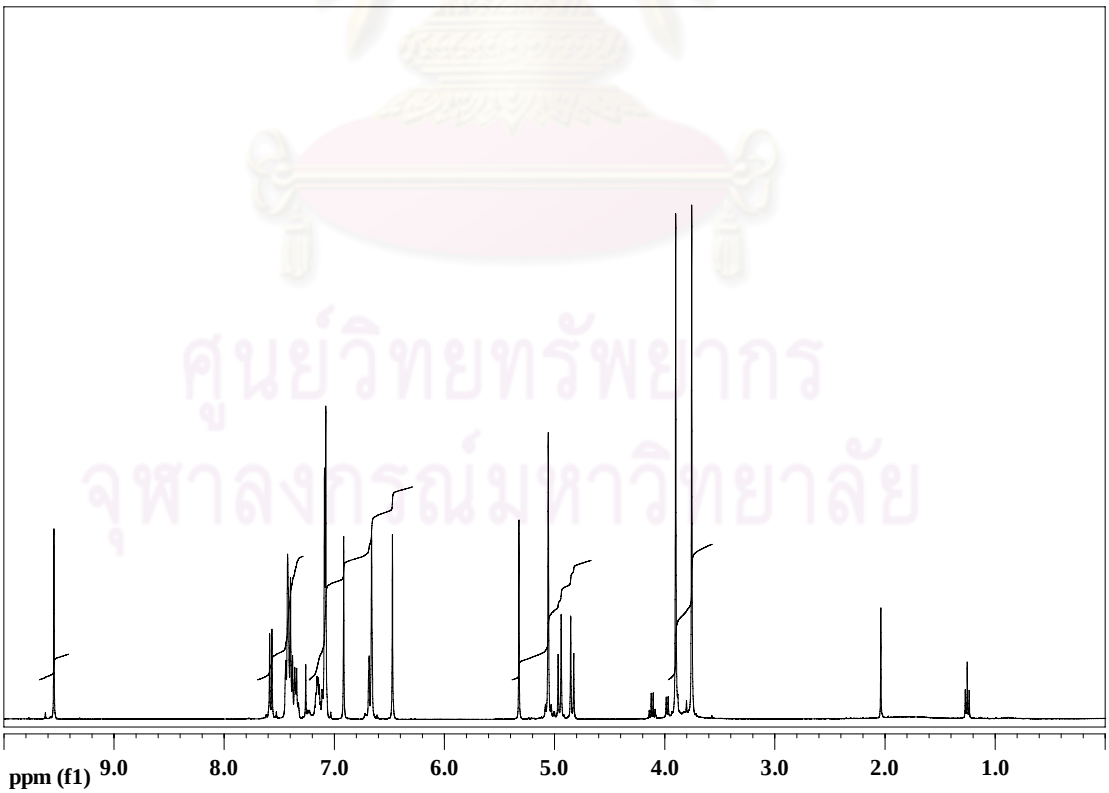

Figure 53 ^{1}H-NMR spectra of compound **171**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

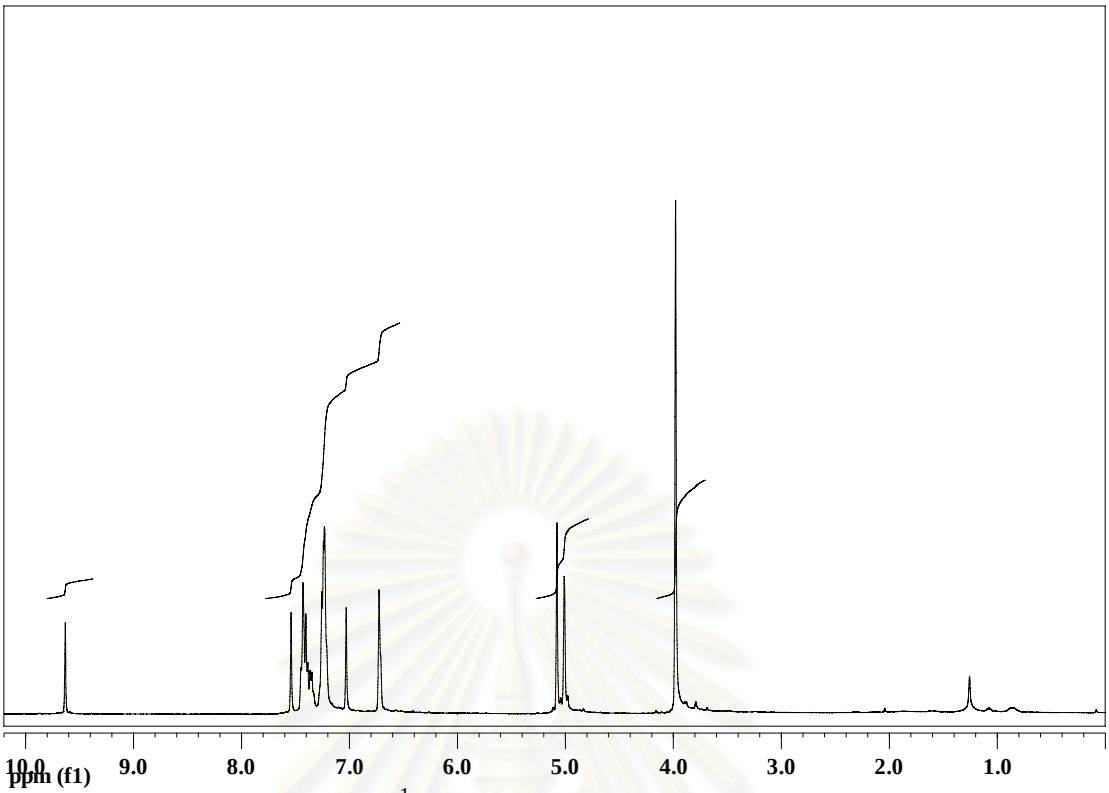

Figure 54 ^{1}H-NMR spectra of compound **172**

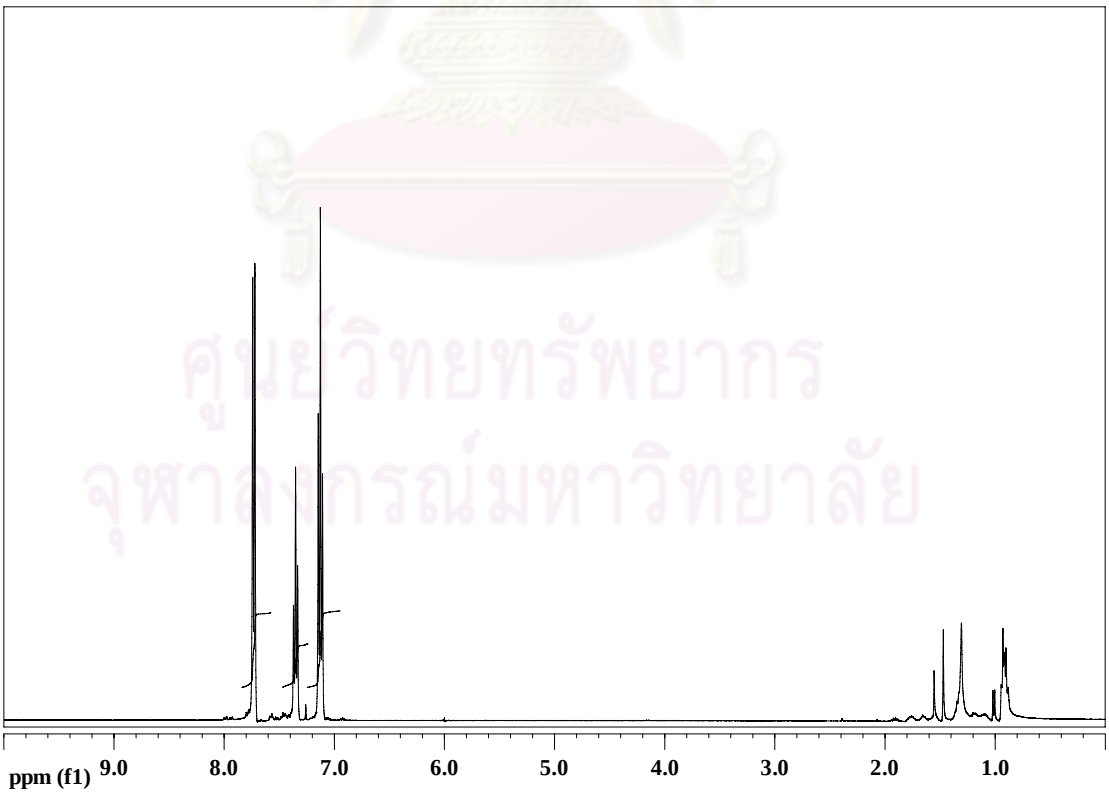

Figure 55 ^{1}H-NMR spectra of compound **174a**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

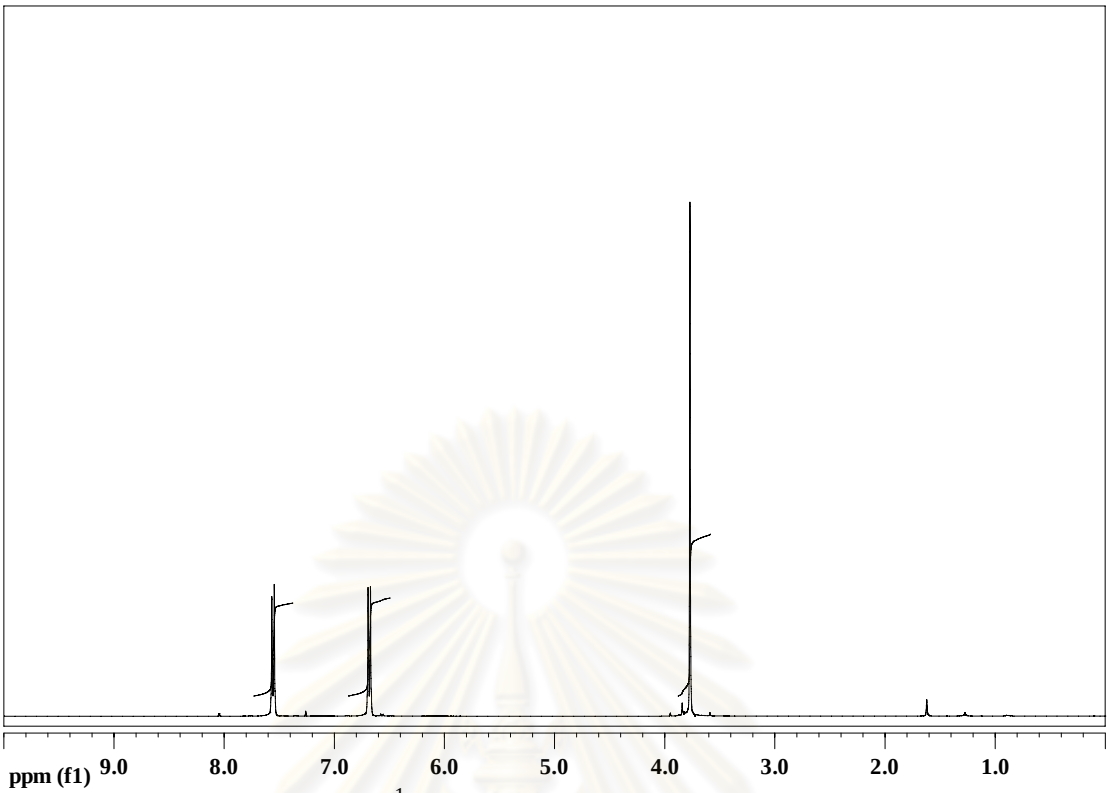

Figure 56 ^{1}H-NMR spectra of compound **174b**

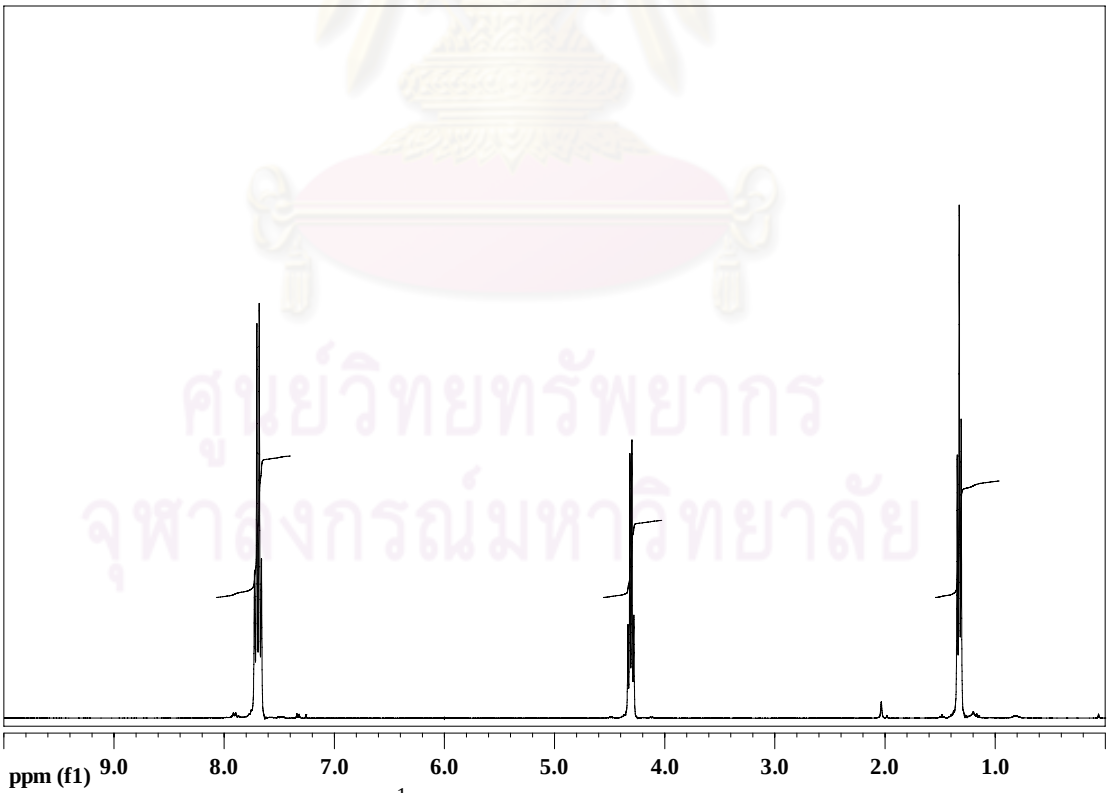

Figure 57 ^{1}H-NMR spectra of compound **174c**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

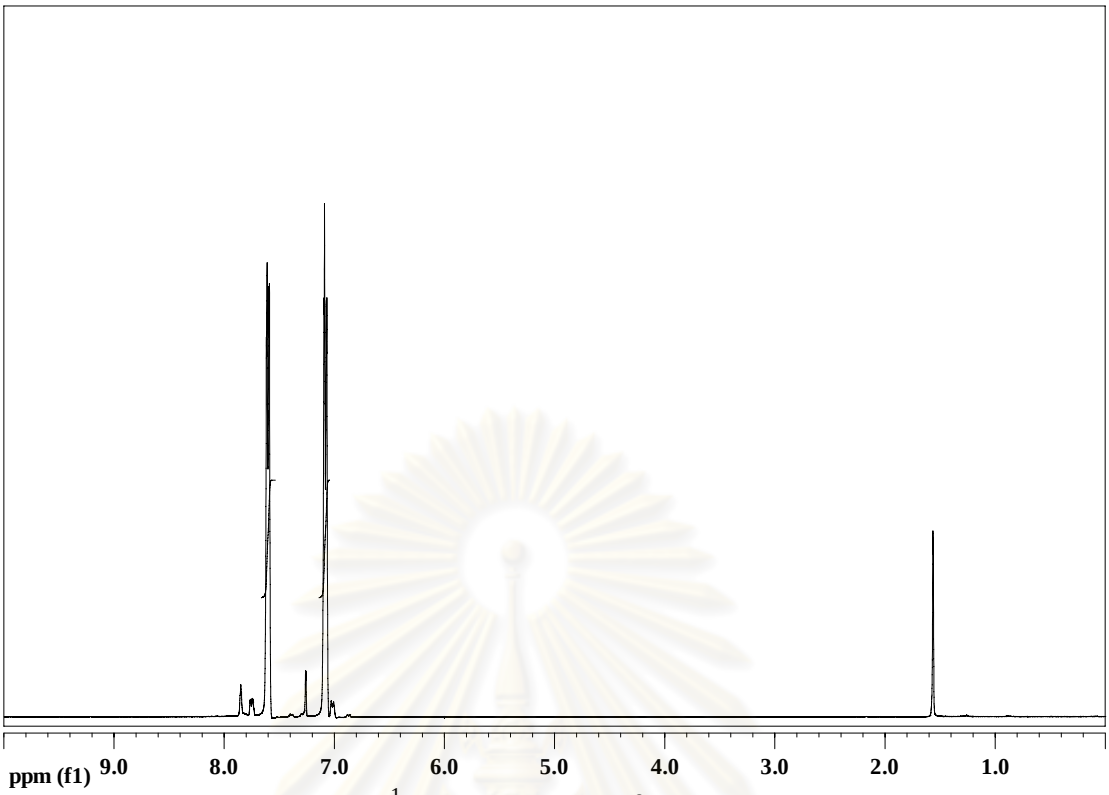

Figure 58 ^{1}H-NMR spectra of compound **174d**

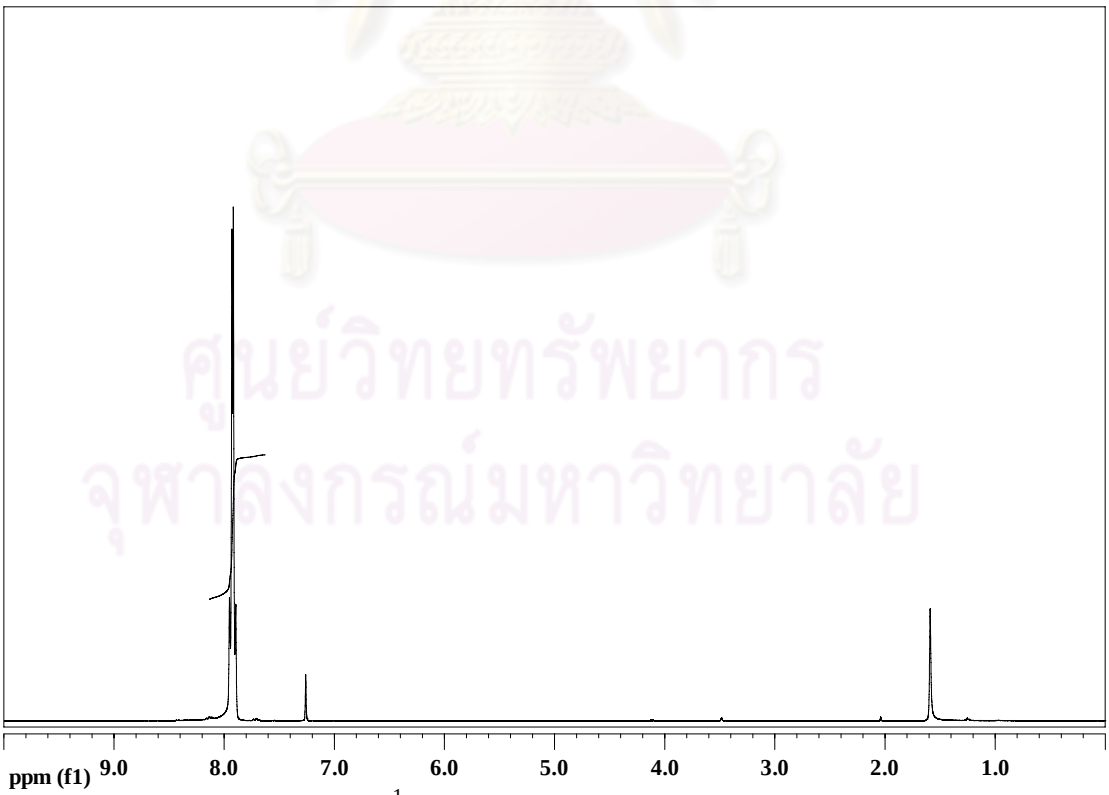

Figure 59 ^{1}H-NMR spectra of compound **174e**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

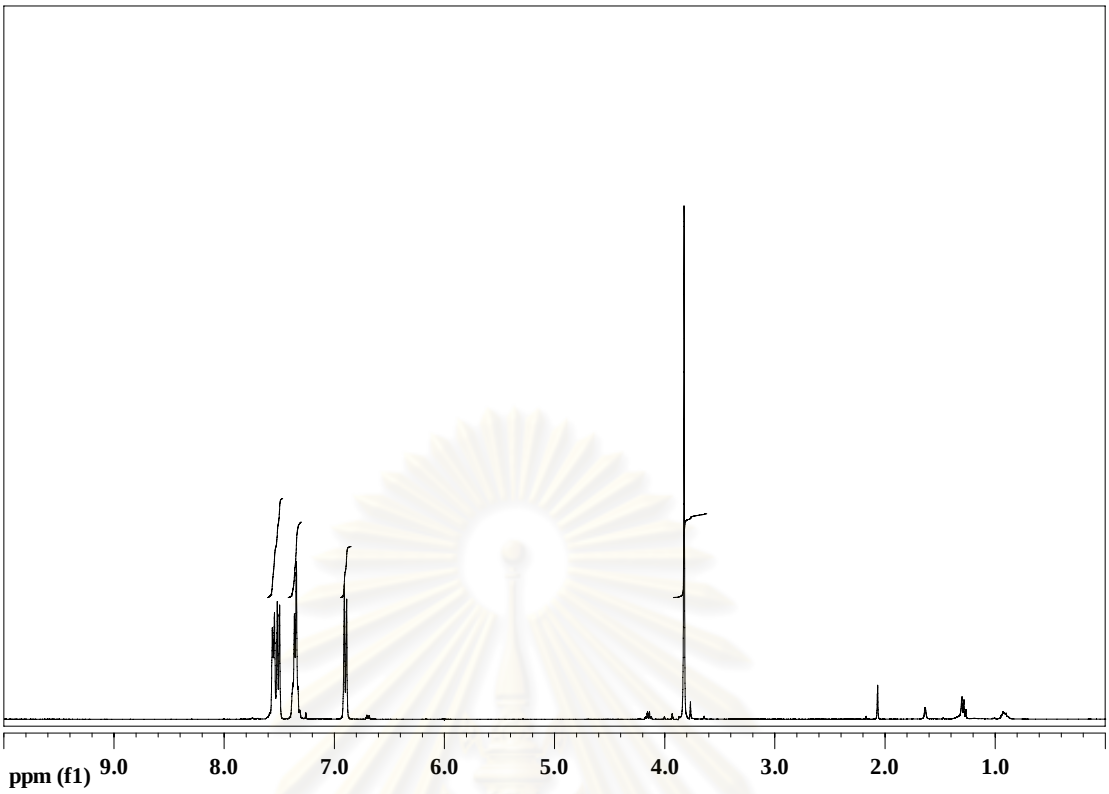

Figure 60 ^{1}H-NMR spectra of compound **176a**

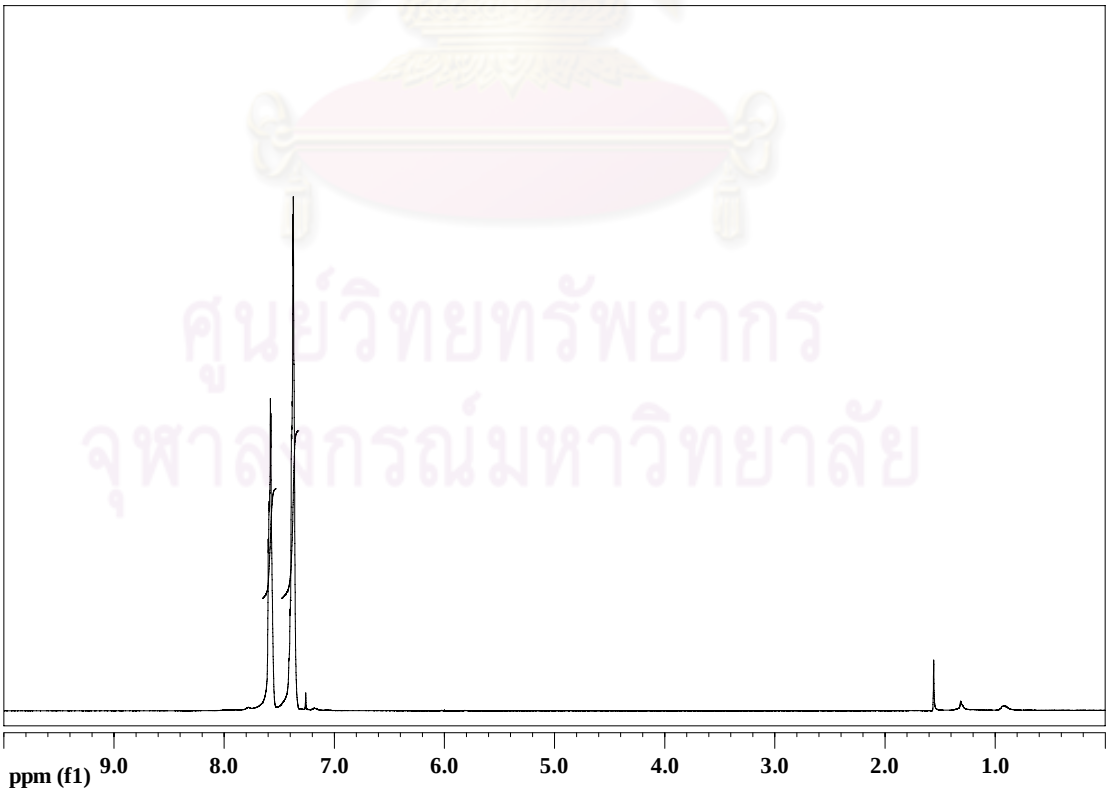

Figure 61 ^{1}H-NMR spectra of compound **176b**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

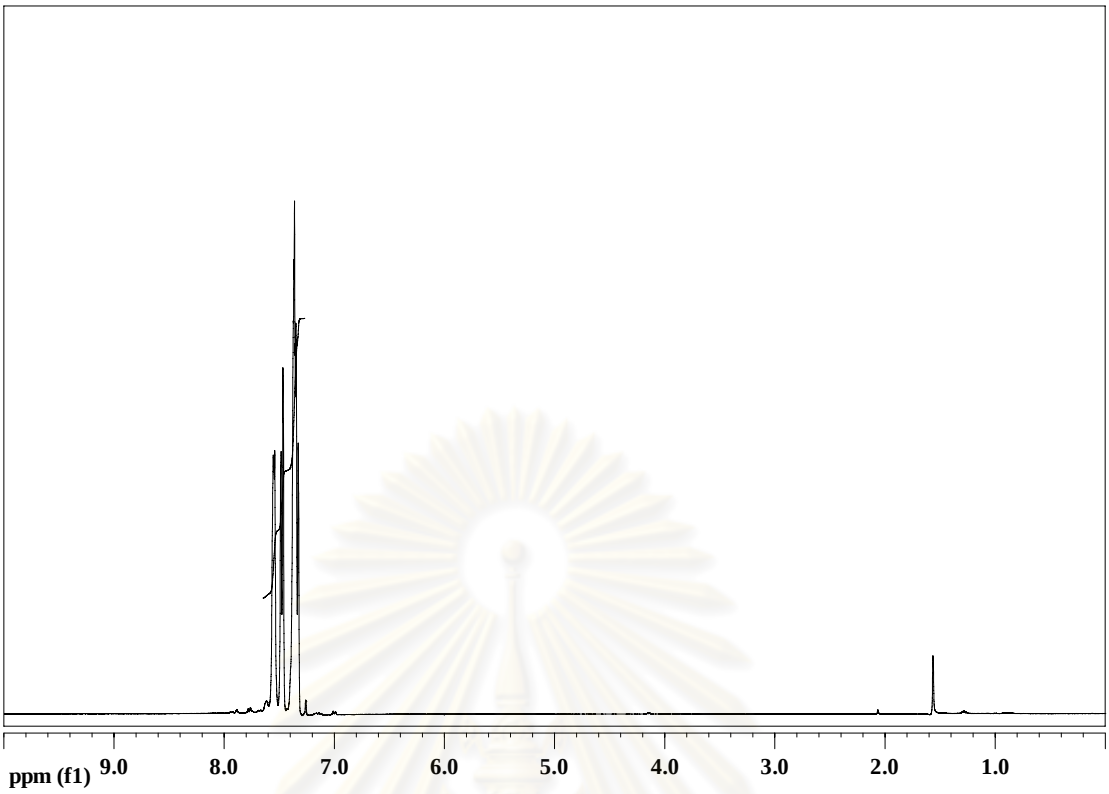

Figure 62 ^{1}H-NMR spectra of compound **176c**

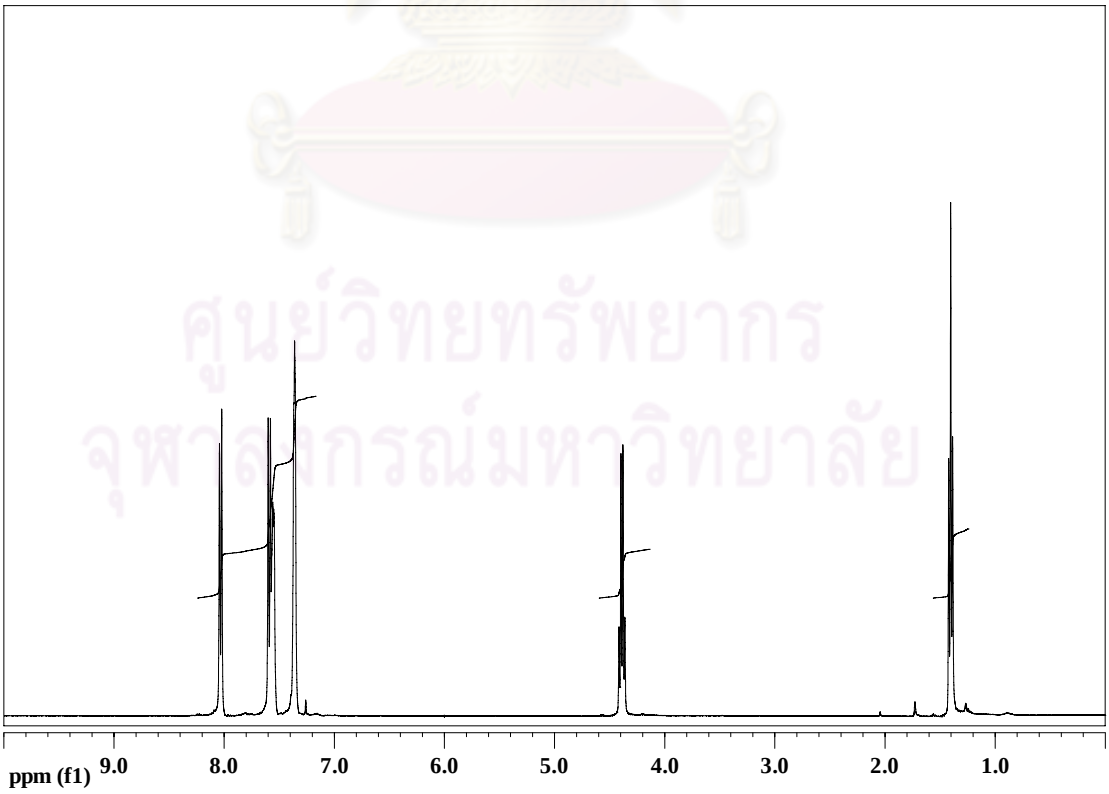

Figure 63 ^{1}H-NMR spectra of compound **176d**

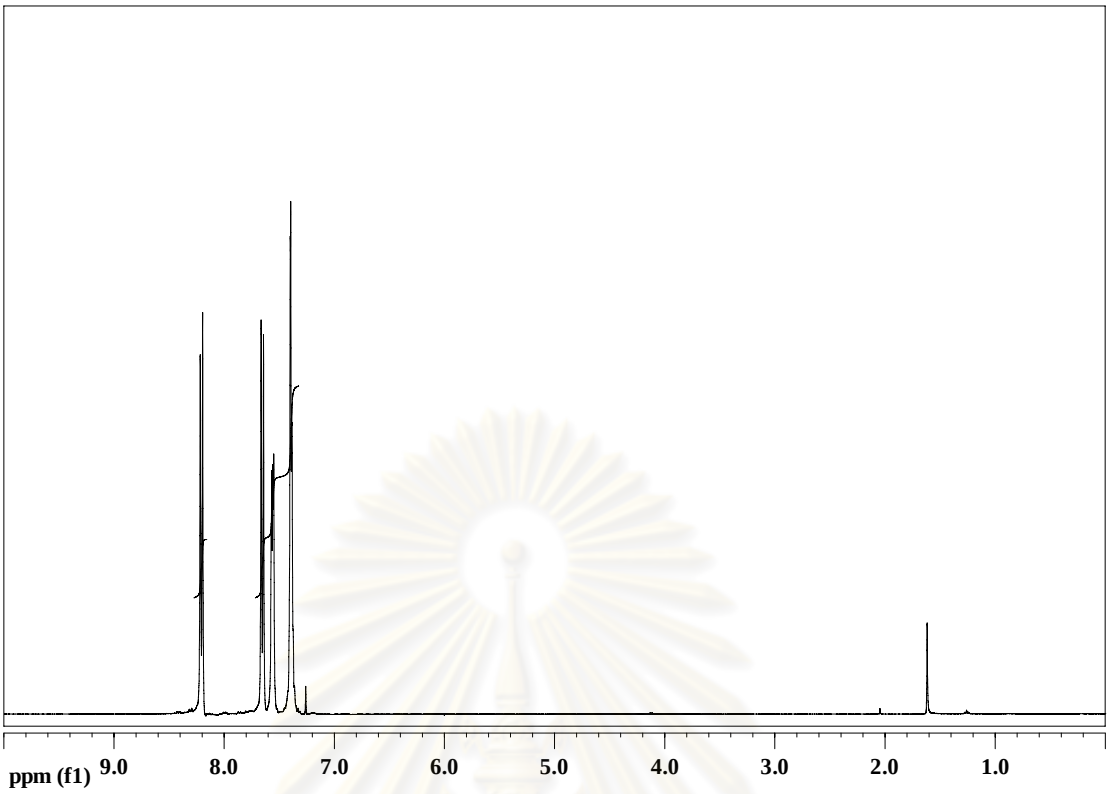

Figure 64 ^{1}H-NMR spectra of compound **176e**

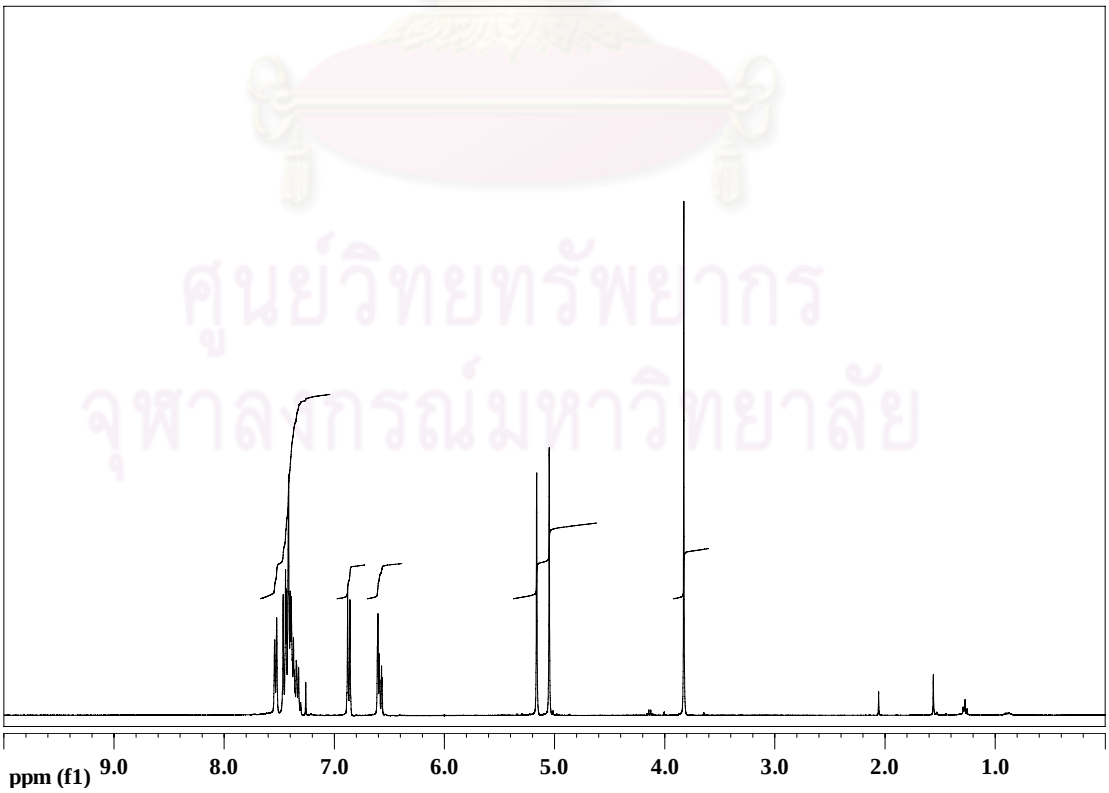

Figure 65 ^{1}H-NMR spectra of compound **176f**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

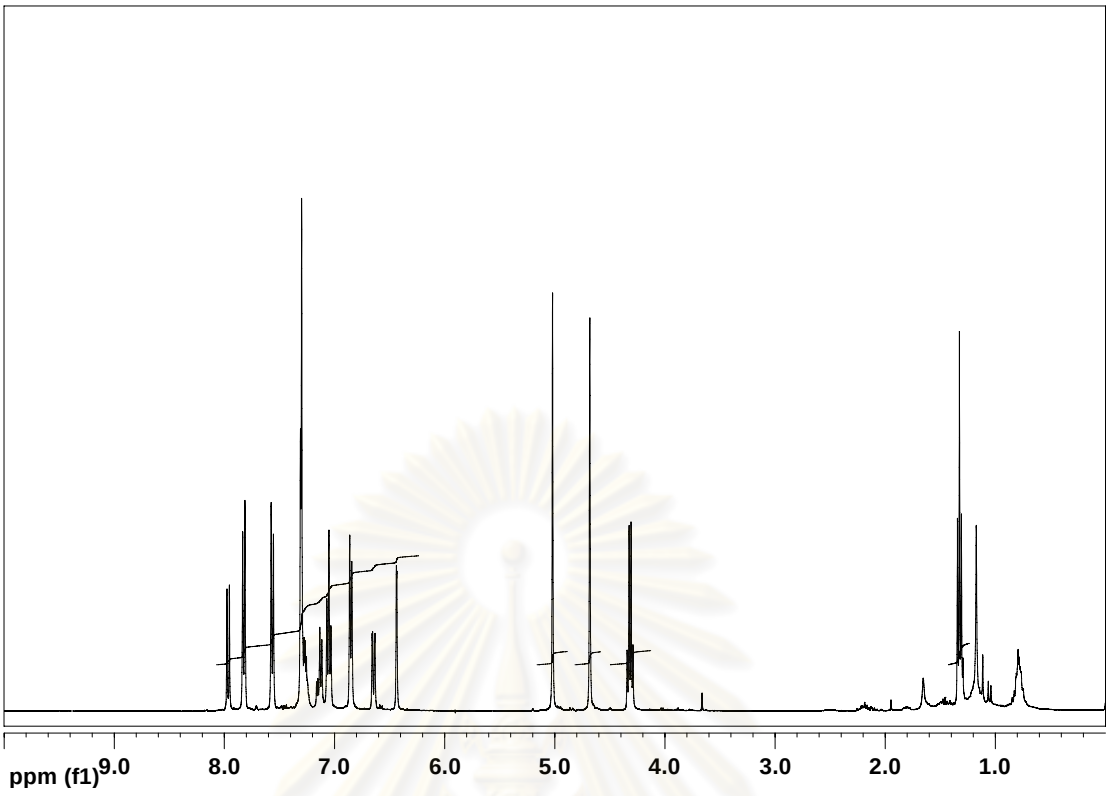

Figure 66 ^{1}H-NMR spectra of compound **176g**

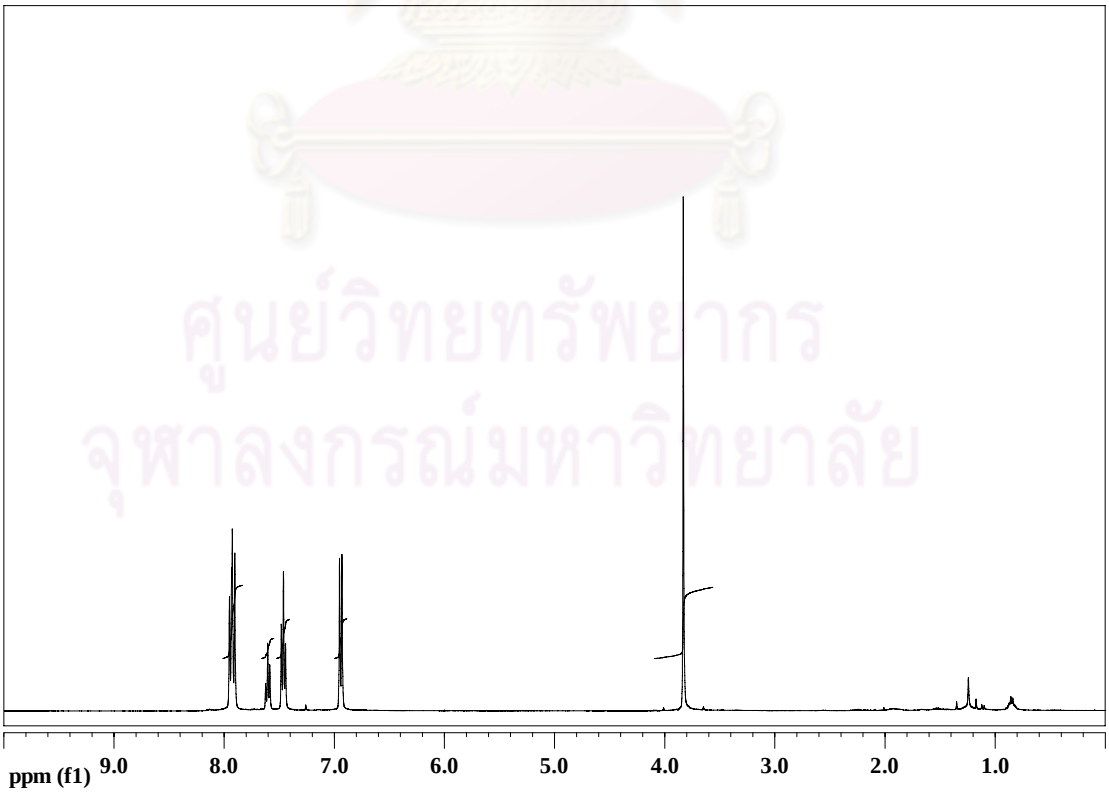

Figure 67 ^{1}H-NMR spectra of compound **177a**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

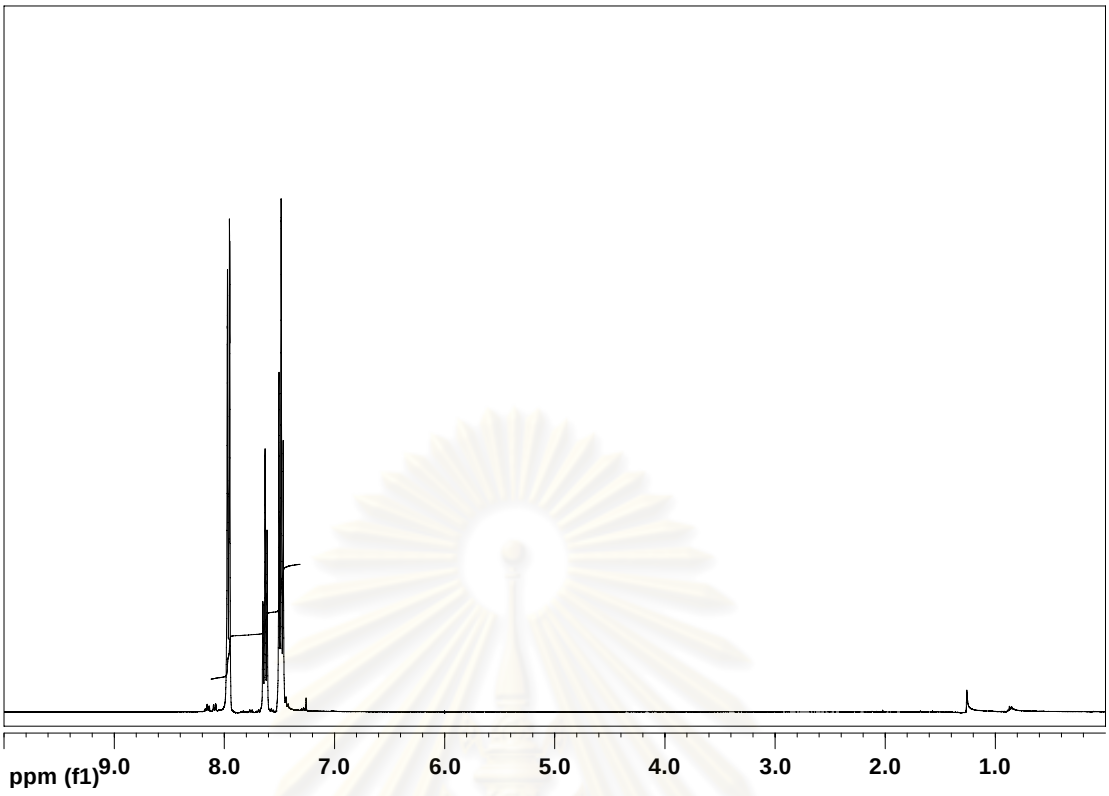

Figure 68 ^{1}H-NMR spectra of compound **177b**

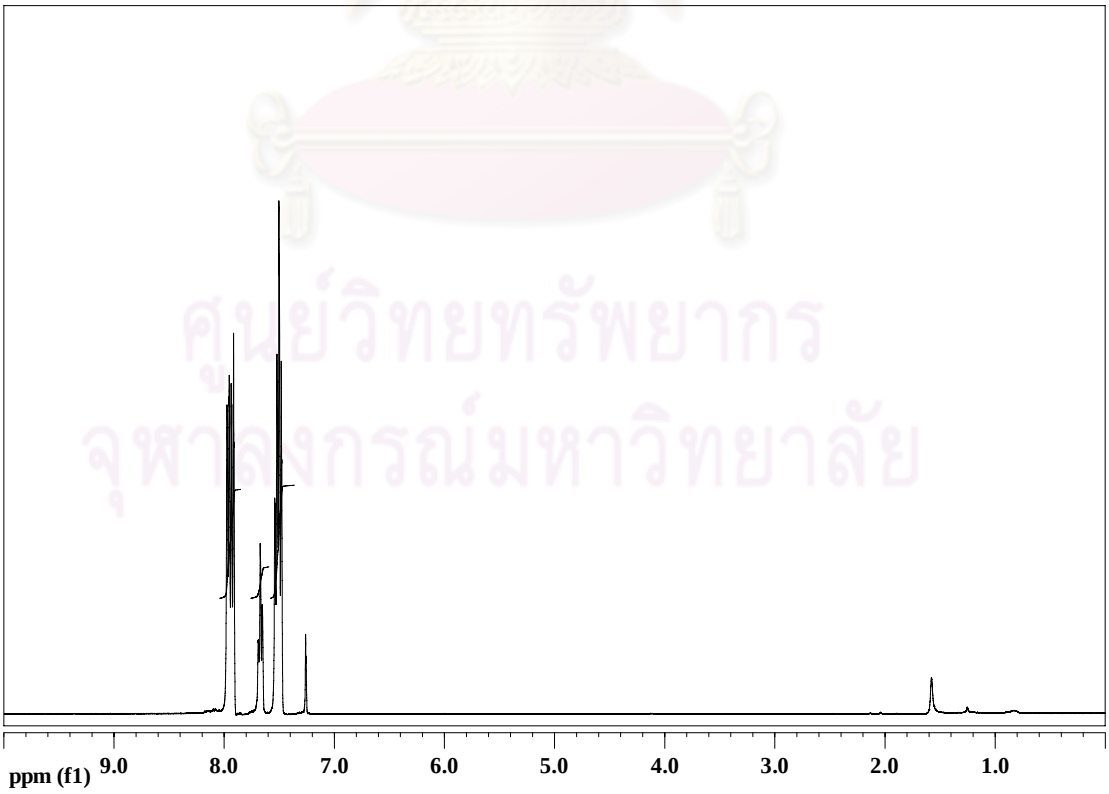

Figure 69 ^{1}H-NMR spectra of compound **177c**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

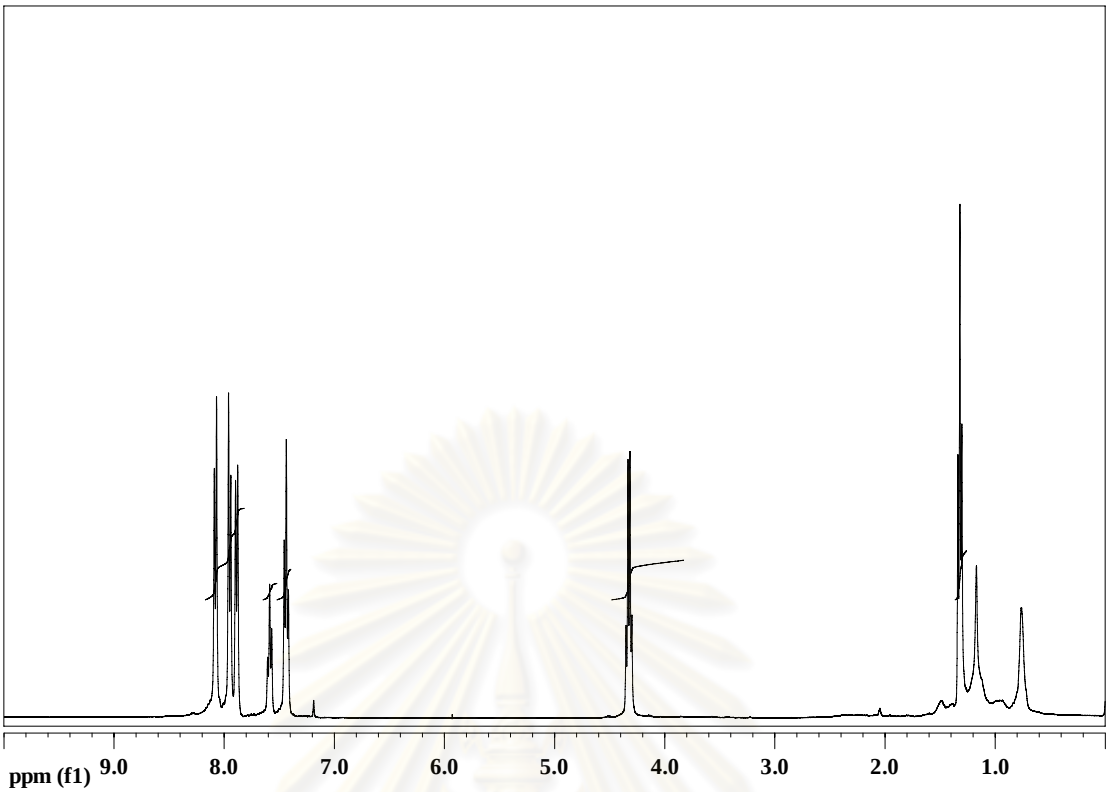

Figure 70 ^{1}H-NMR spectra of compound **177d**

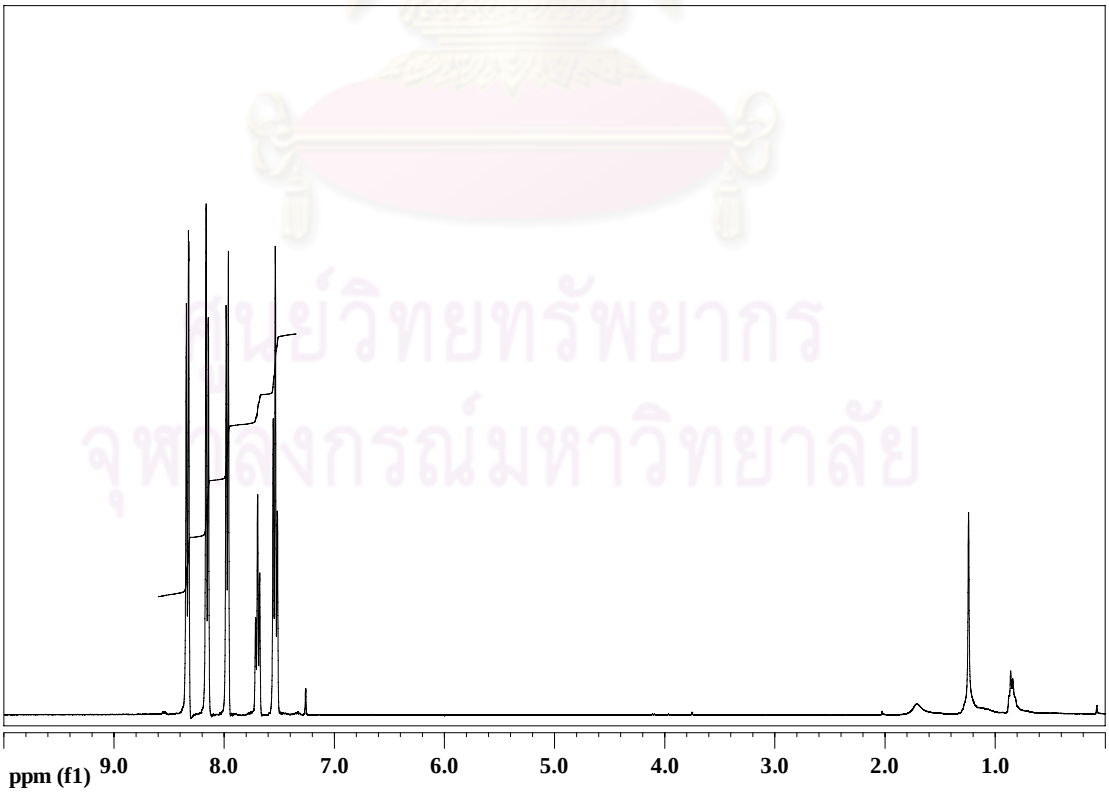

Figure 71 ^{1}H-NMR spectra of compound **177e**

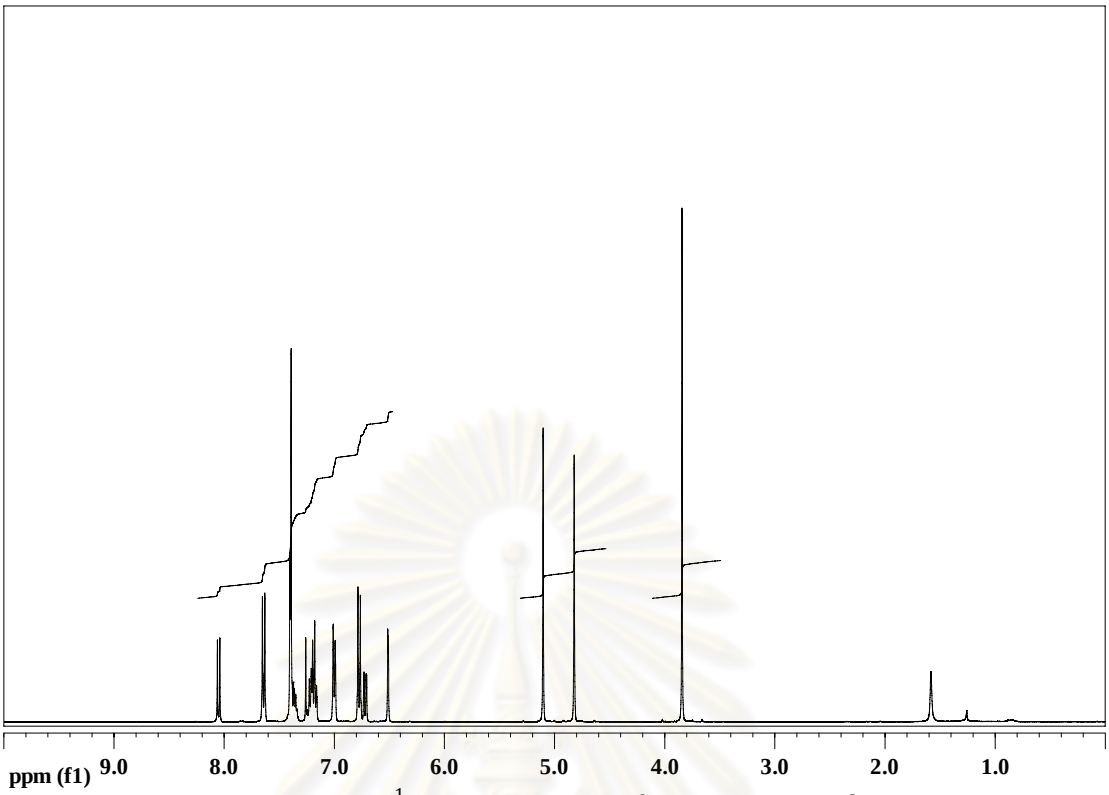

Figure 72 ^{1}H-NMR spectra of compound **177f**

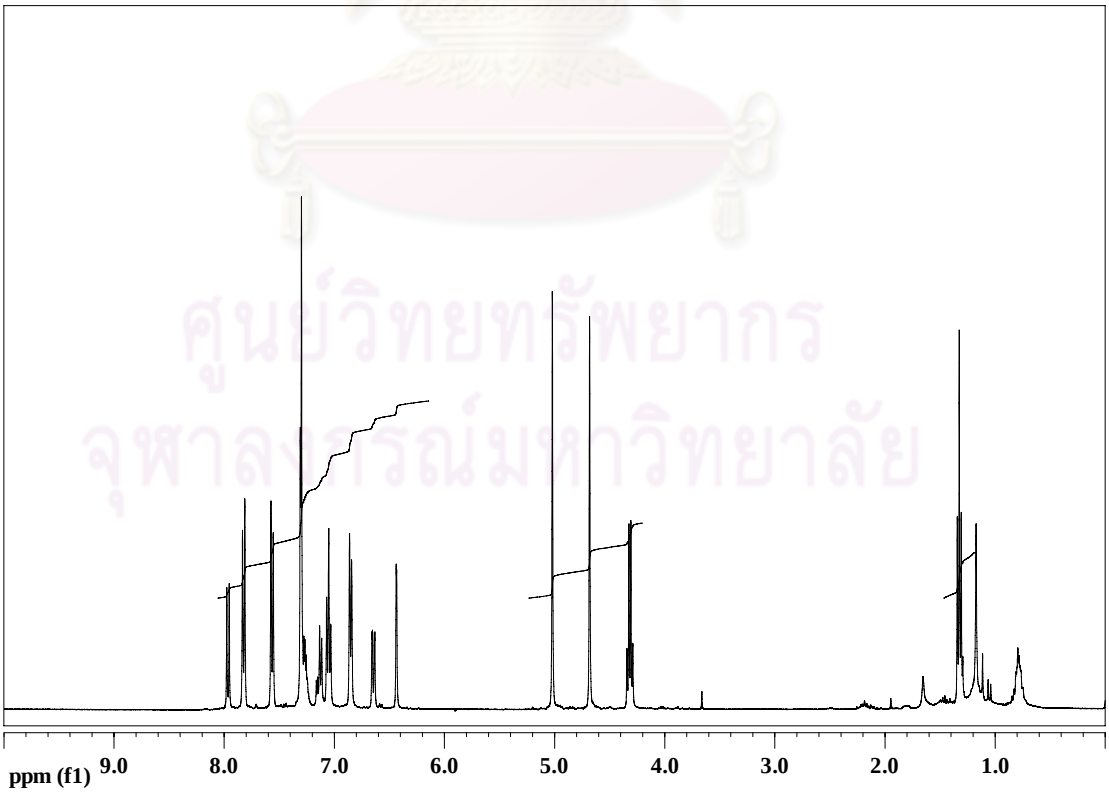

Figure 73 ^{1}H-NMR spectra of compound **177g**

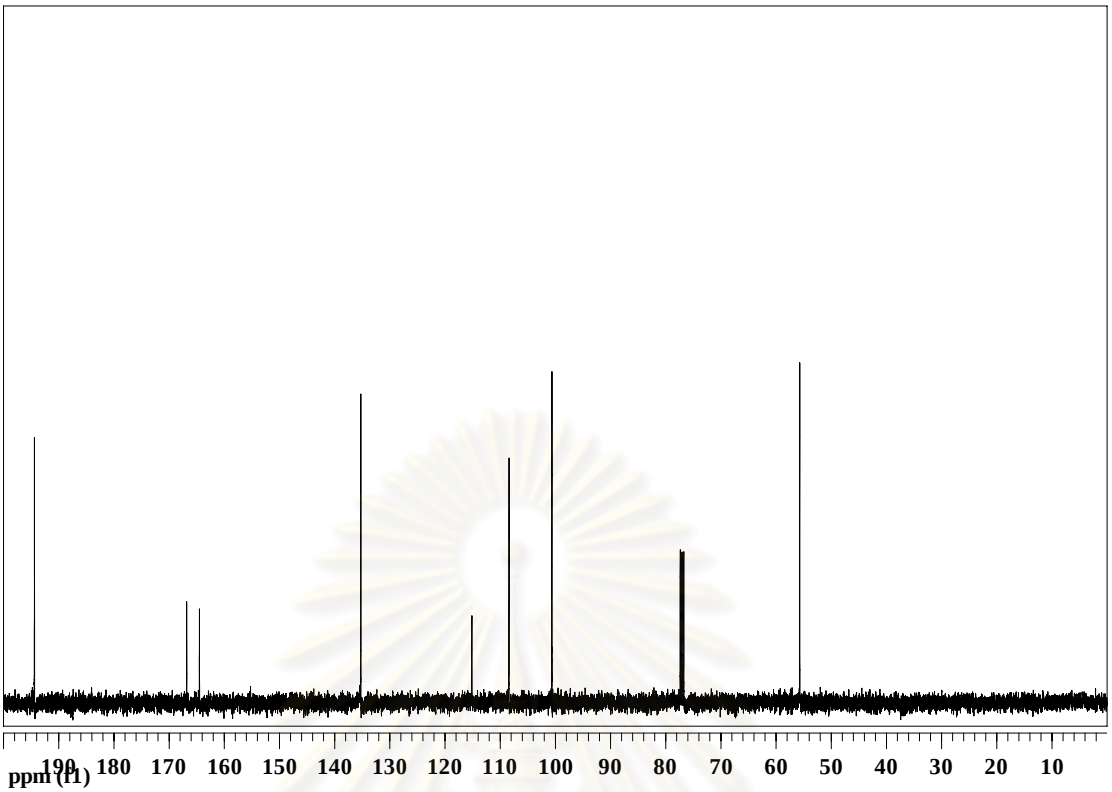

Figure 74 ^{13}C-NMR spectra of compound **146**

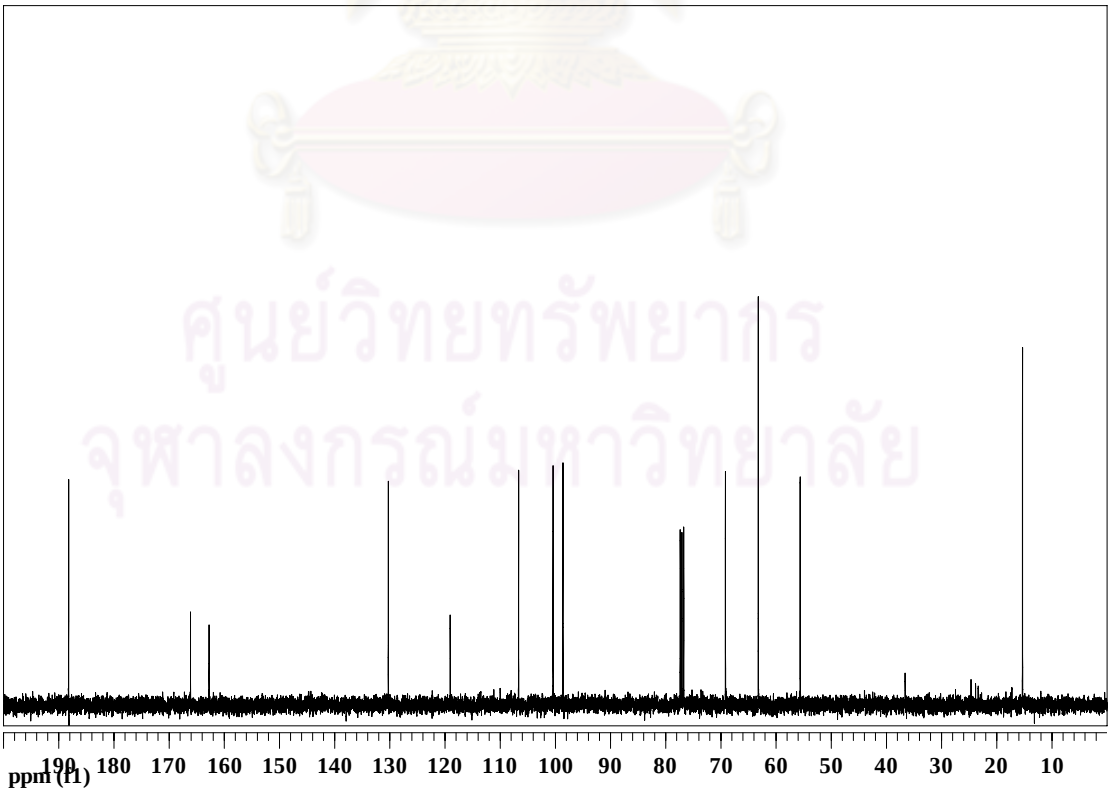

Figure 75 ^{13}C-NMR spectra of compound **147**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

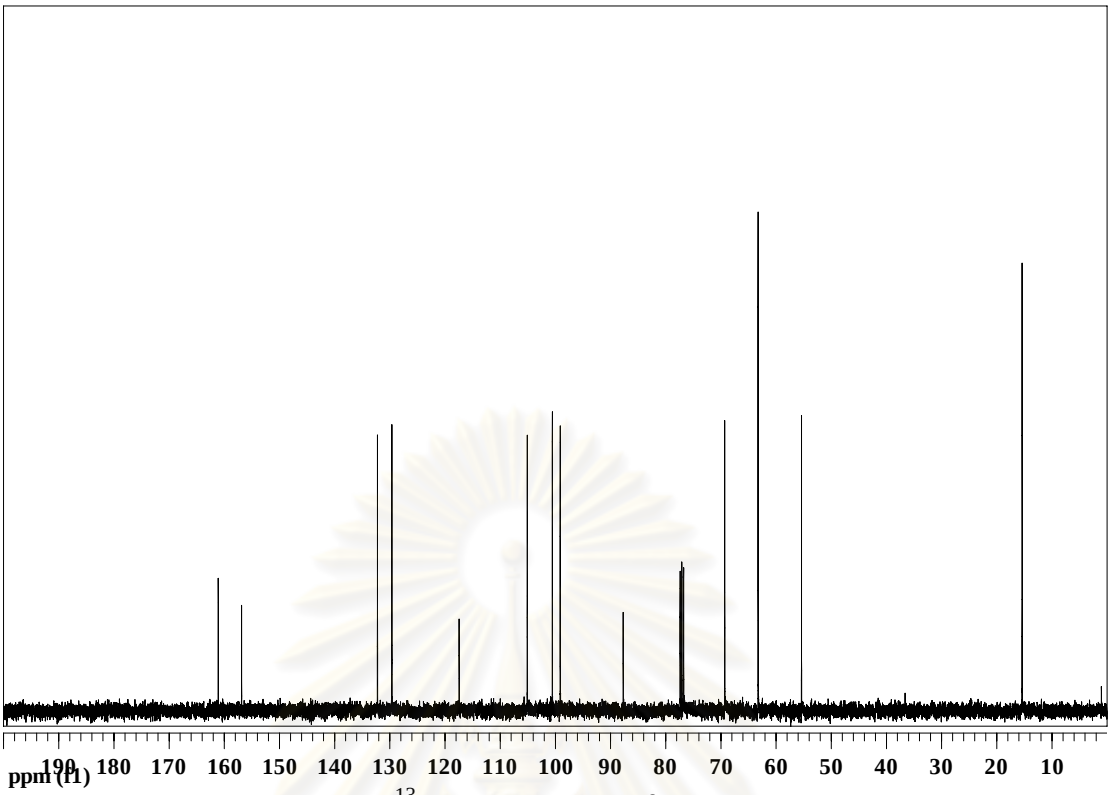

Figure 76 ^{13}C-NMR spectra of compound **148**

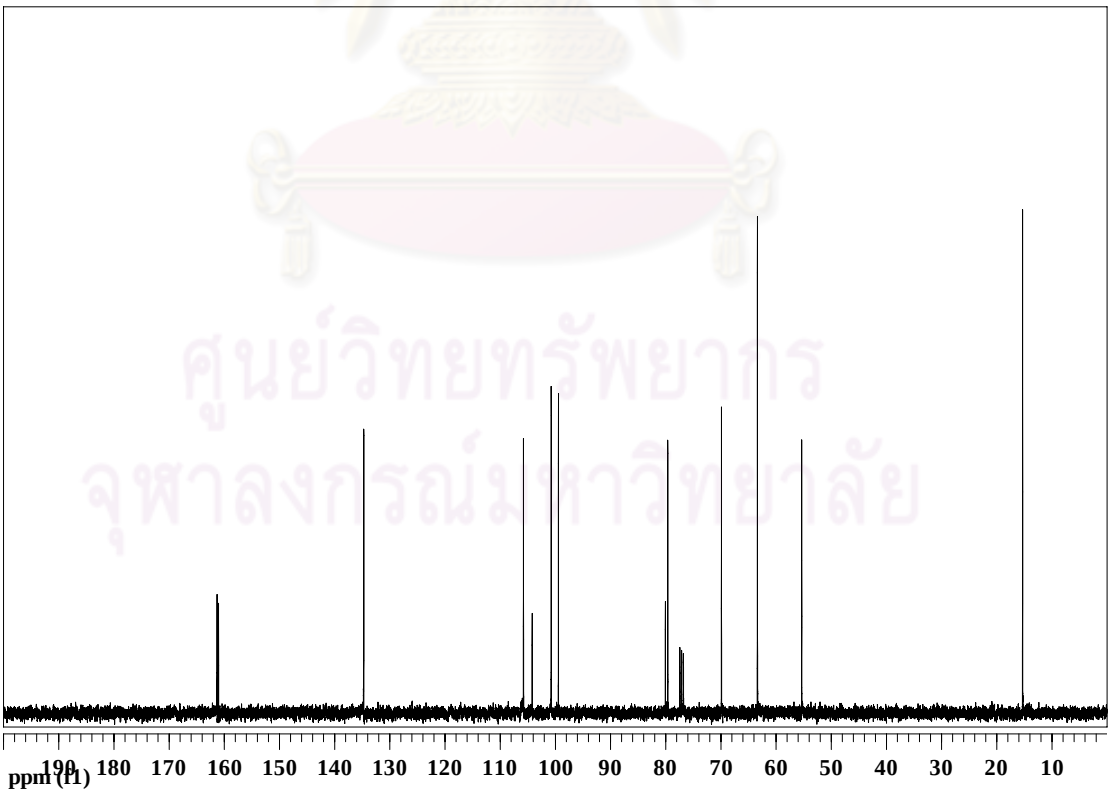

Figure 77 ^{13}C-NMR spectra of compound **20**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

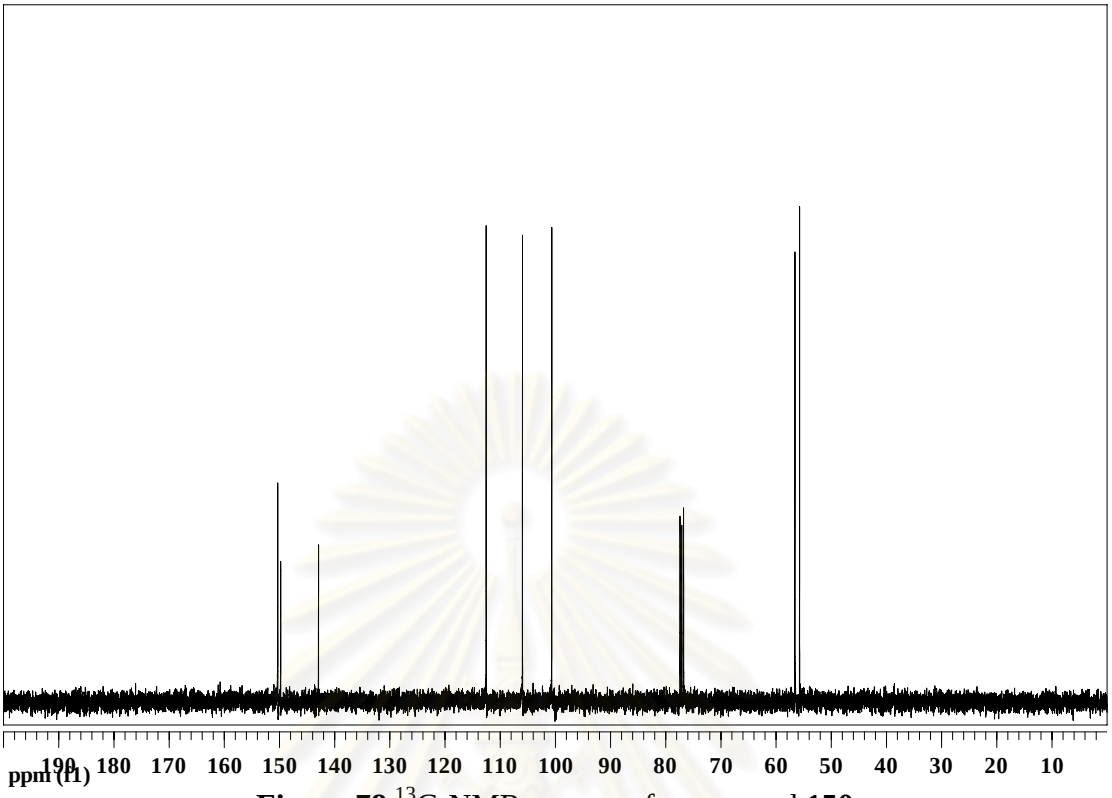

Figure 78 ^{13}C-NMR spectra of compound **150**

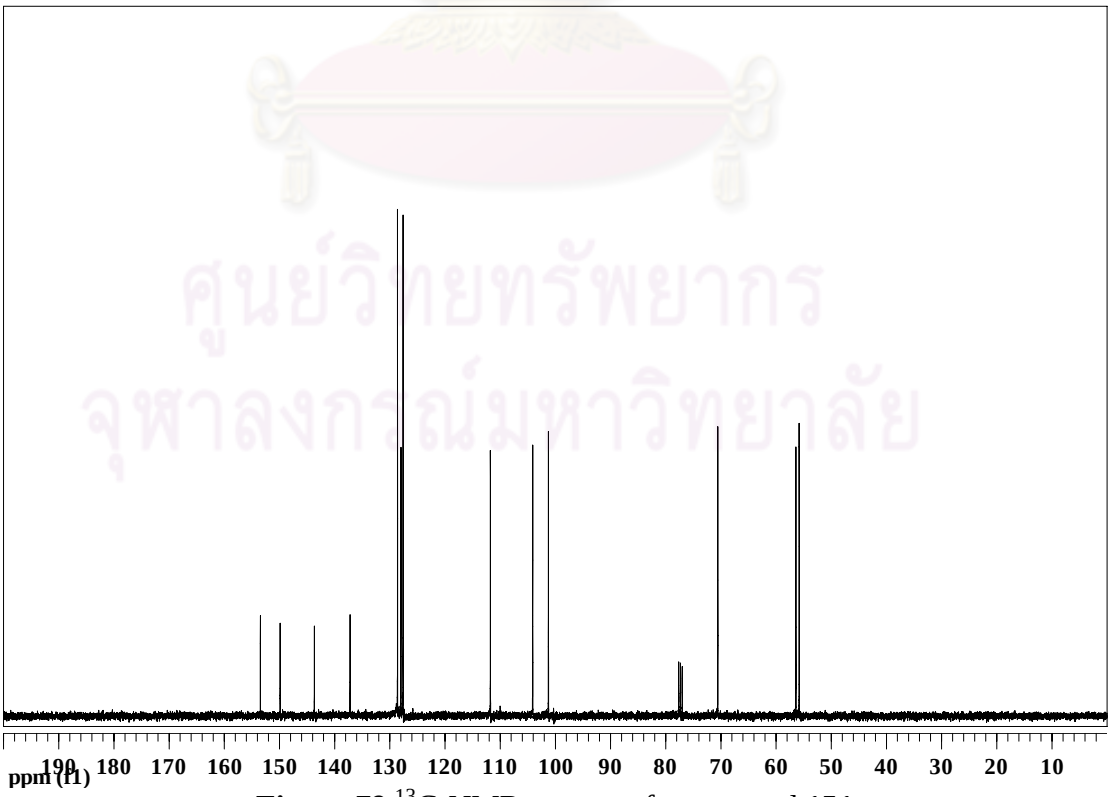

Figure 79 ^{13}C-NMR spectra of compound **151**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

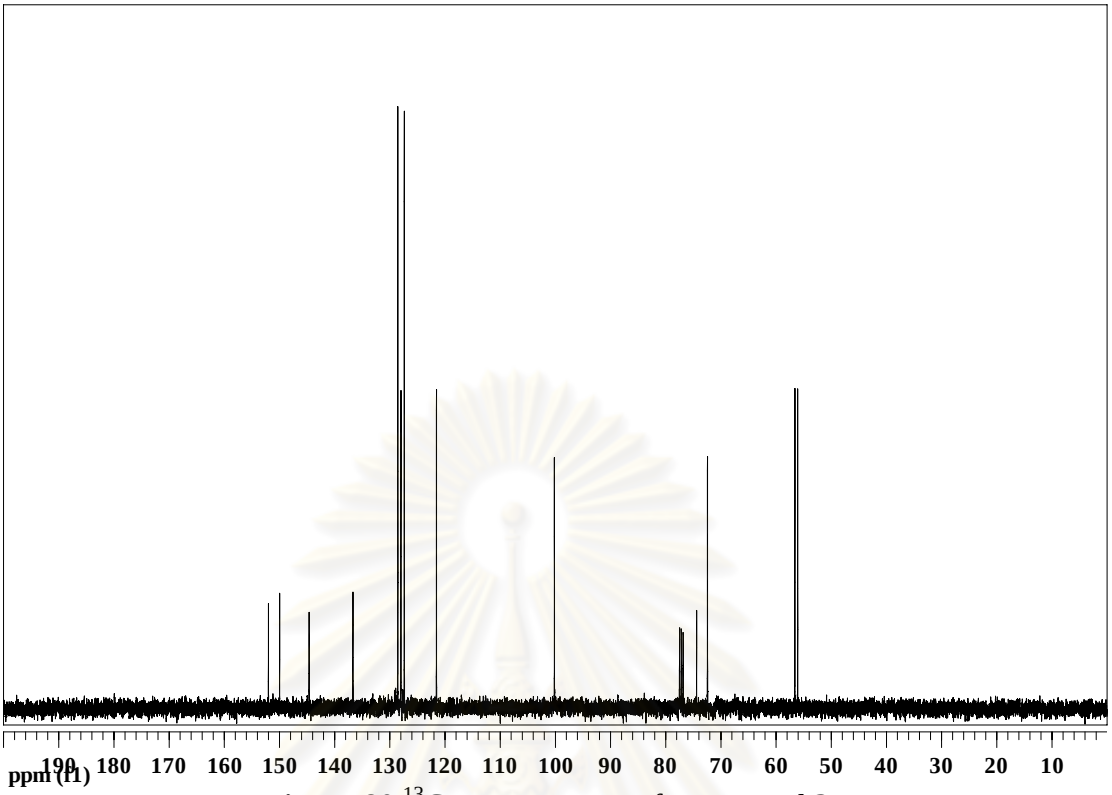

Figure 80 ^{13}C-NMR spectra of compound **21**

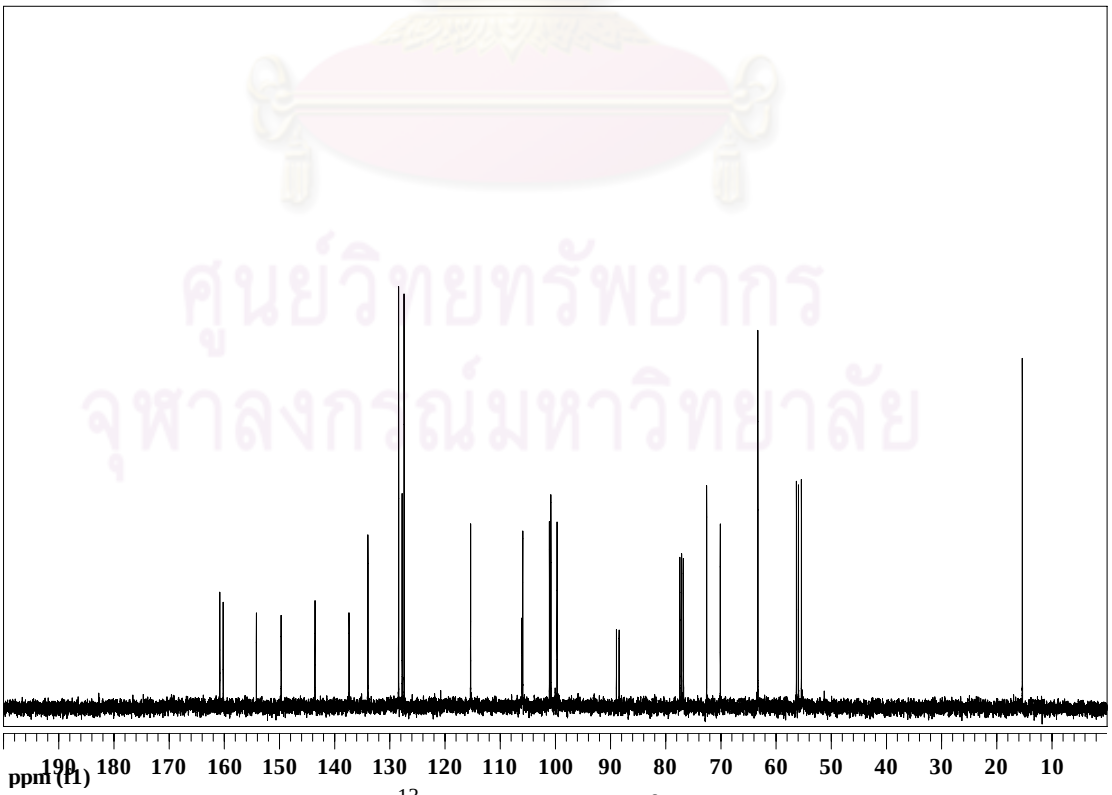

Figure 81 ^{13}C-NMR spectra of compound **152**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

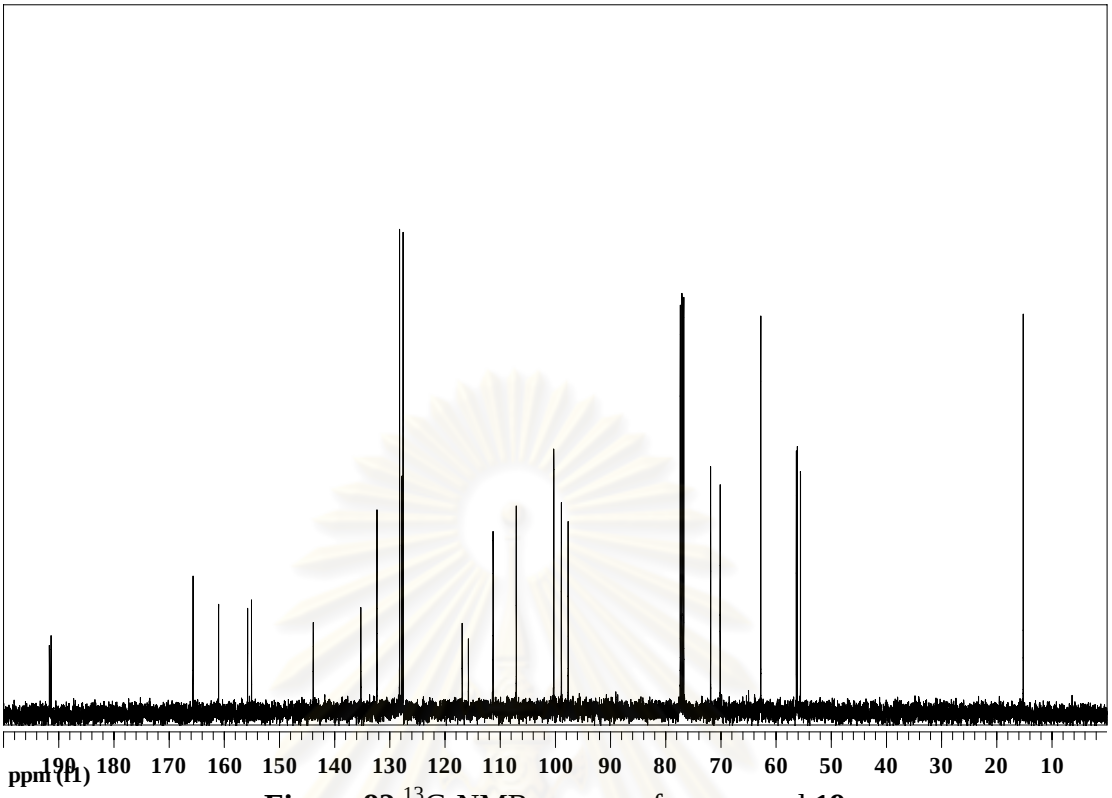

Figure 82 ^{13}C-NMR spectra of compound **19**

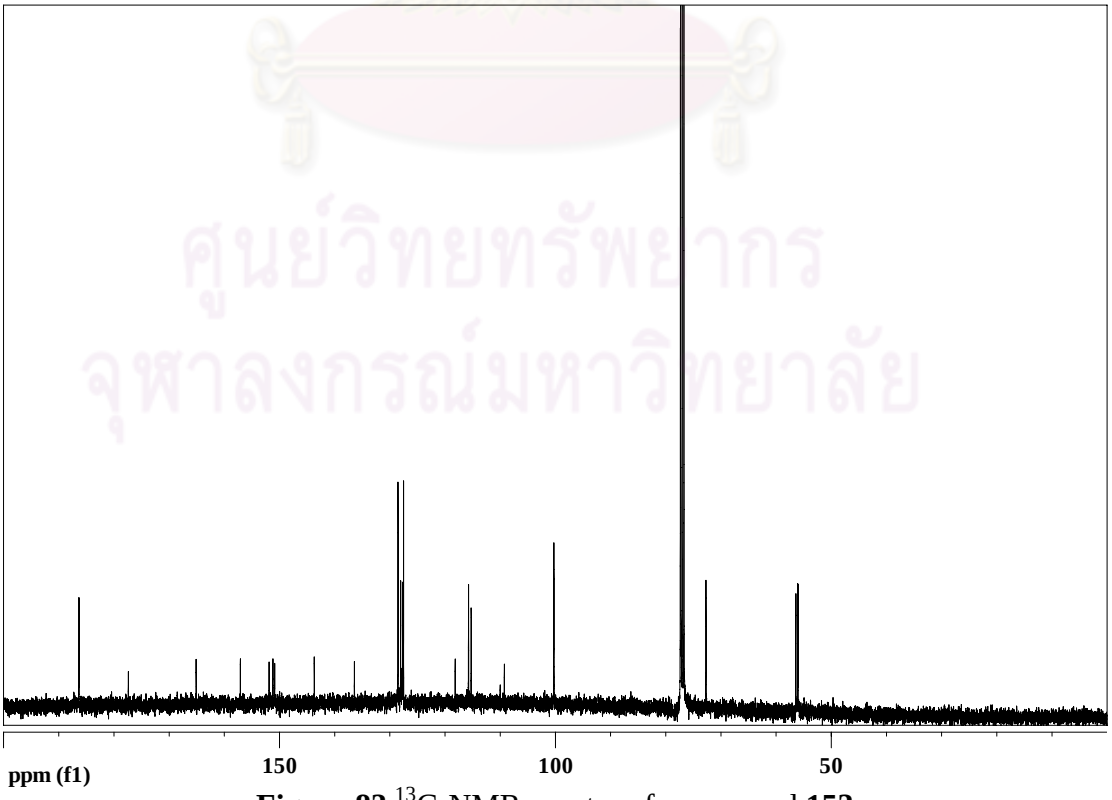

Figure 83 ^{13}C-NMR spectra of compound **153**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

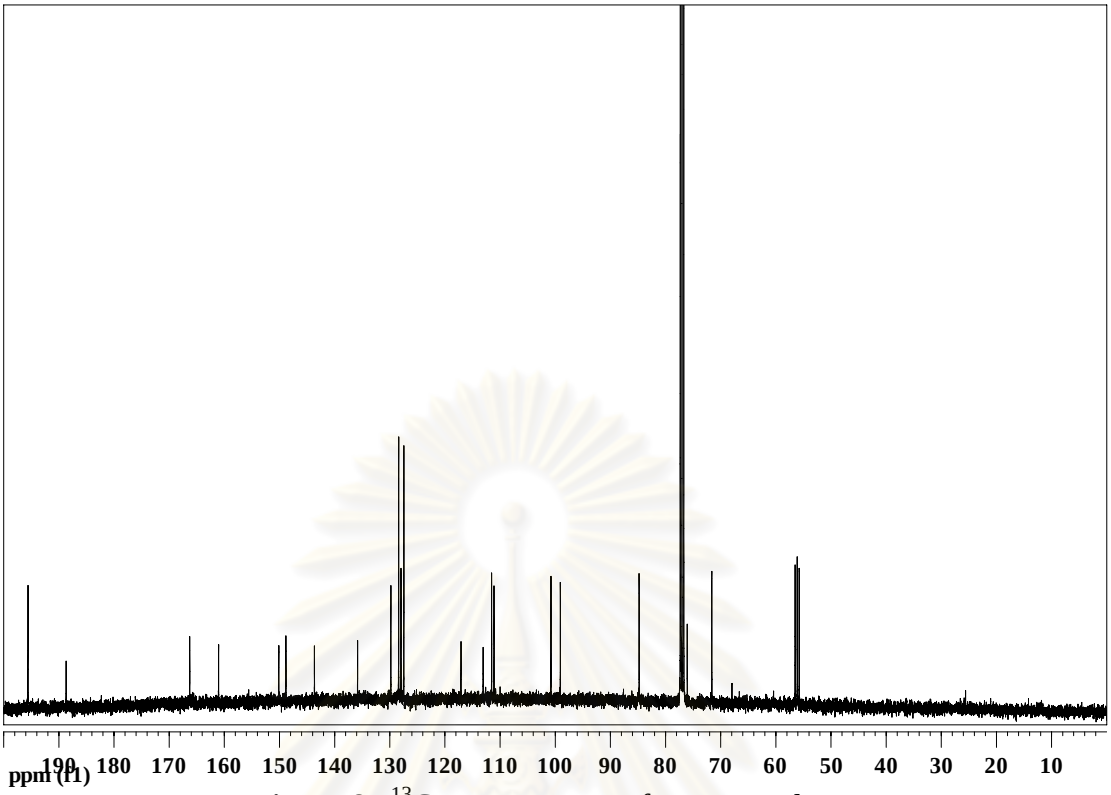

Figure 84 ^{13}C-NMR spectra of c ompound **154**

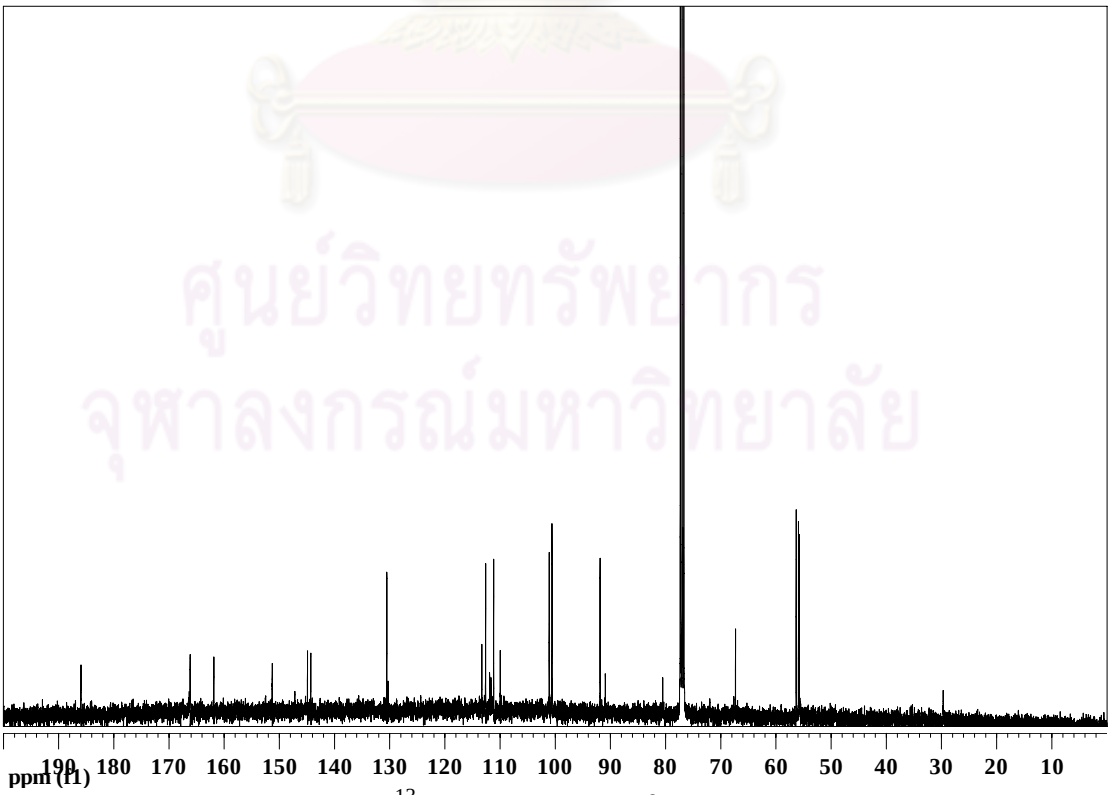

Figure 85 ^{13}C-NMR spectra of compound **155**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

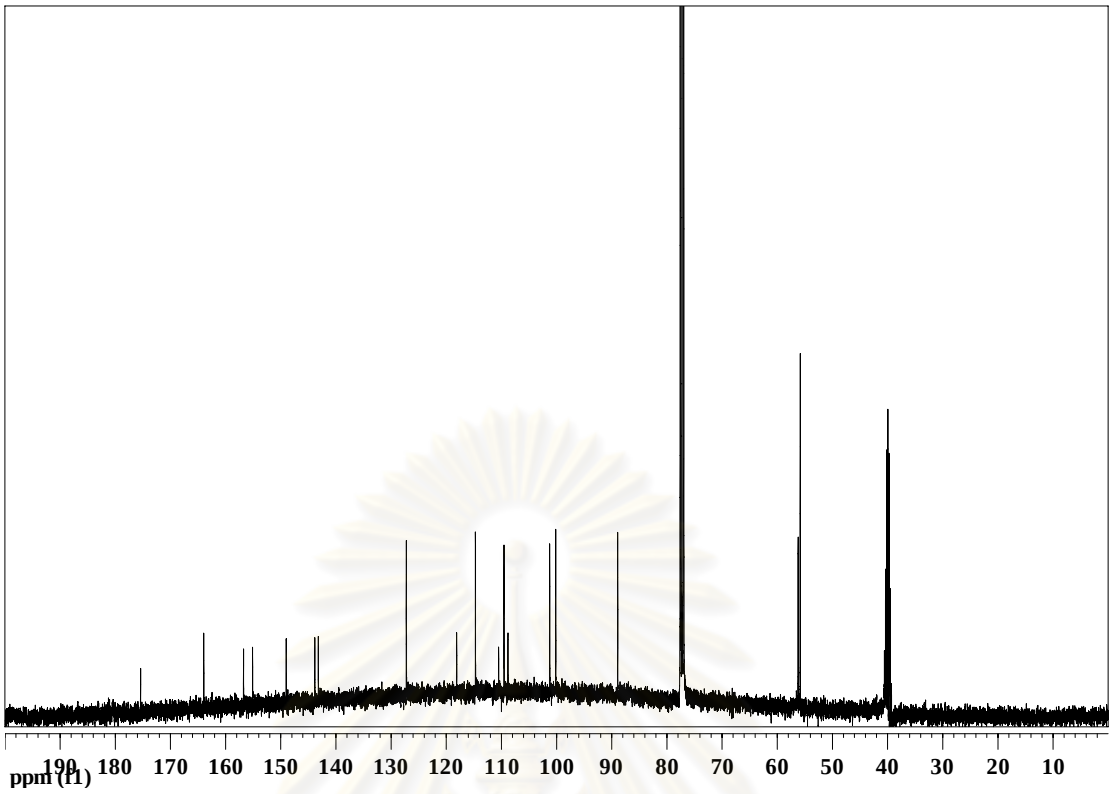

Figure 86 ^{13}C-NMR spectra of compound **1**

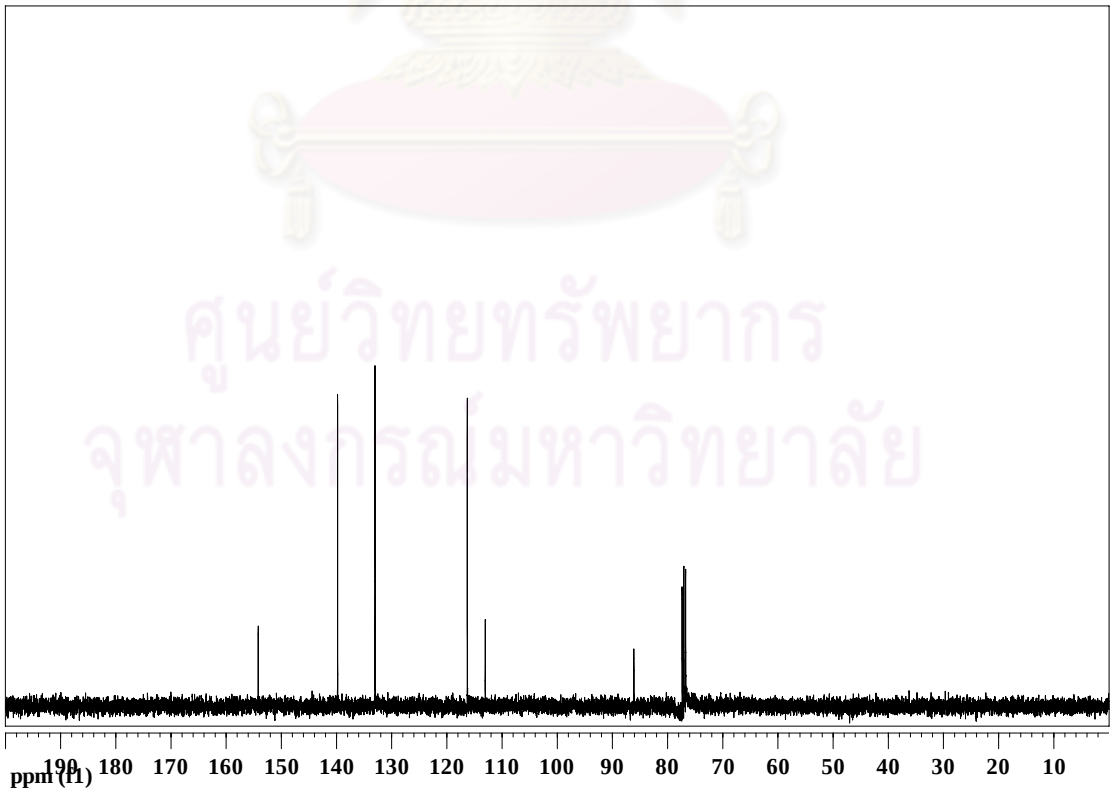

Figure 87 ^{13}C-NMR spectra of compound **1**57

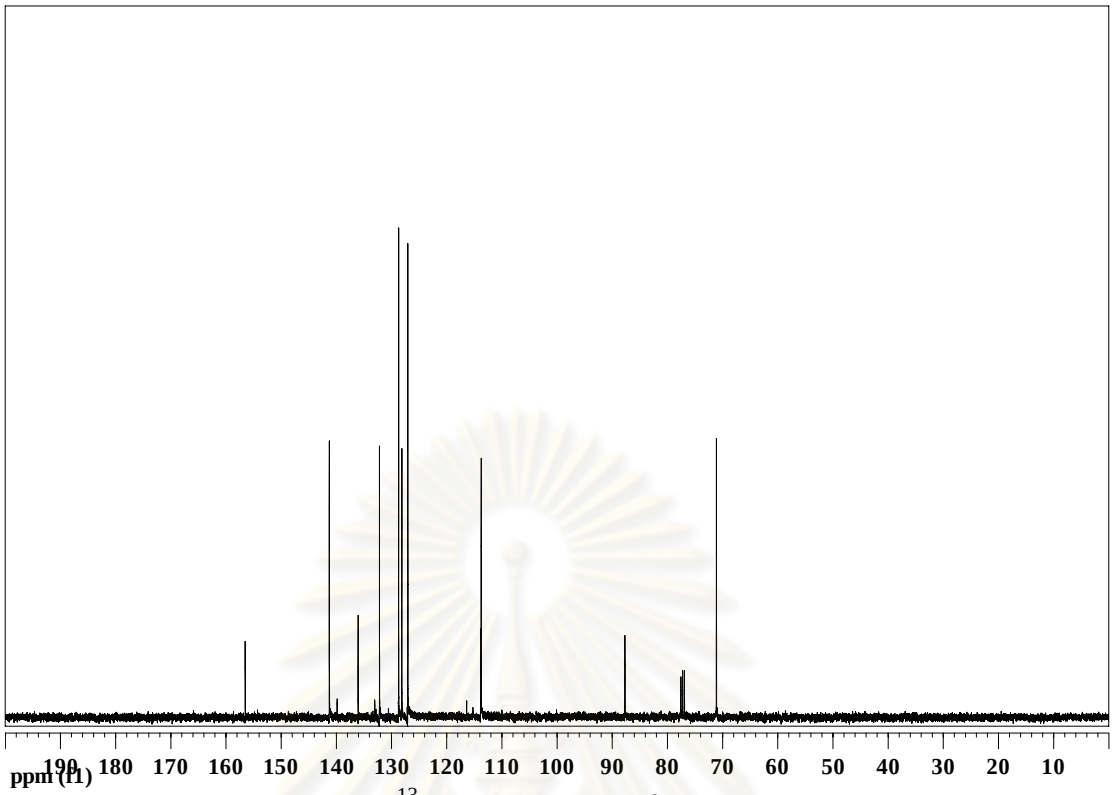

Figure 88 ^{13}C-NMR spectra of compound **158**

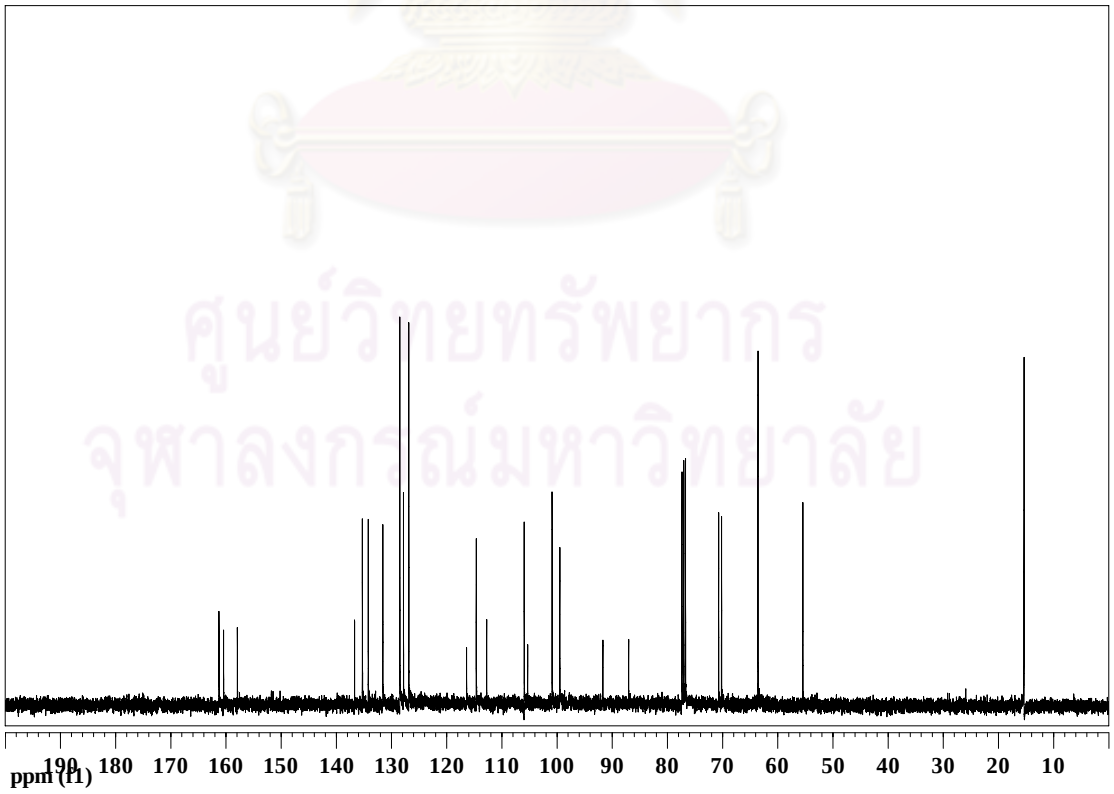

Figure 89 ^{13}C-NMR spectra of compound **159**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

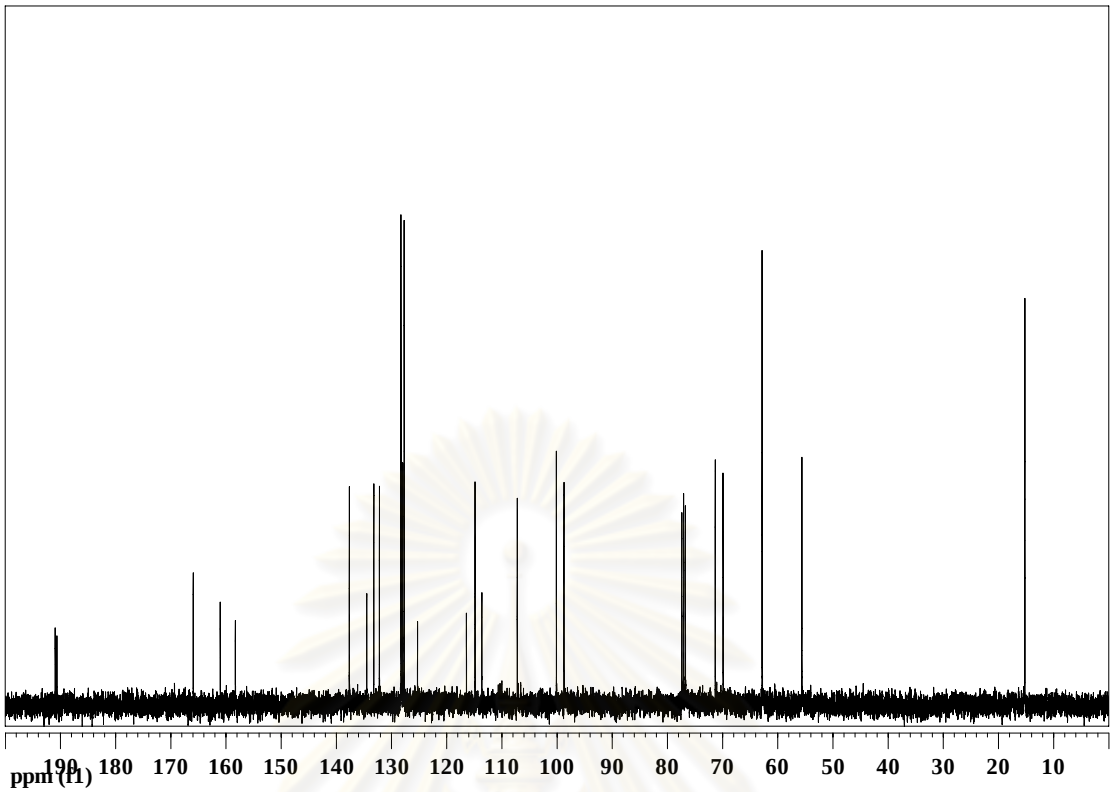

Figure 90 ^{13}C-NMR spectra of compound **160**

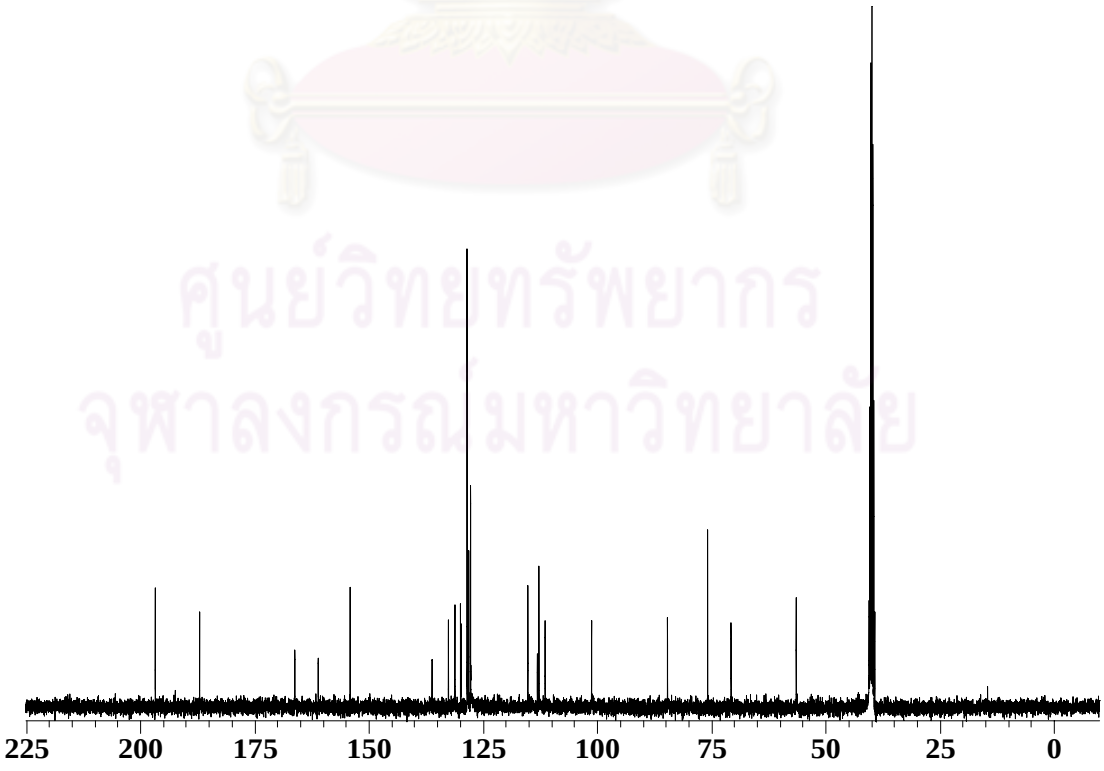

Figure 91 ^{13}C-NMR spectra of compound **161**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

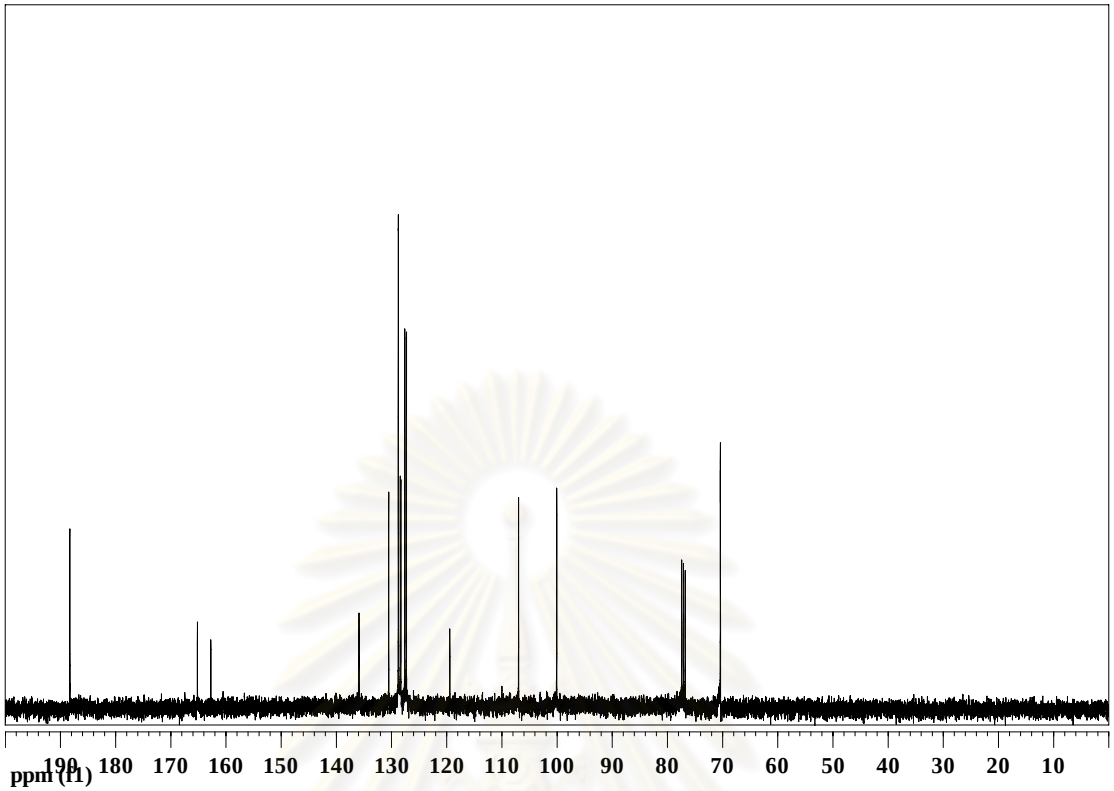

Figure 92 ^{13}C-NMR spectra of compound **164**

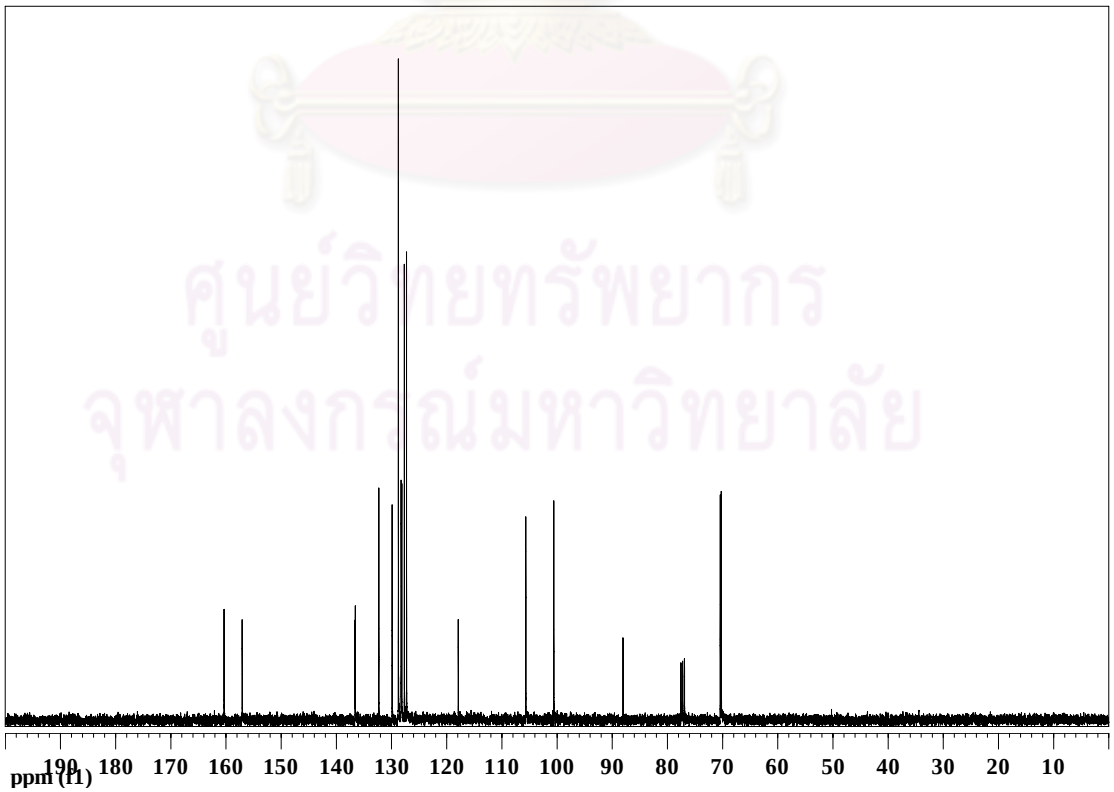

Figure 93 ^{13}C-NMR spectra of compound **165**

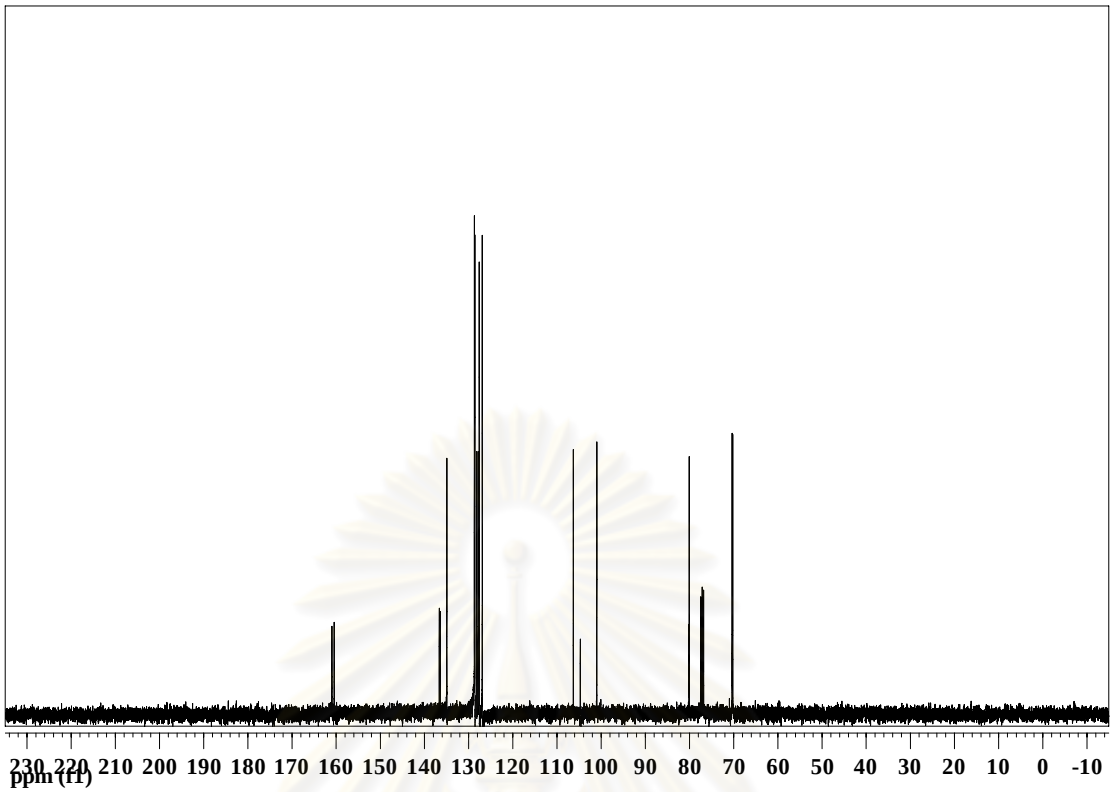

Figure 94 ^{13}C-NMR spectra of compound **166**

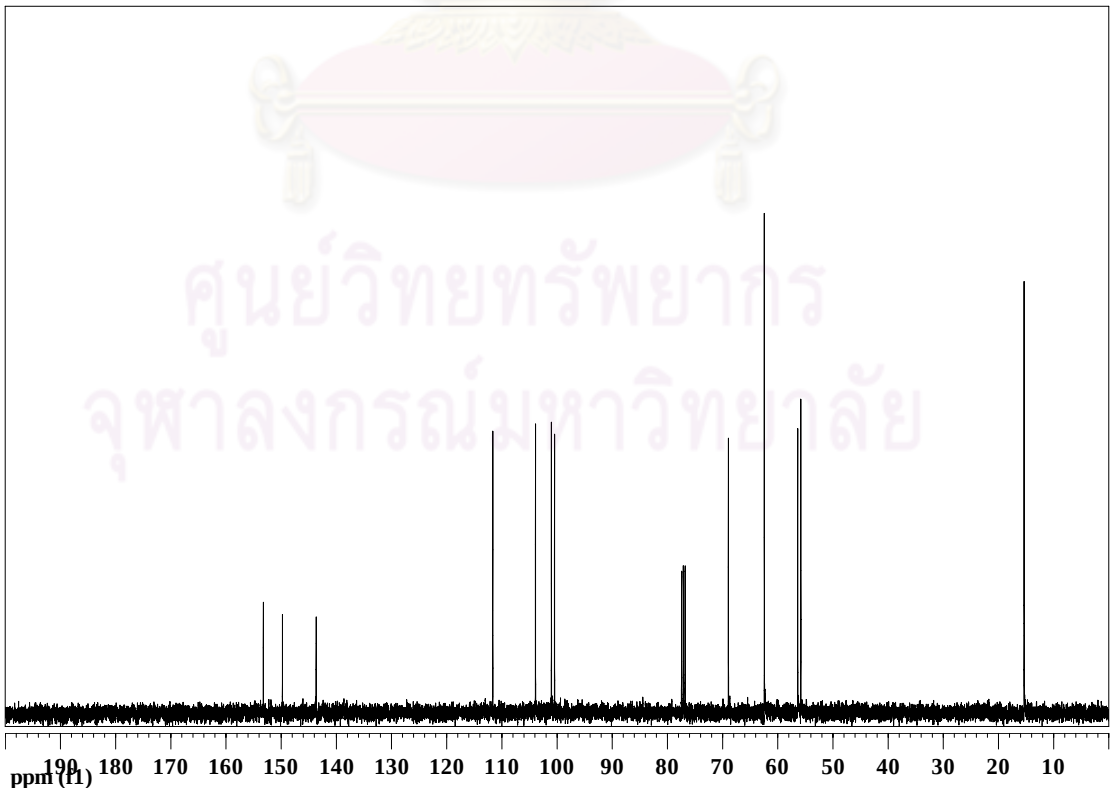

Figure 95 ^{13}C-NMR spectra of compound **167**

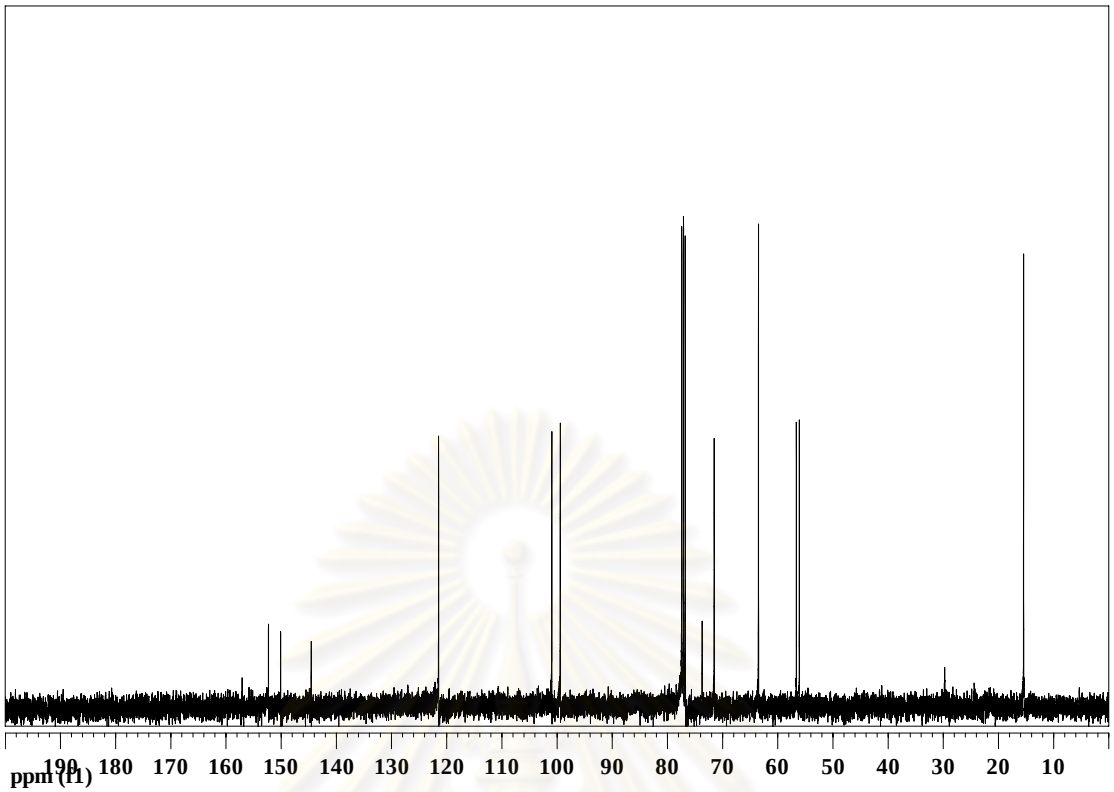

Figure 96 ^{13}C-NMR spectra of compound **168**

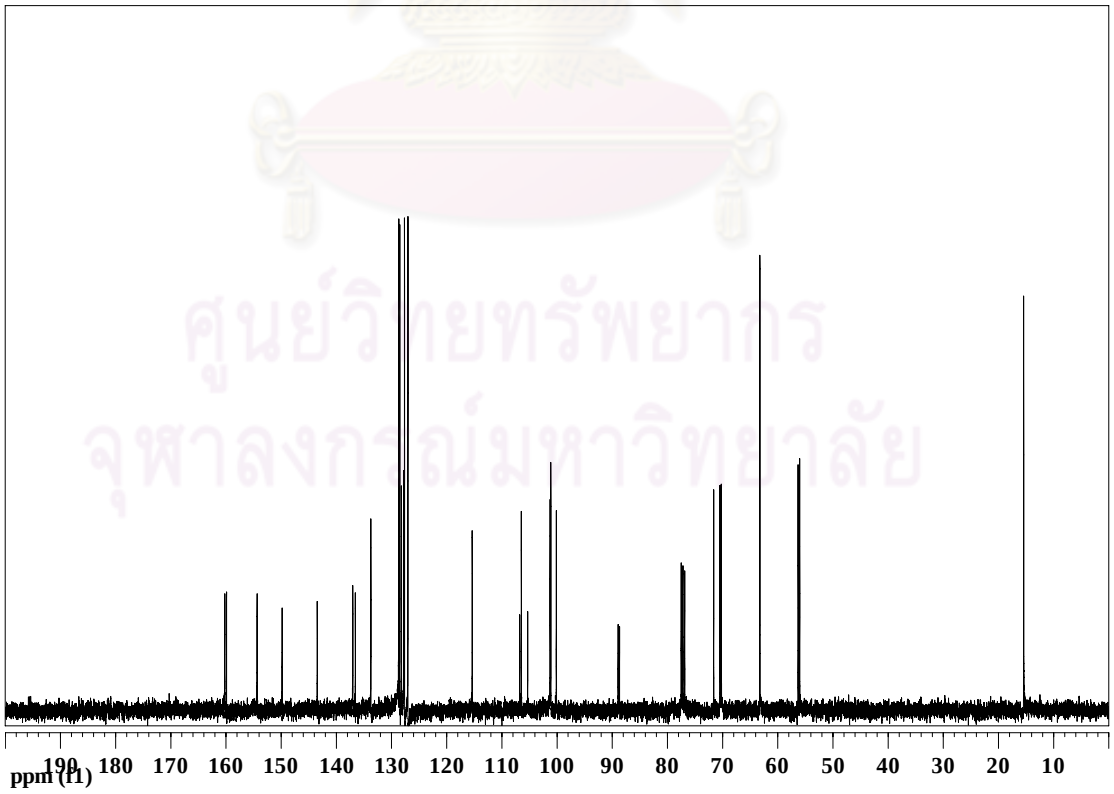

Figure 97 ^{13}C-NMR spectra of compound **169**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

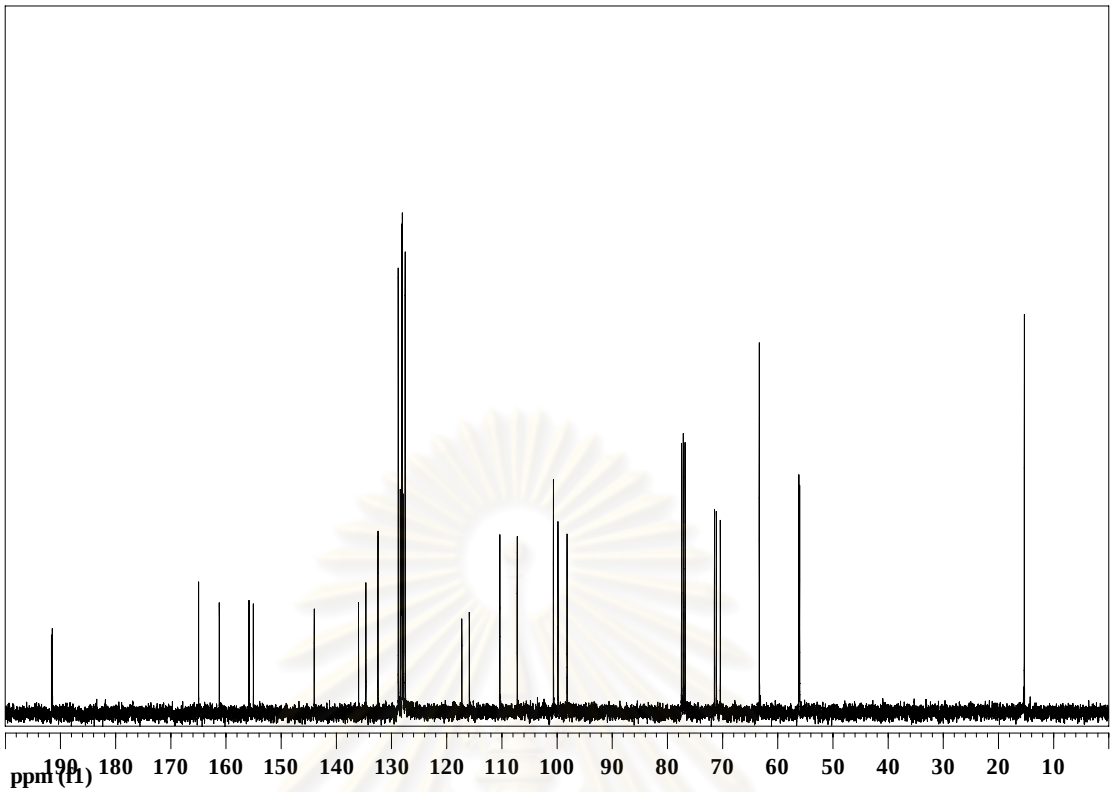

Figure 98 ^{13}C-NMR spectra of compound **170**

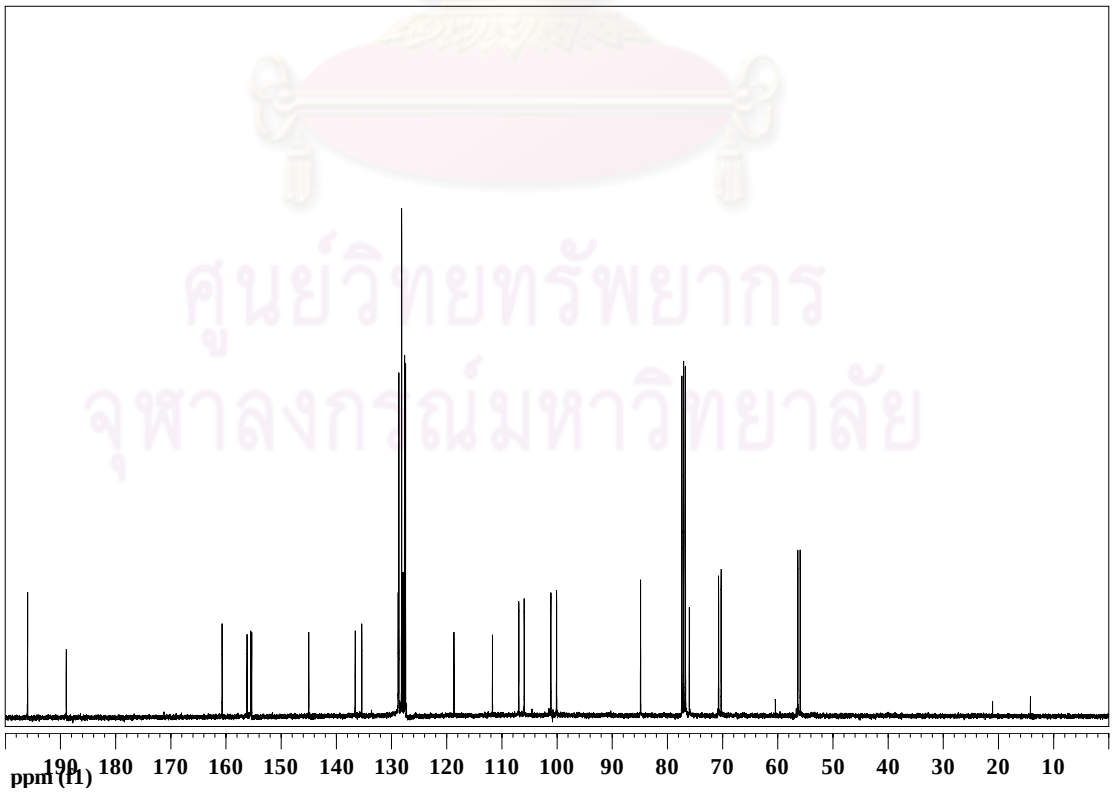

Figure 99 ^{13}C-NMR spectra of compound **171**

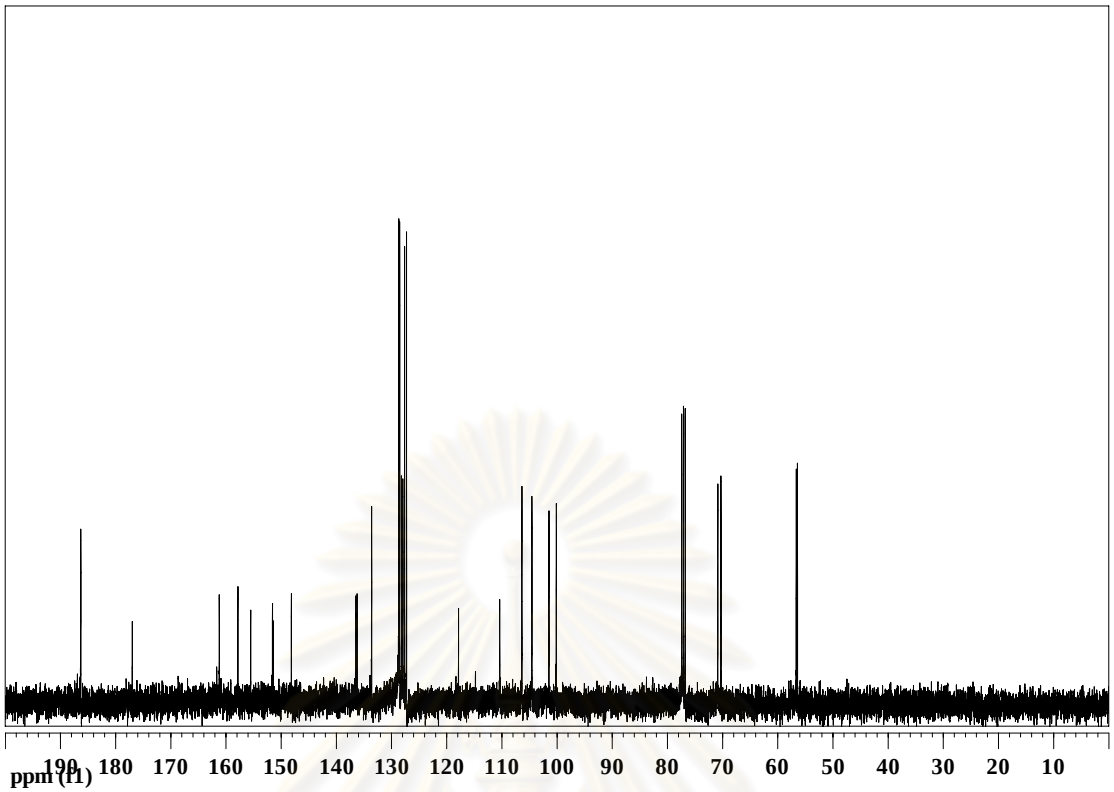

Figure 100 ^{13}C-NMR spectra of compound **172**

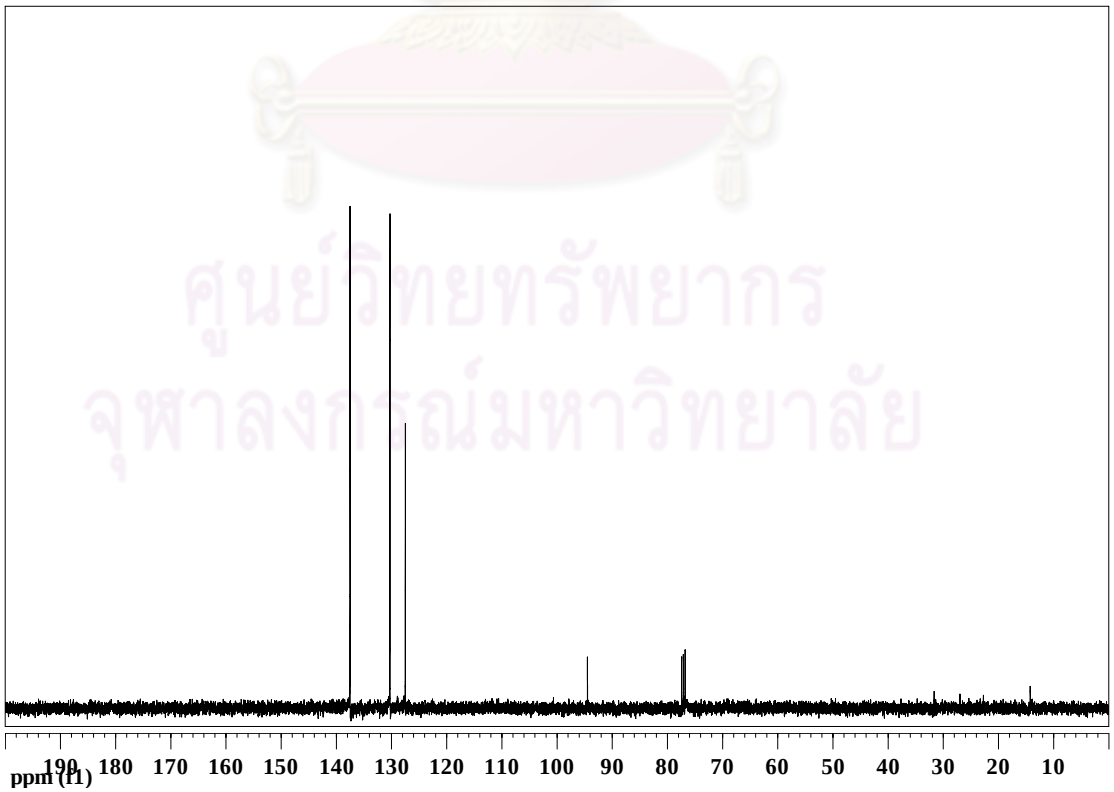

Figure 101 ^{13}C-NMR spectra of compound **174a**

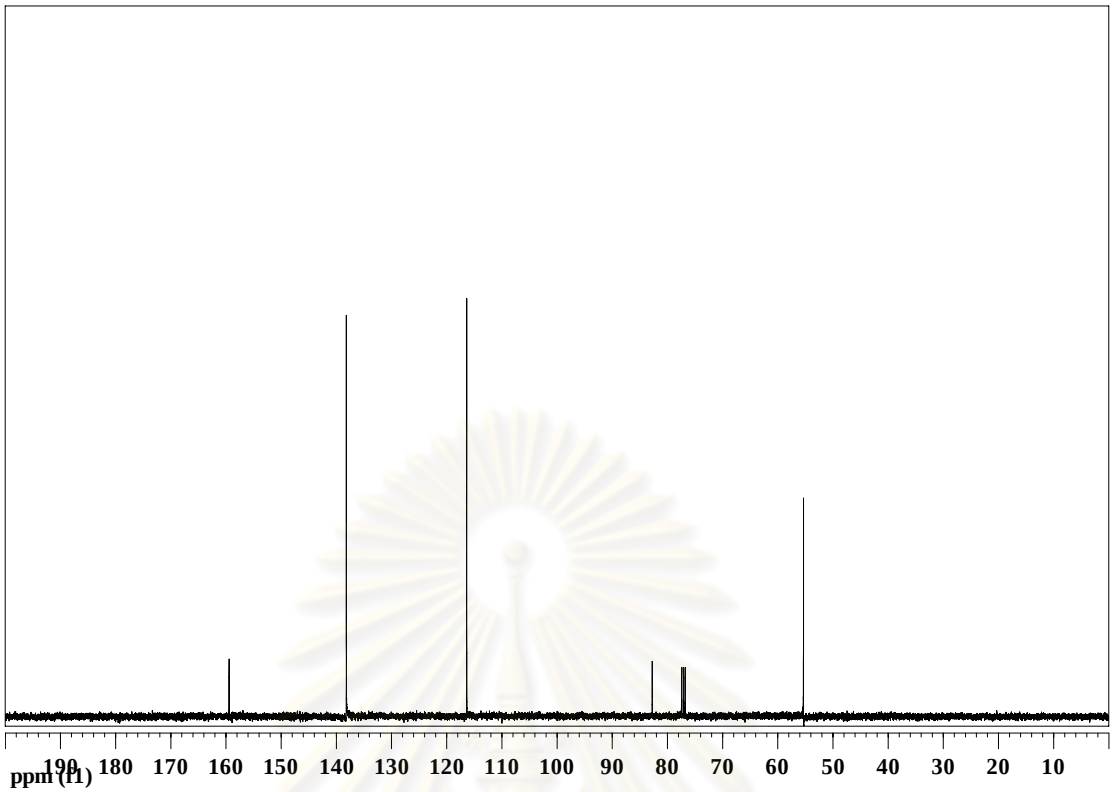

Figure 102 ^{13}C-NMR spectra of compound **174b**

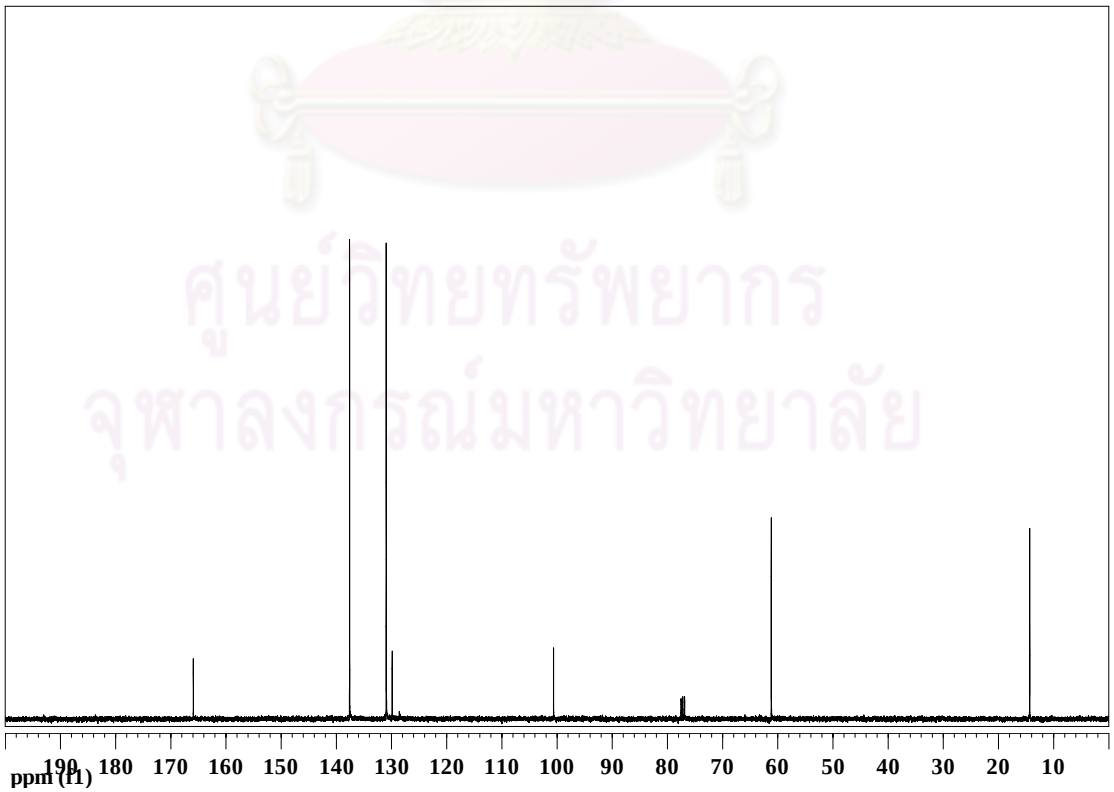

Figure 103 ^{13}C-NMR spectra of compound **174c**

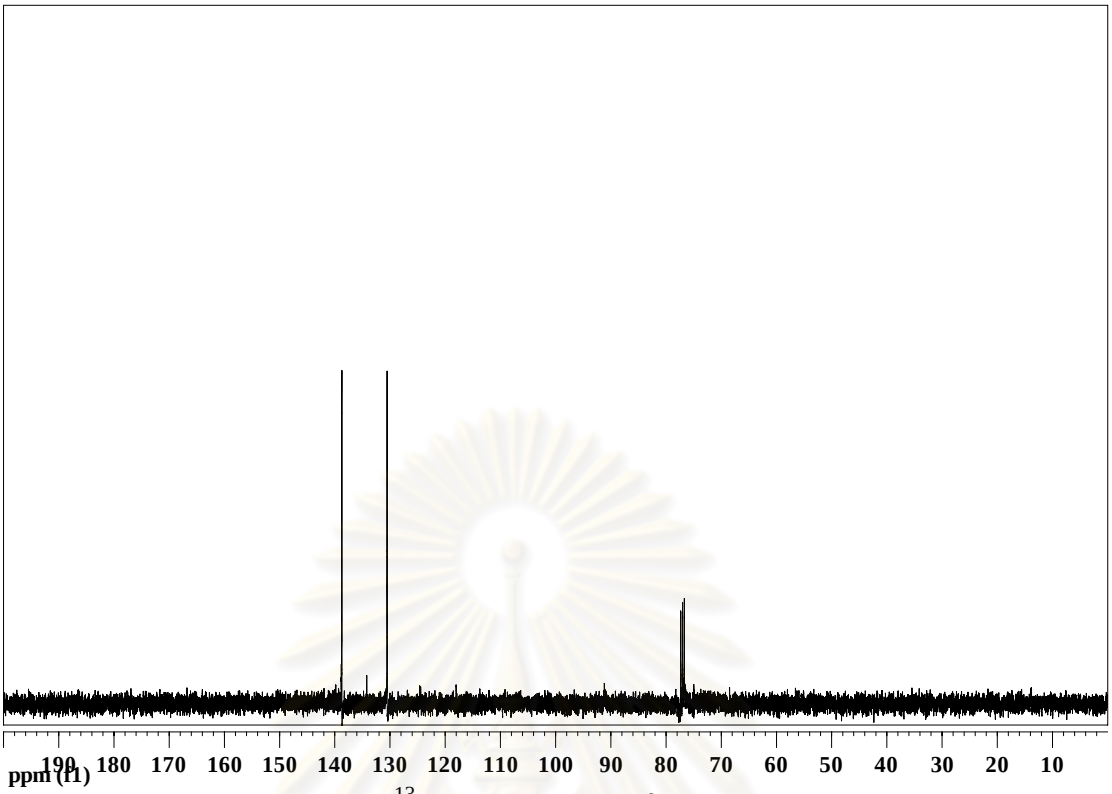

Figure 104 ^{13}C-NMR spectra of compound **174d**

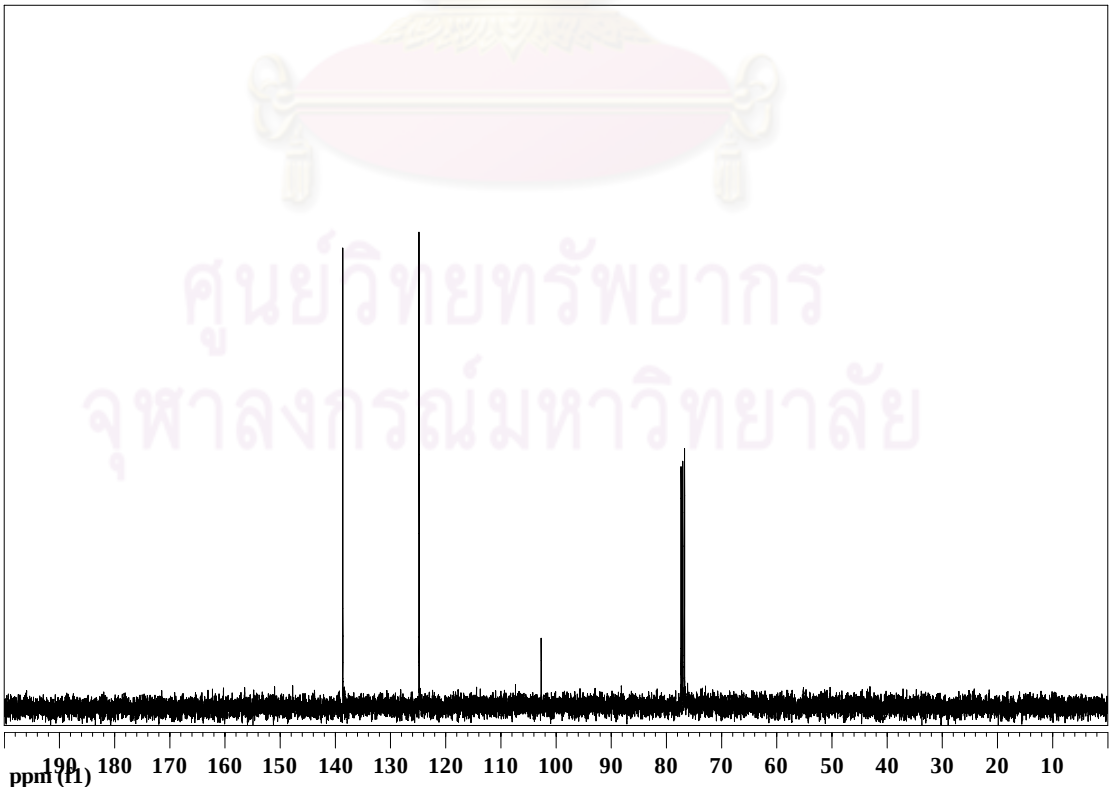

Figure 105 ^{13}C-NMR spectra of compound **174e**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

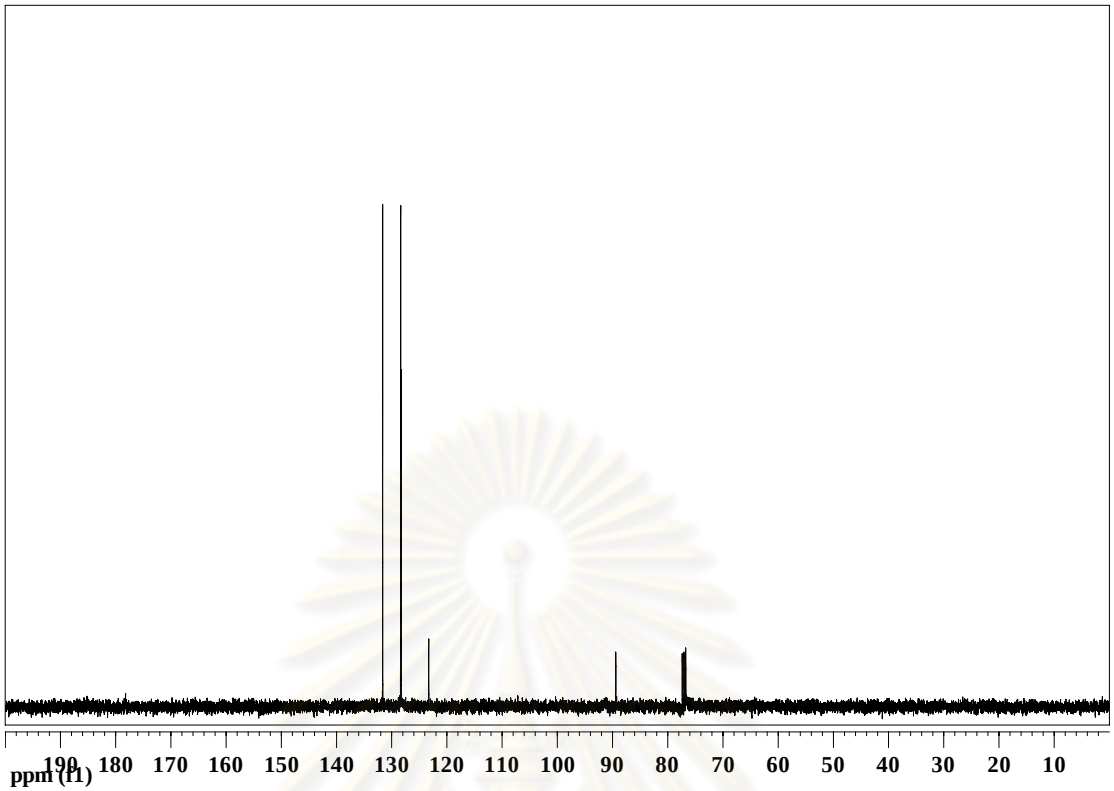

Figure 106 ^{13}C-NMR spectra of compound **176a**

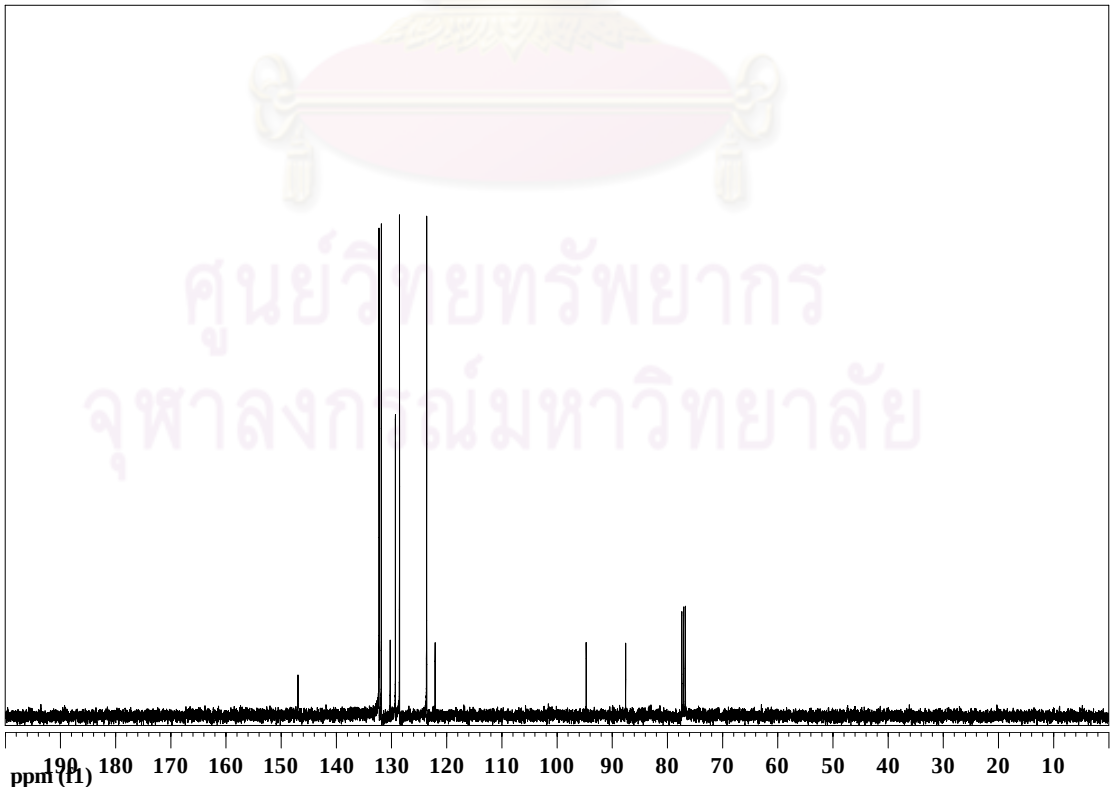

Figure 107 ^{13}C-NMR spectra of compound **176b**

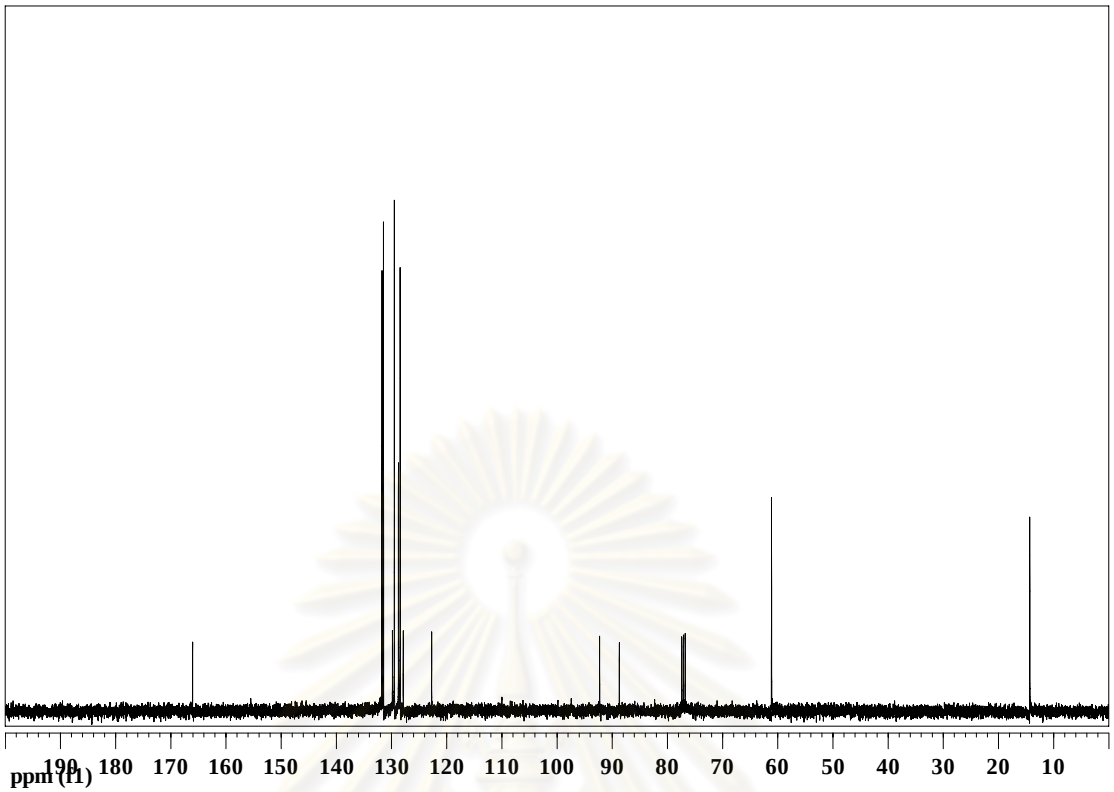

Figure 108 ^{13}C-NMR spectra of compound **176c**

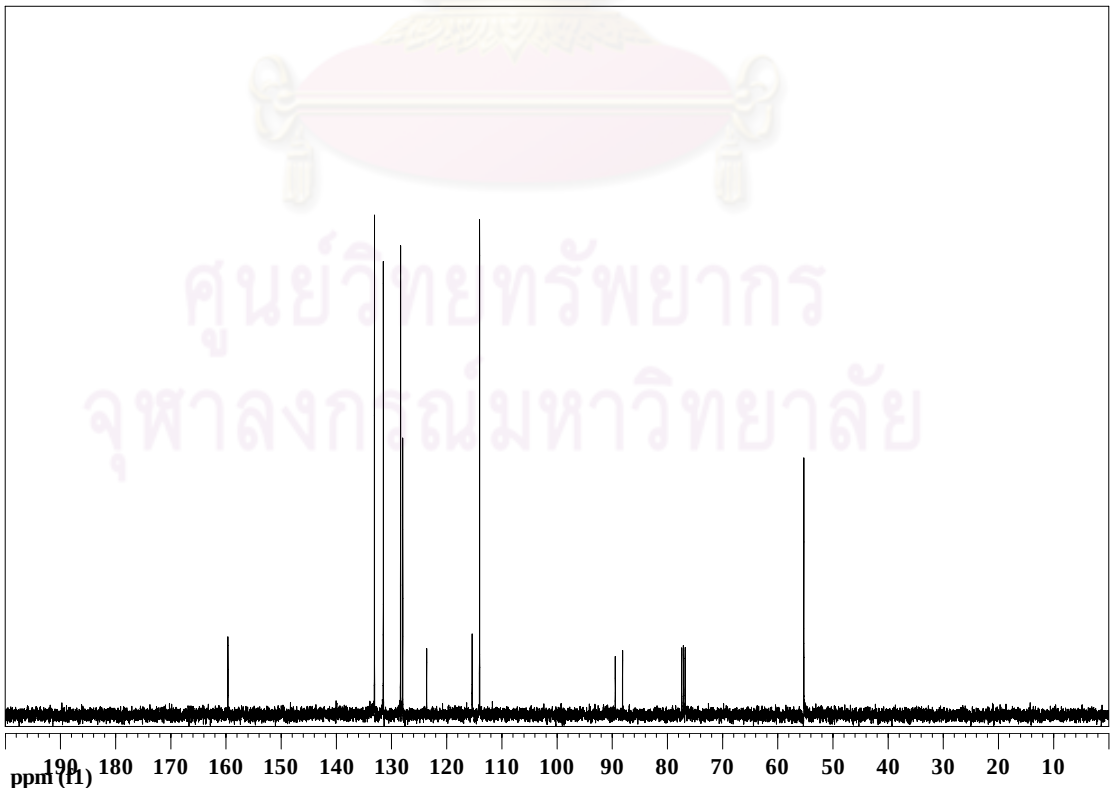

Figure 109 ^{13}C-NMR spectra of compound **176d**

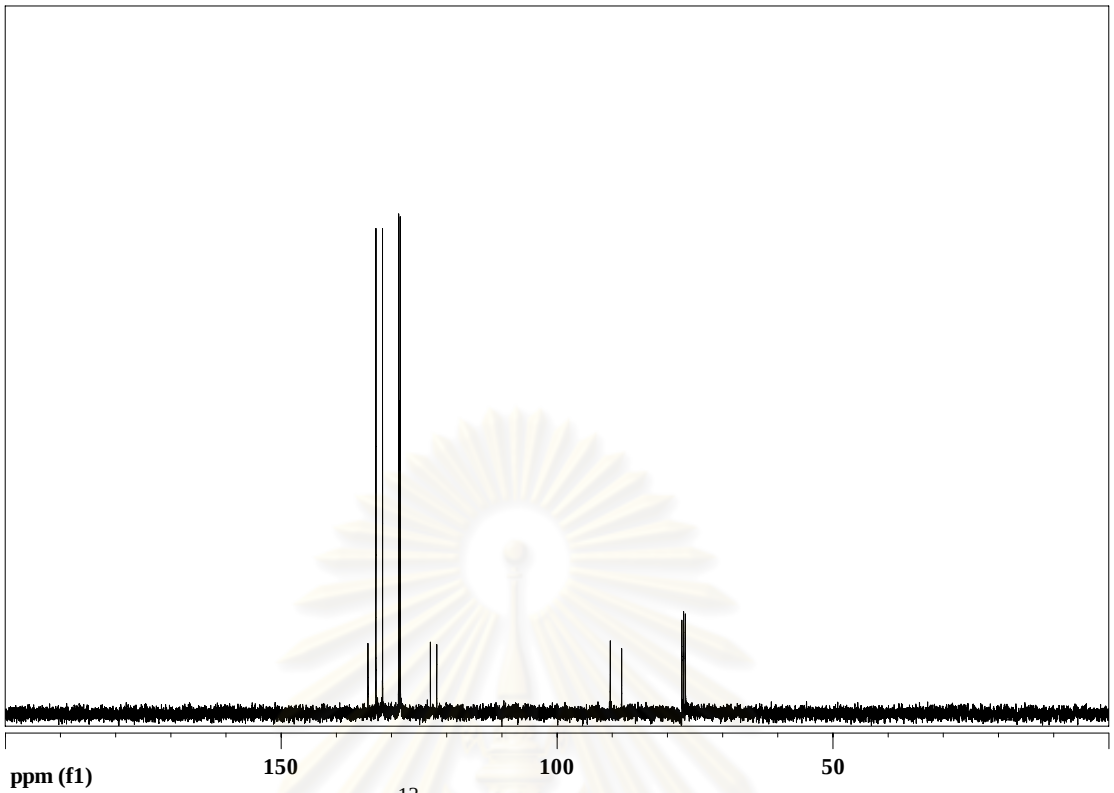

Figure 110 ^{13}C-NMR spectra of compound **176e**

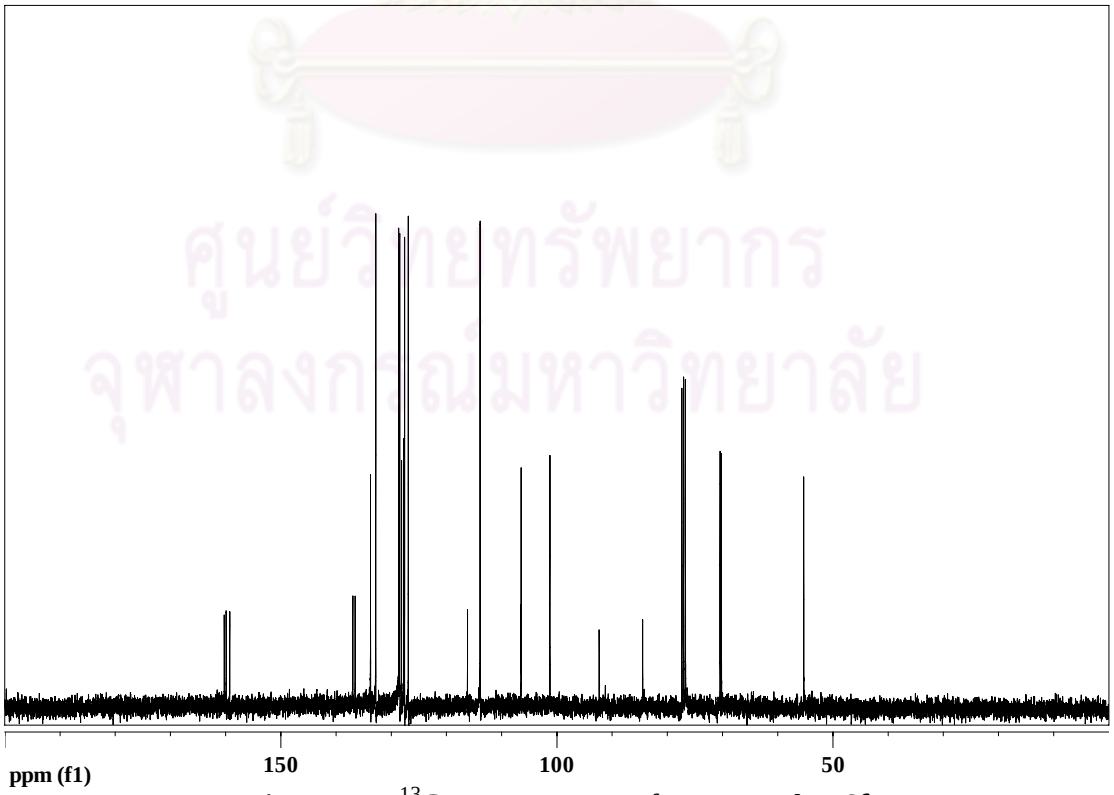

Figure 111 ^{13}C-NMR spectra of compound **176f**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

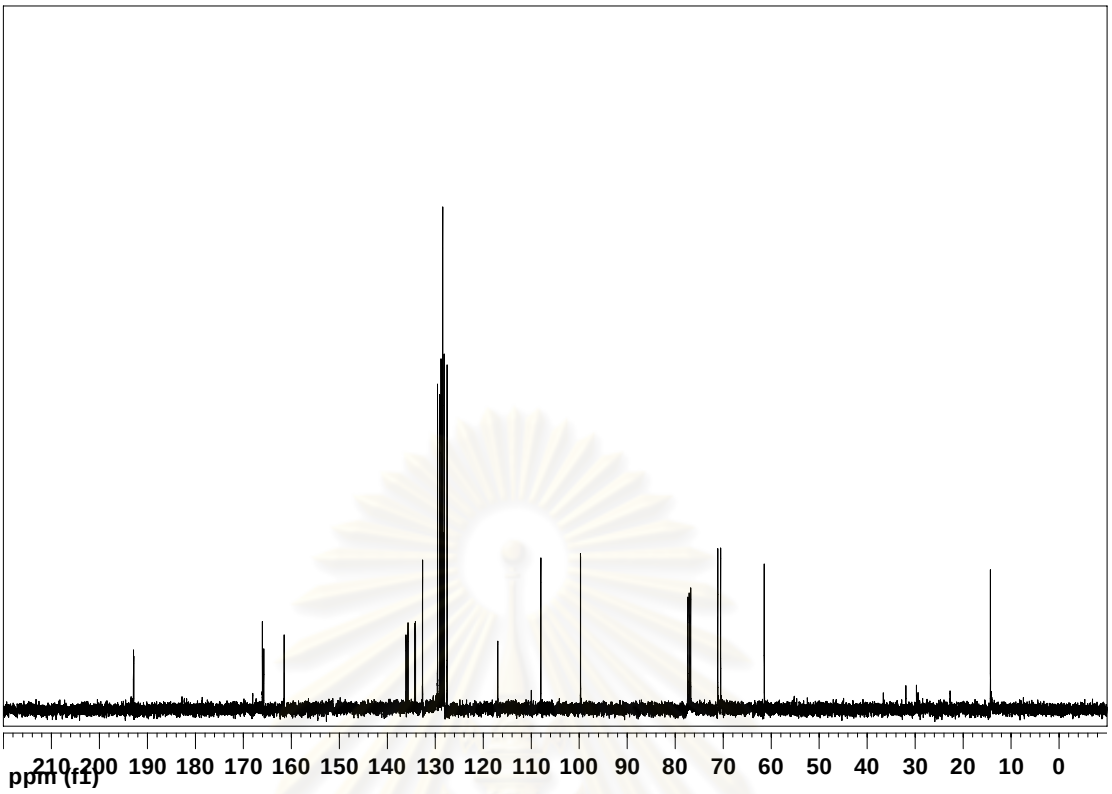

Figure 112 ^{13}C-NMR spectra of compound **176g**

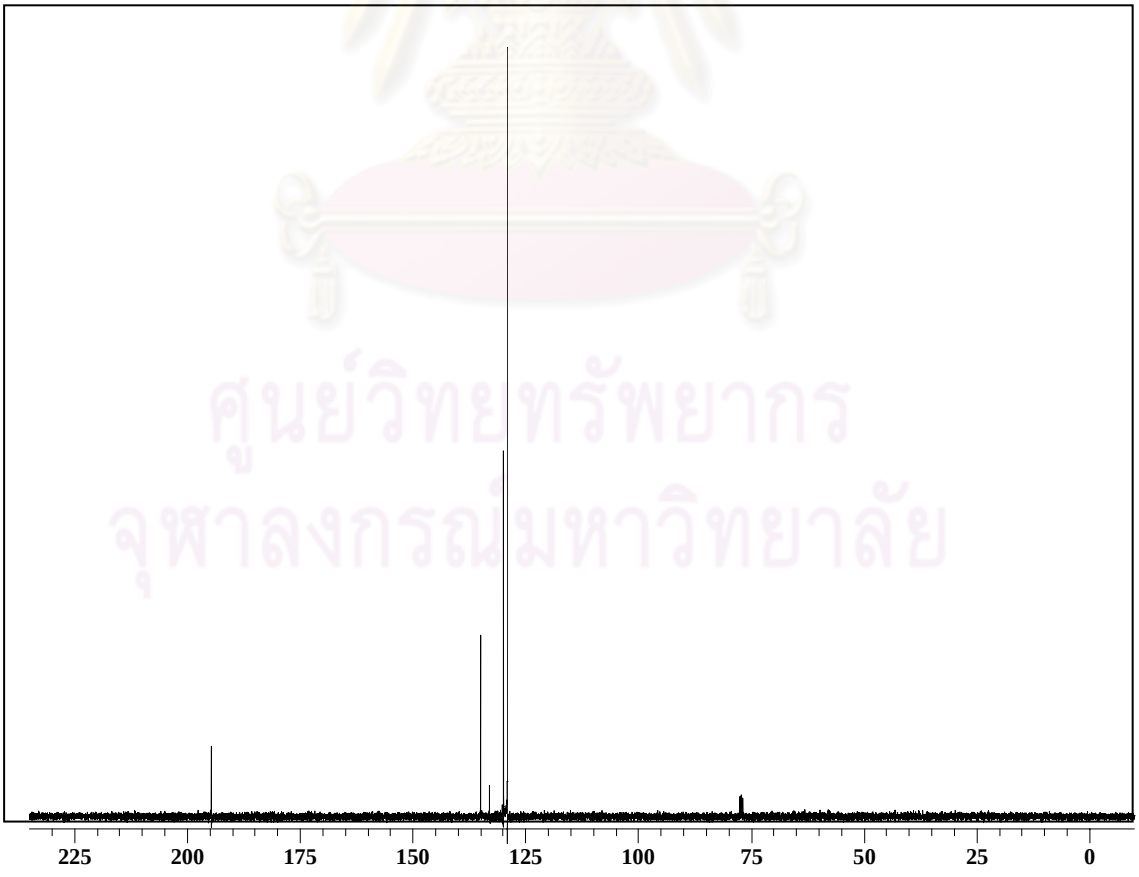

Figure 113 ^{13}C-NMR spectra of compound **177a**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

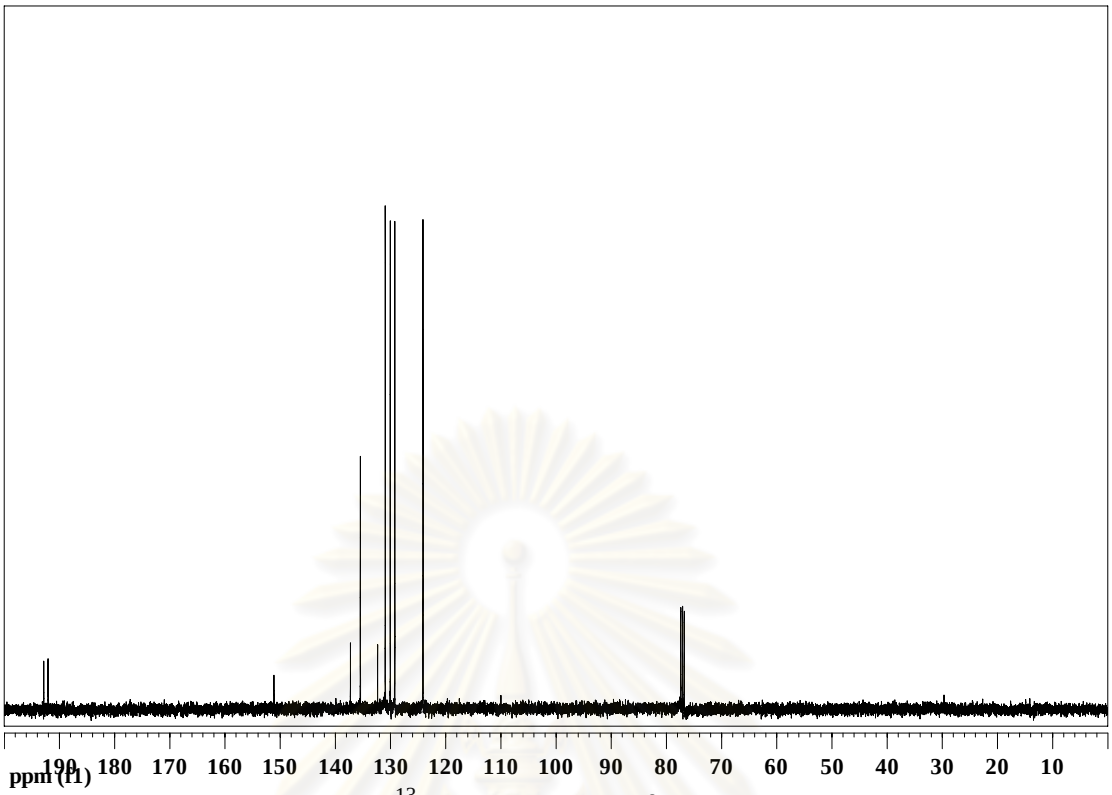

Figure 114 ^{13}C-NMR spectra of compound **177b**

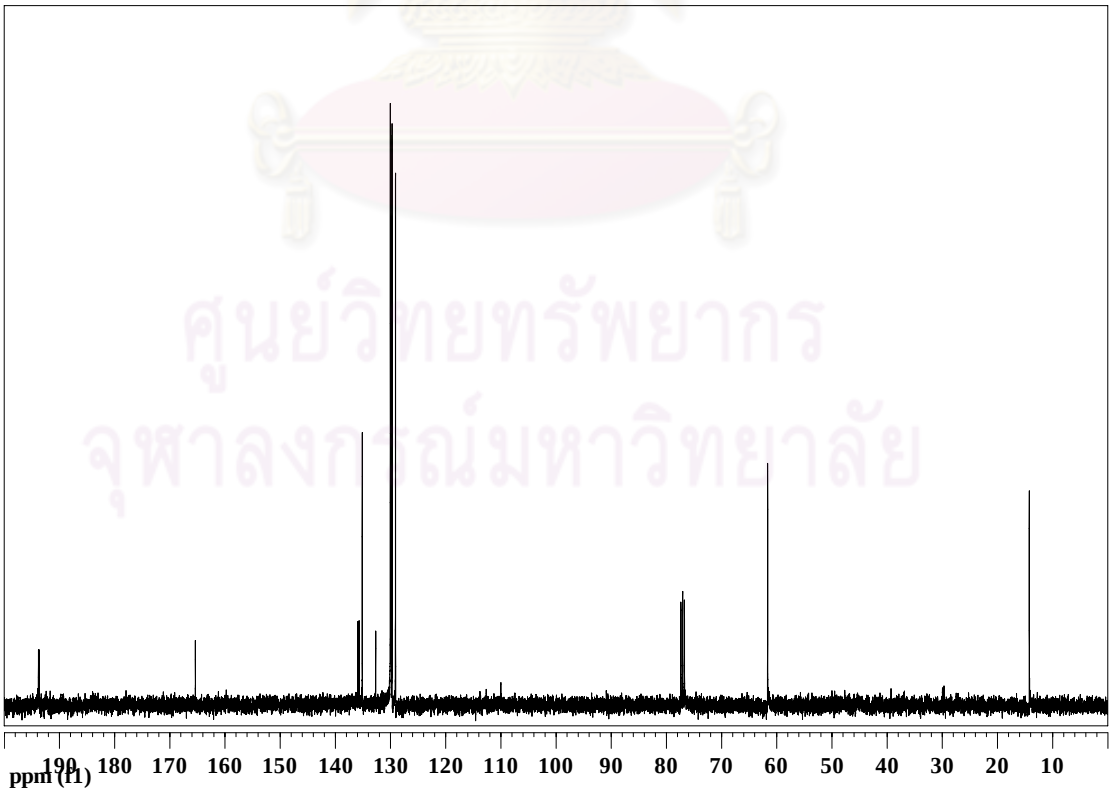

Figure 115 ^{13}C-NMR spectra of compound **177c**

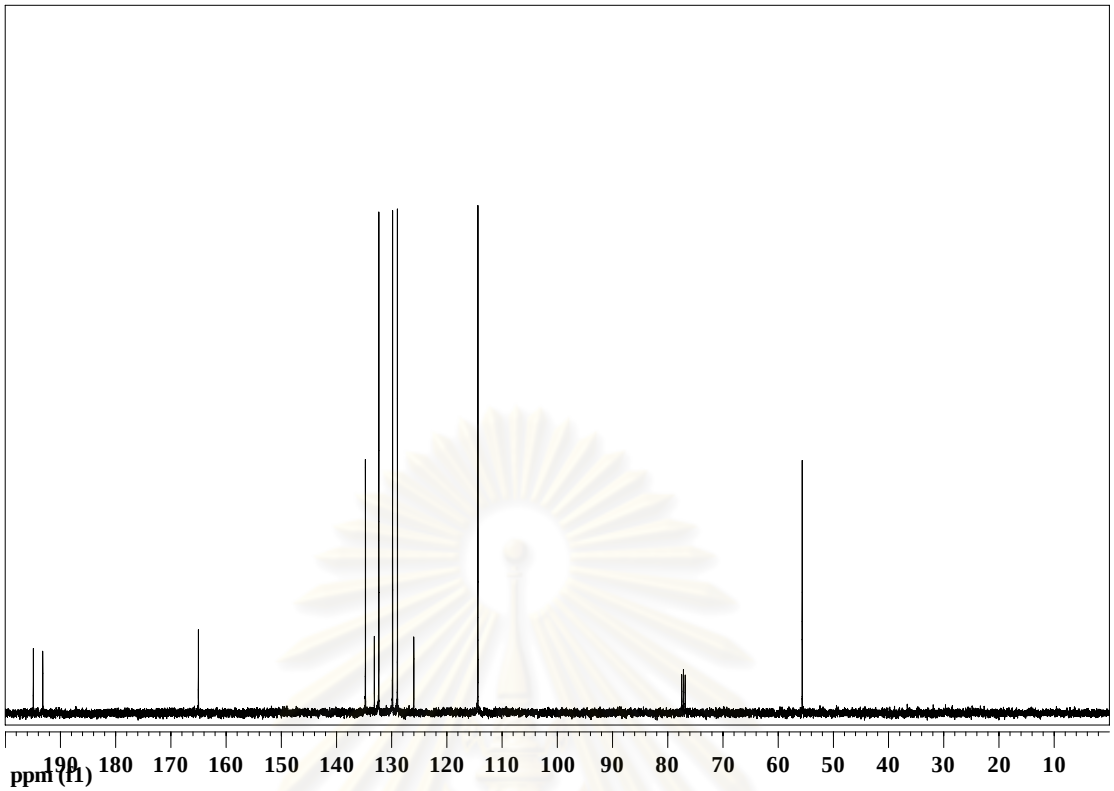

Figure 116 ^{13}C-NMR spectra of compound **177d**

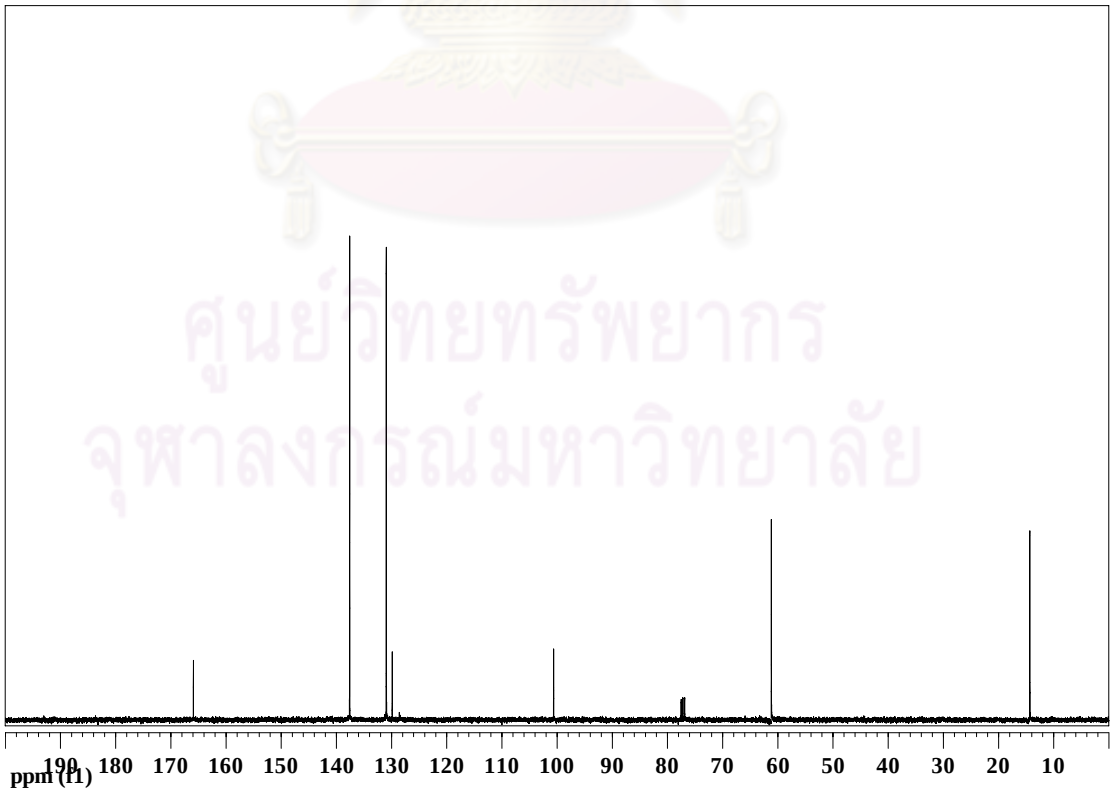

Figure 117 ^{13}C-NMR spectra of compound **177e**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

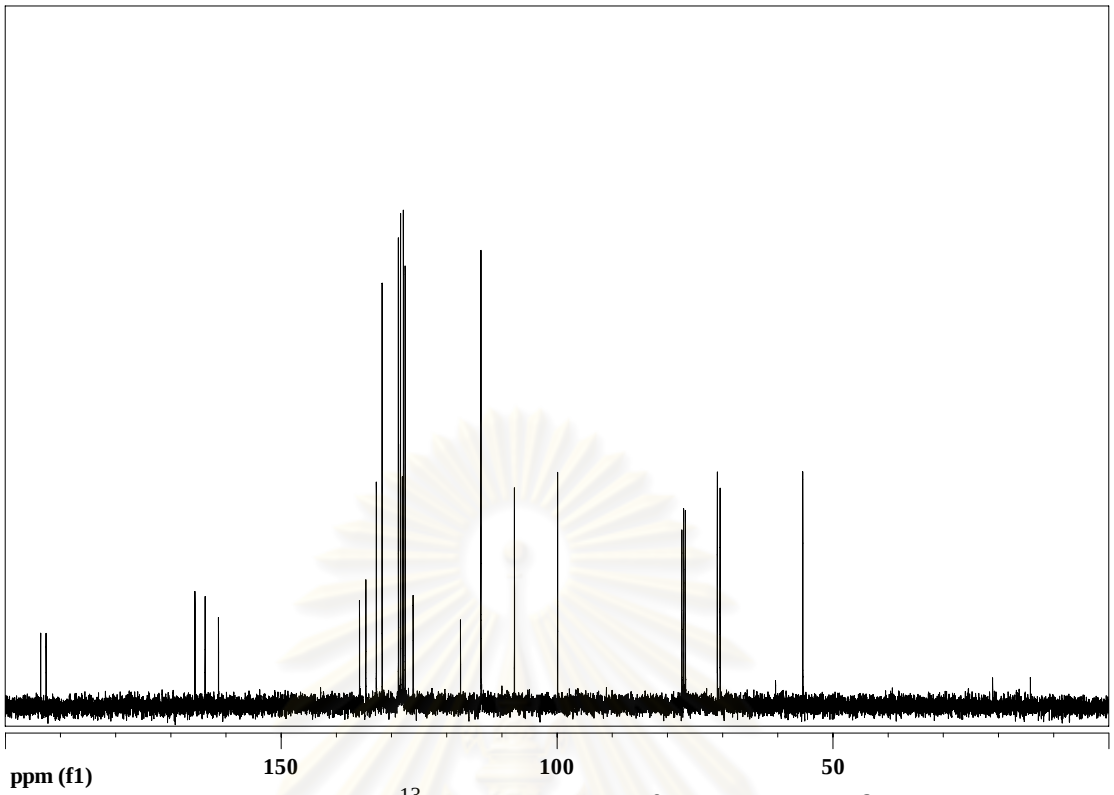

Figure 118 ^{13}C-NMR spectra of compound **177f**

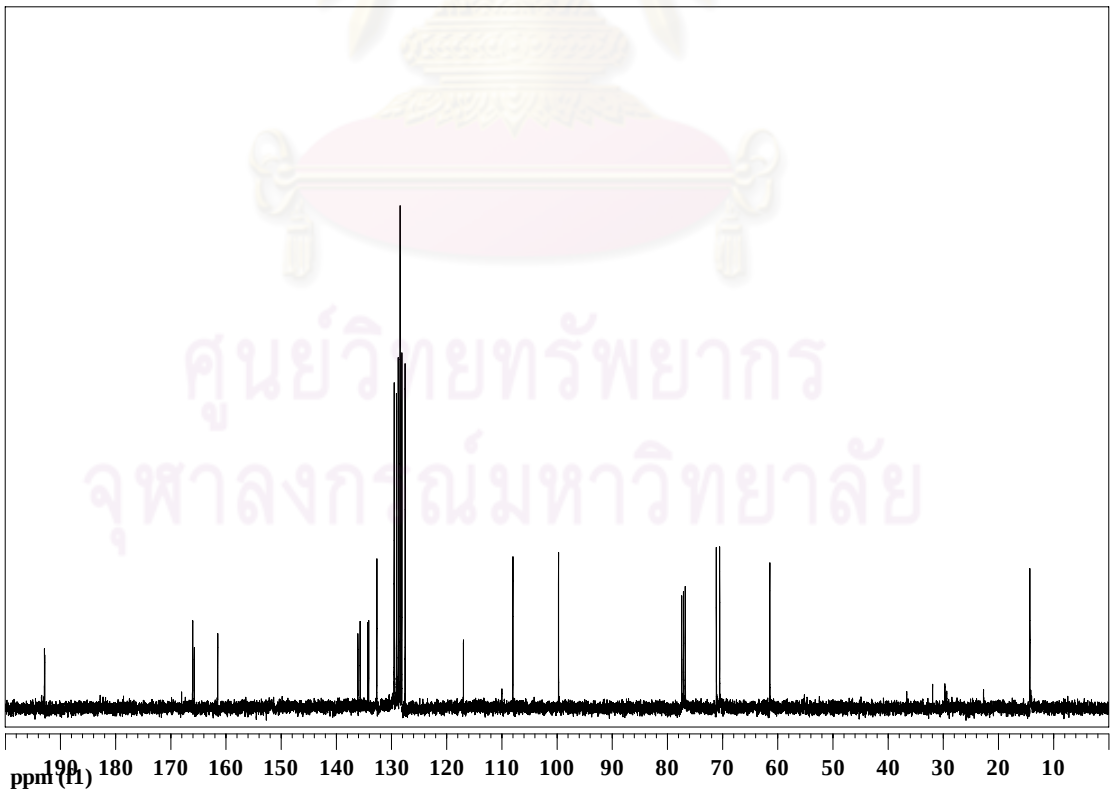

Figure 119 ^{13}C-NMR spectra of compound **177g**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

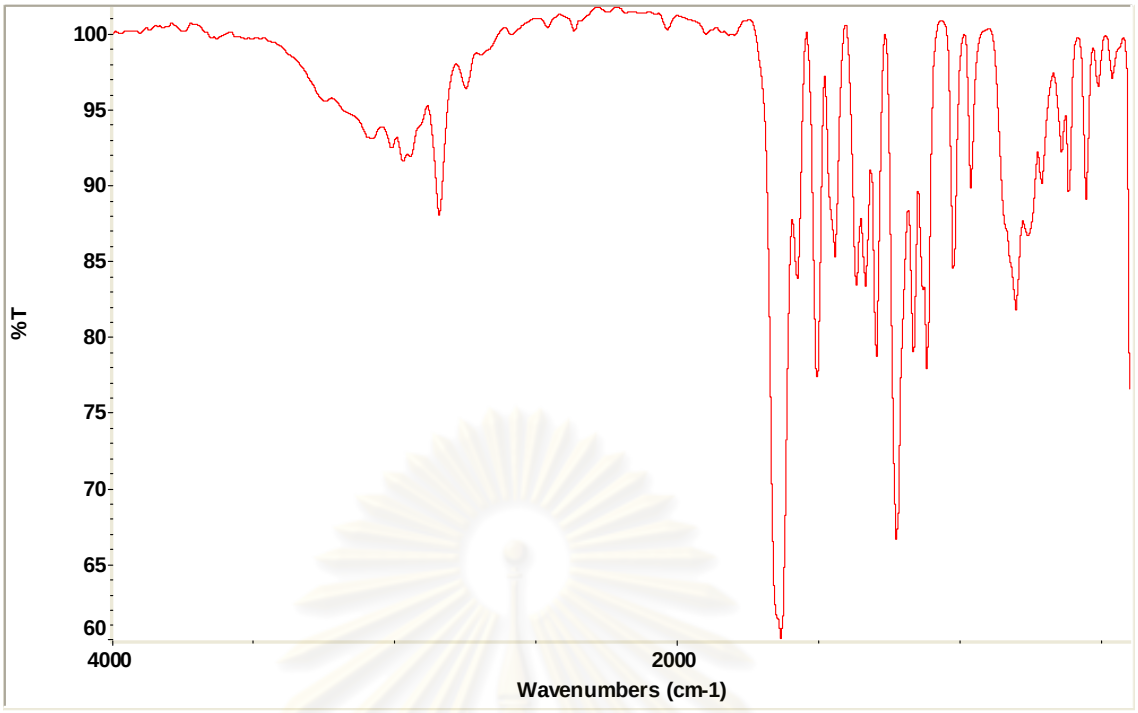

Figure 120 IR spectra of compound **146**

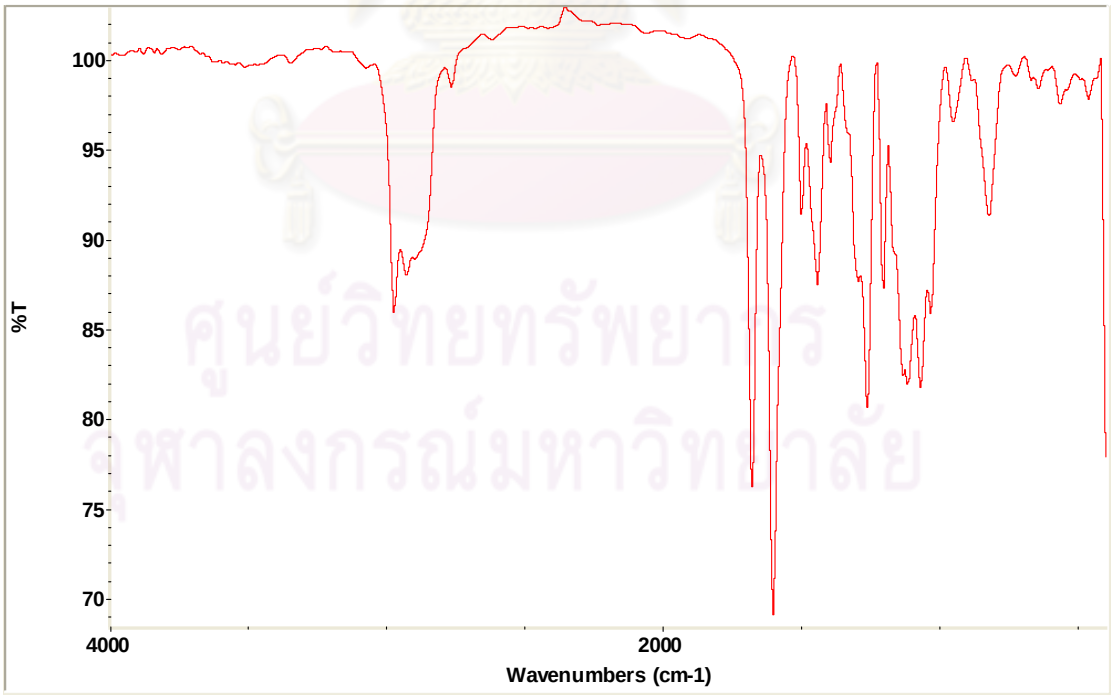

Figure 121 IR spectra of compound **147**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

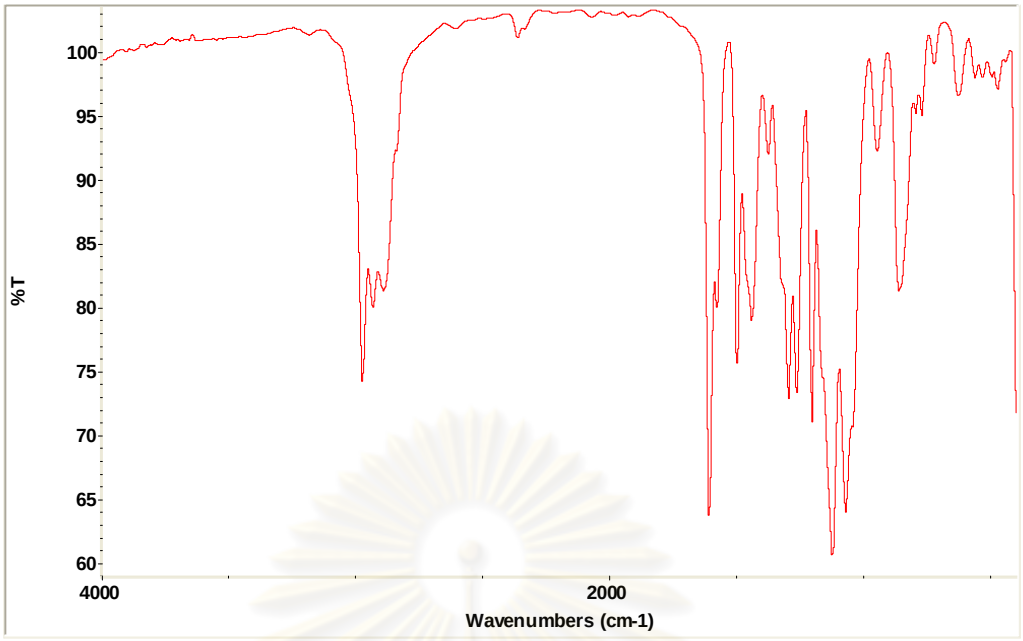

Figure 122 IR spectra of compound **148**

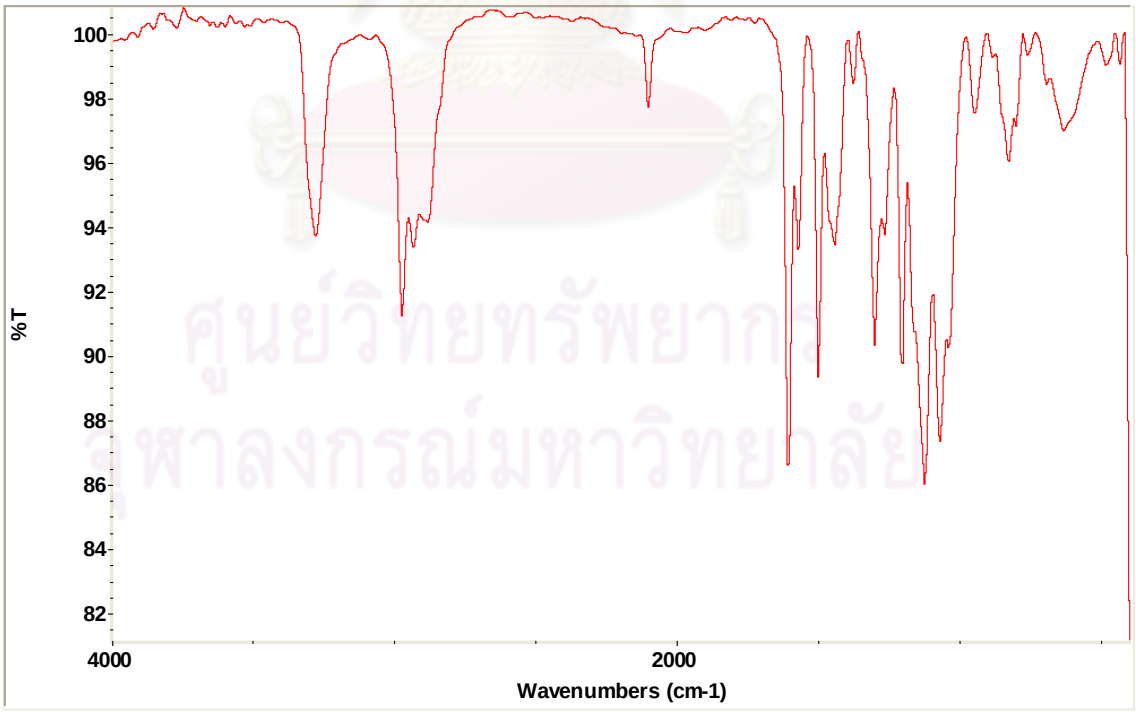

Figure 123 IR spectra of compound **20**

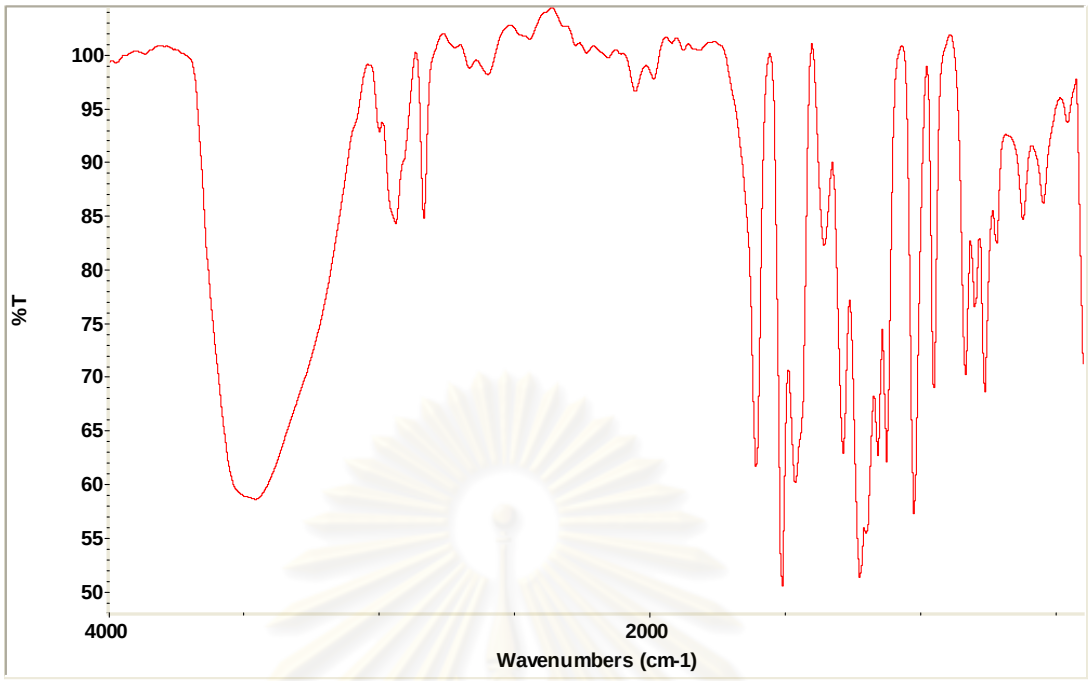

Figure 124 IR spectra of compound **150**

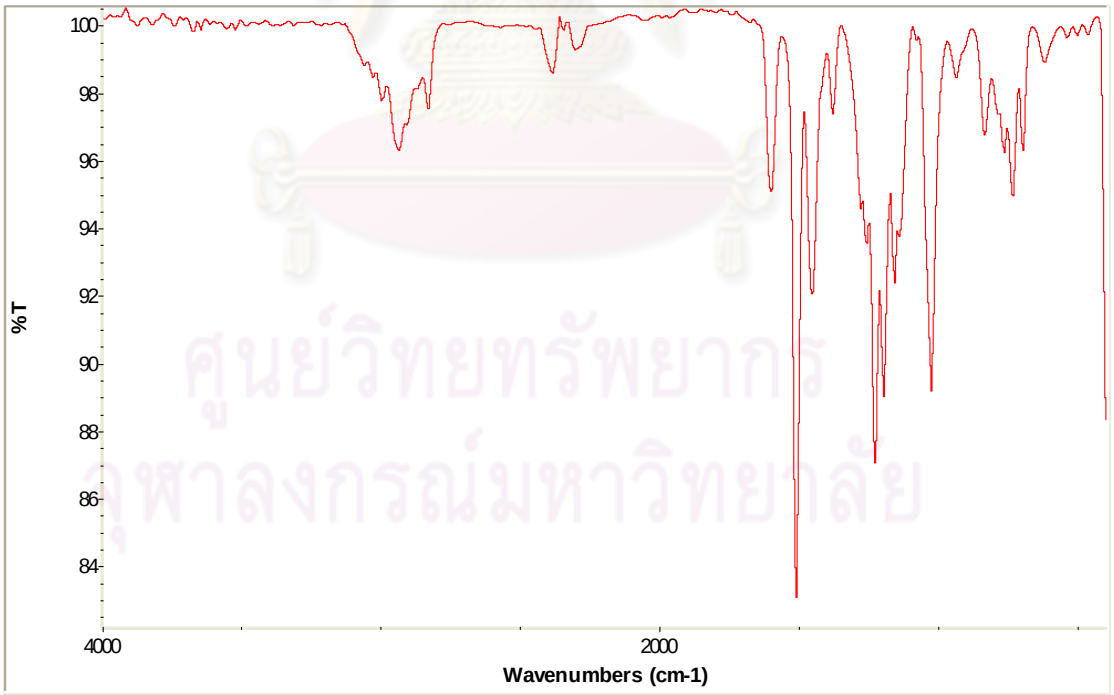

Figure 125 IR spectra of compound **151**

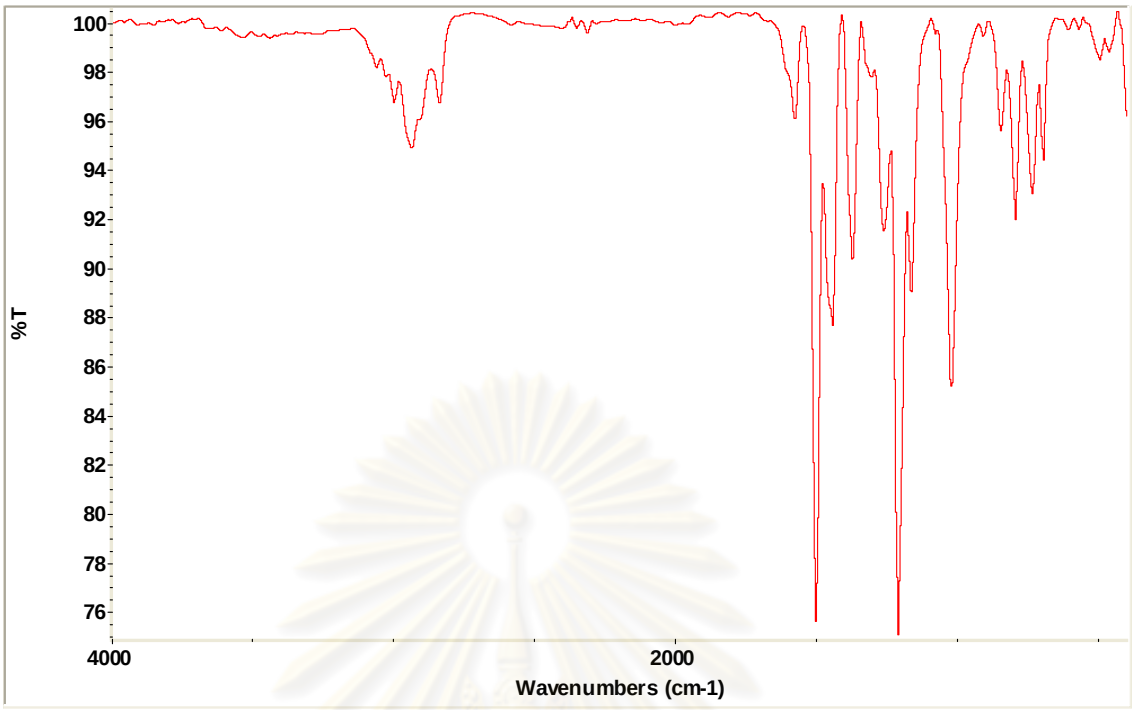

Figure 126 IR spectra of compound **21**

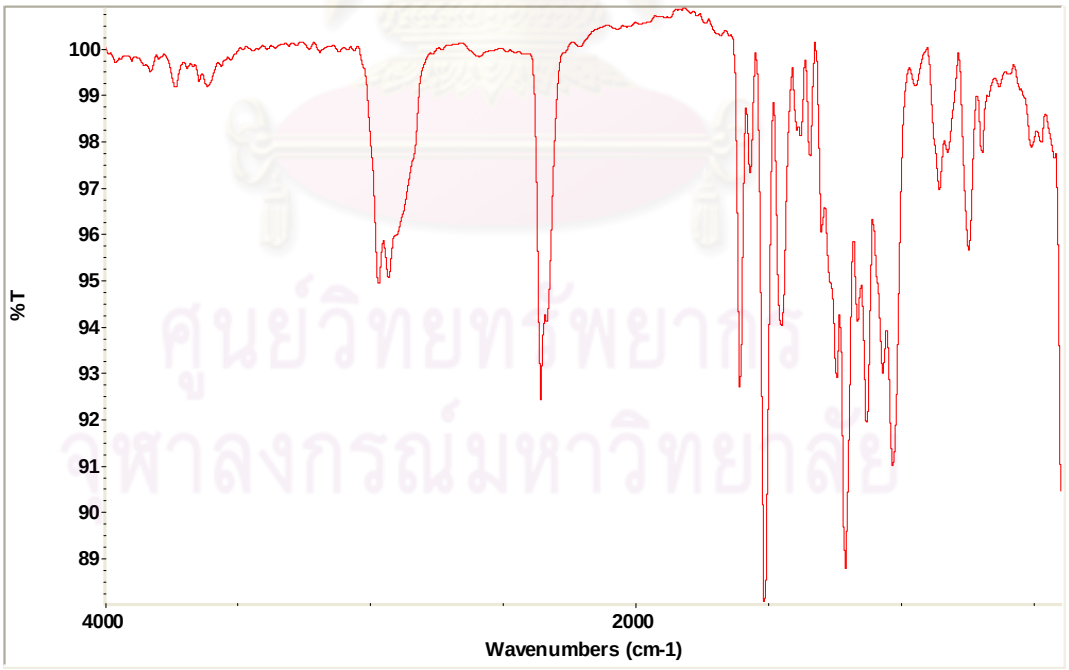

Figure 127 IR spectra of compound **152**

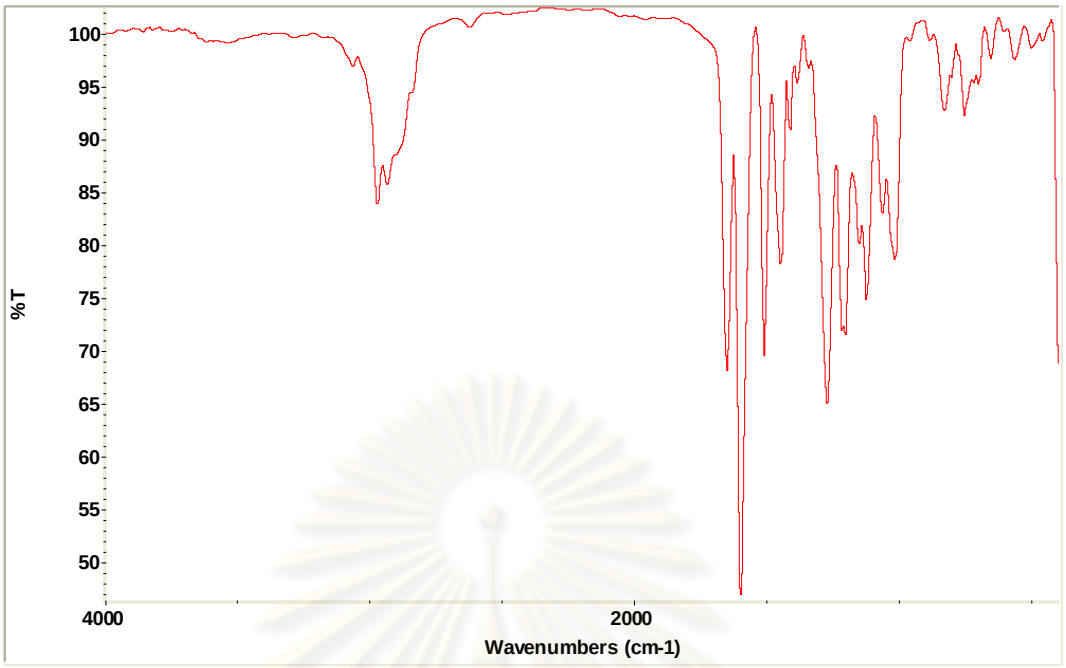

Figure 128 IR spectra of compound **19**

Figure 129 IR spectra of compound **153**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

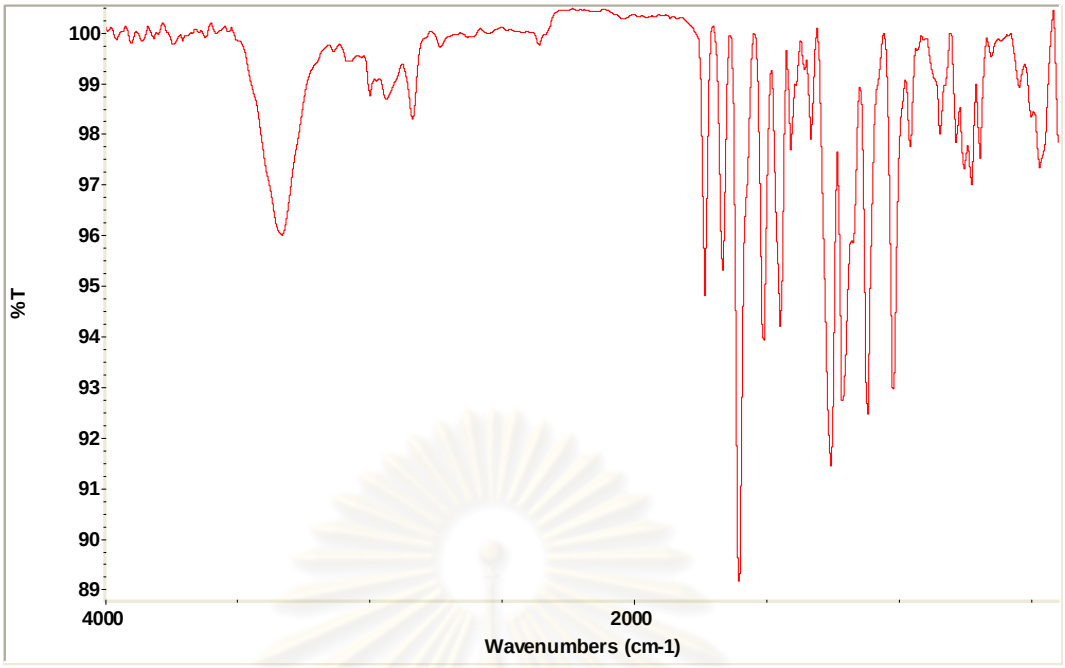

Figure 130 IR spectra of compound **154**

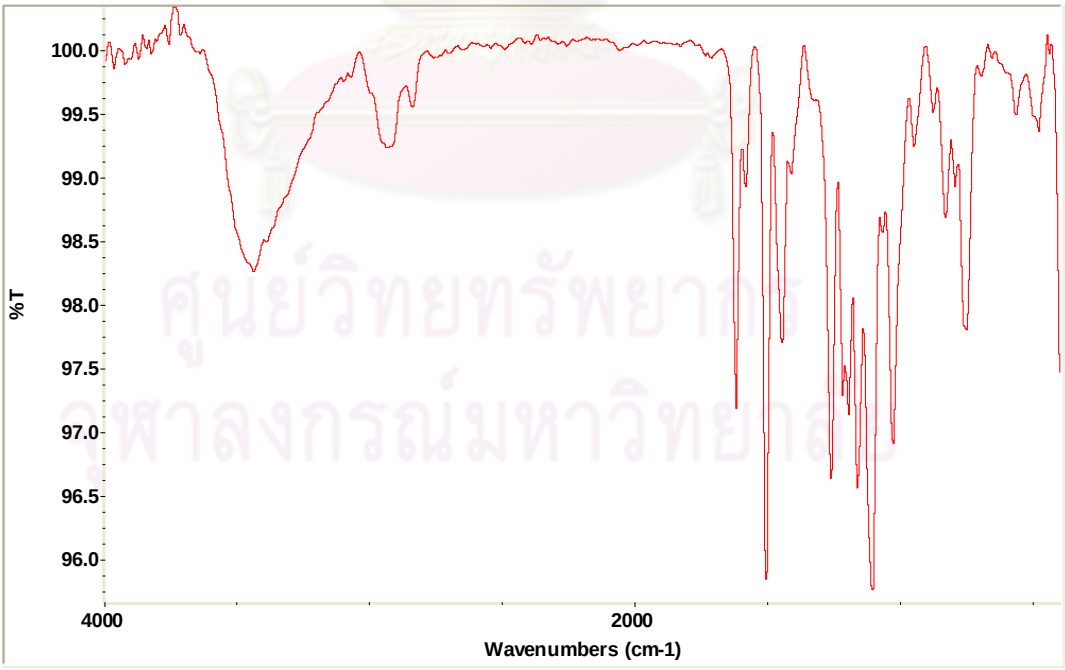

Figure 131 IR spectra of compound **155**

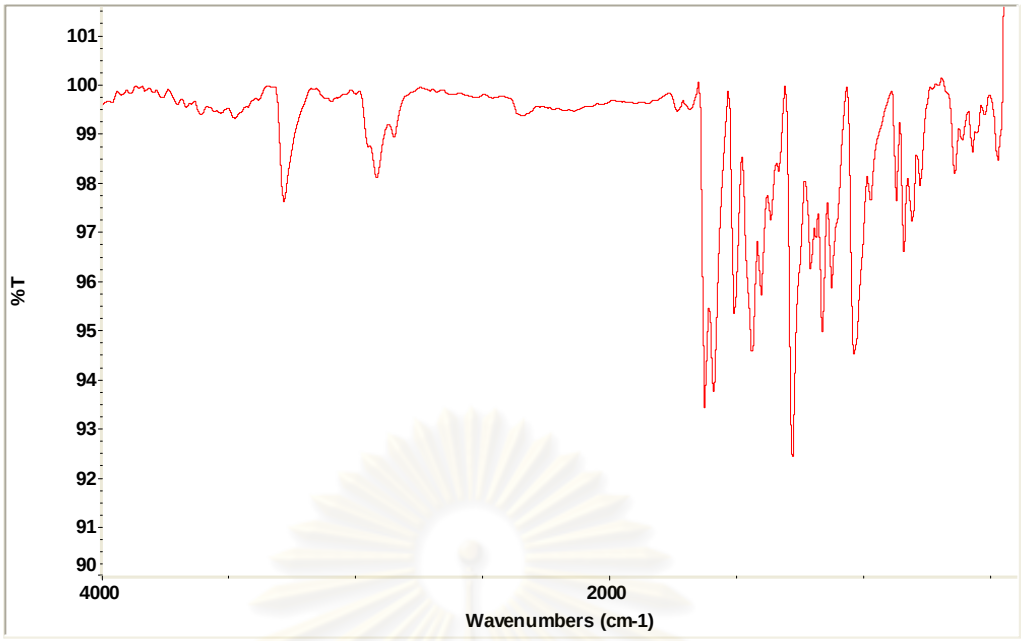

Figure 132 IR spectra of compound **1**

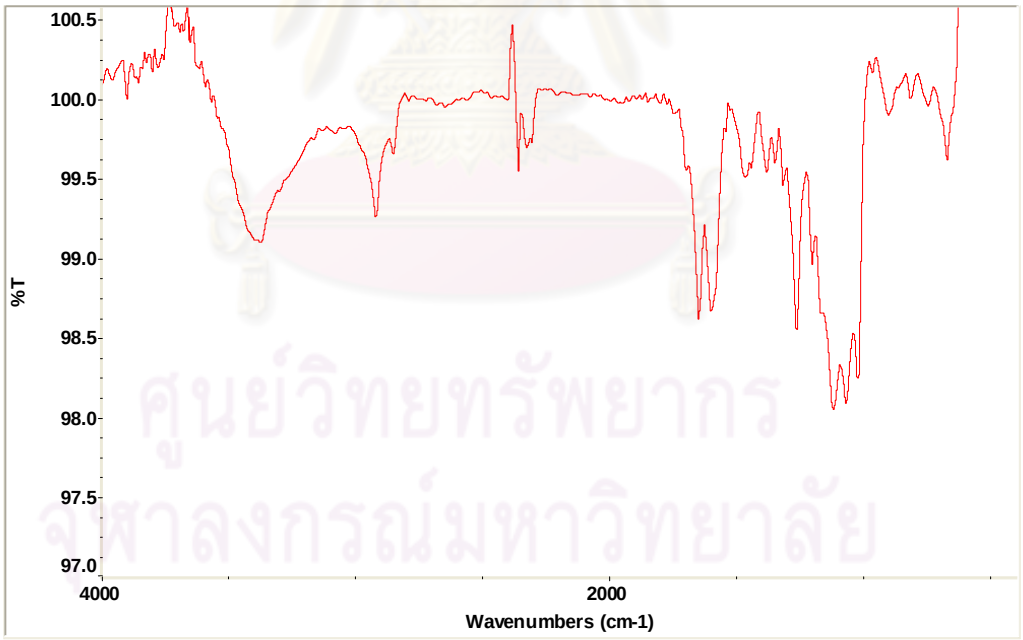

Figure 133 IR spectra of compound **157**

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จุฬาลงกรณ์มหาวิทยาลัย

Figure 134 IR spectra of compound **158**

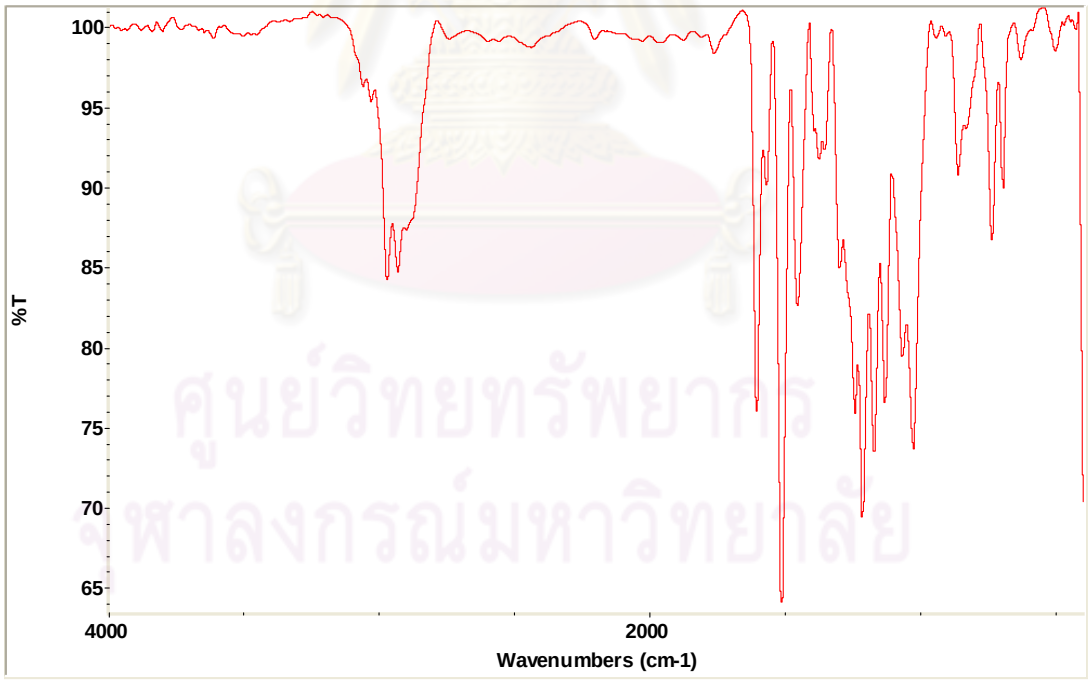

Figure 135 IR spectra of compound **159**

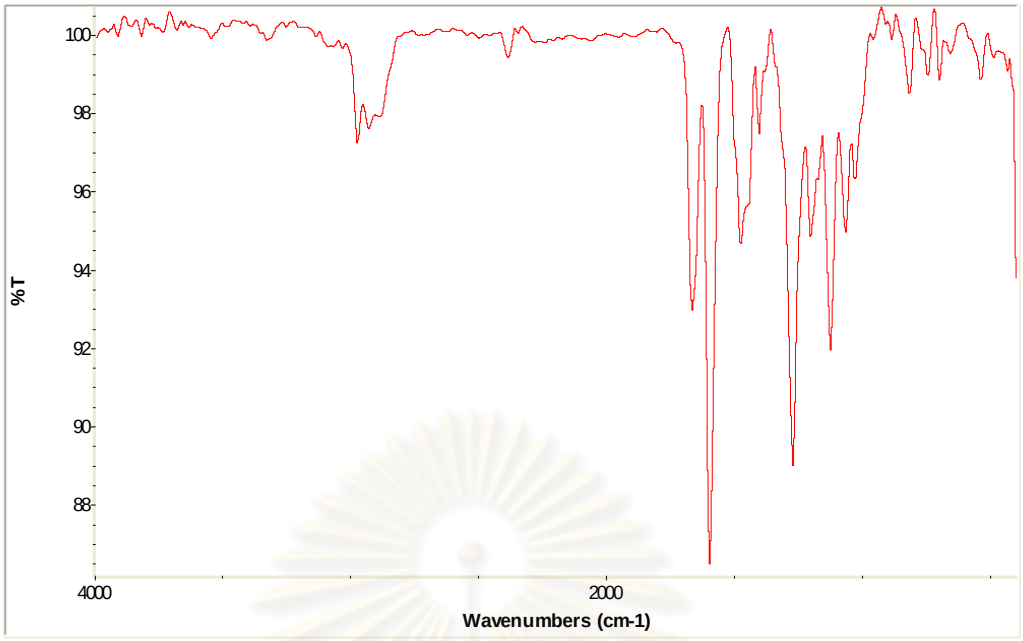

Figure 136 IR spectra of compound **160**

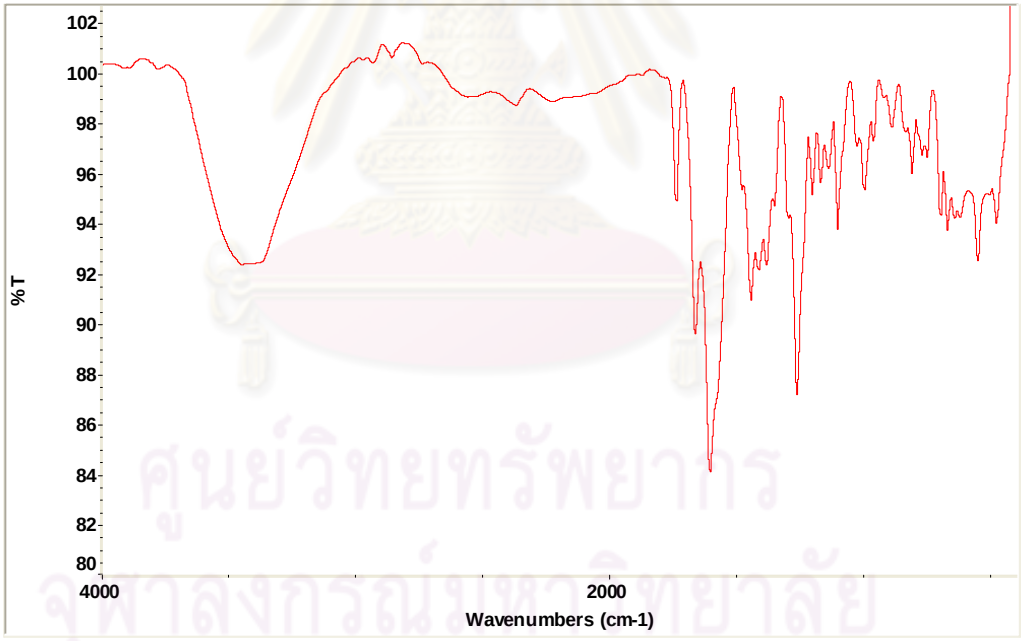

Figure 137 IR spectra of compound **161**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

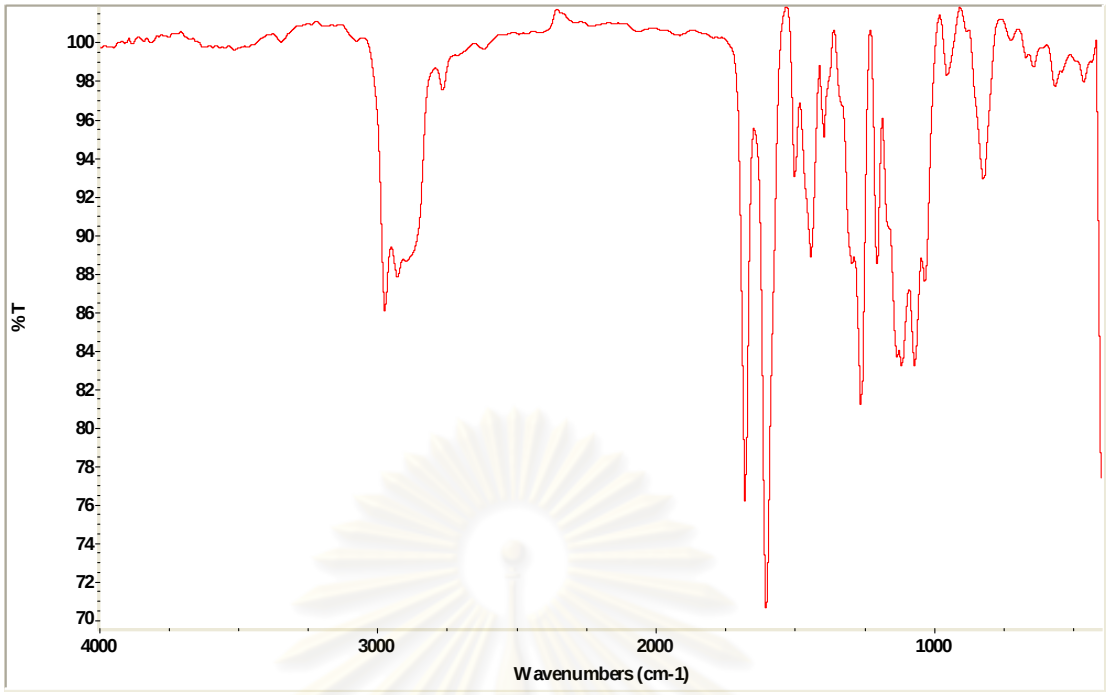

Figure 138 IR spectra of compound **164**

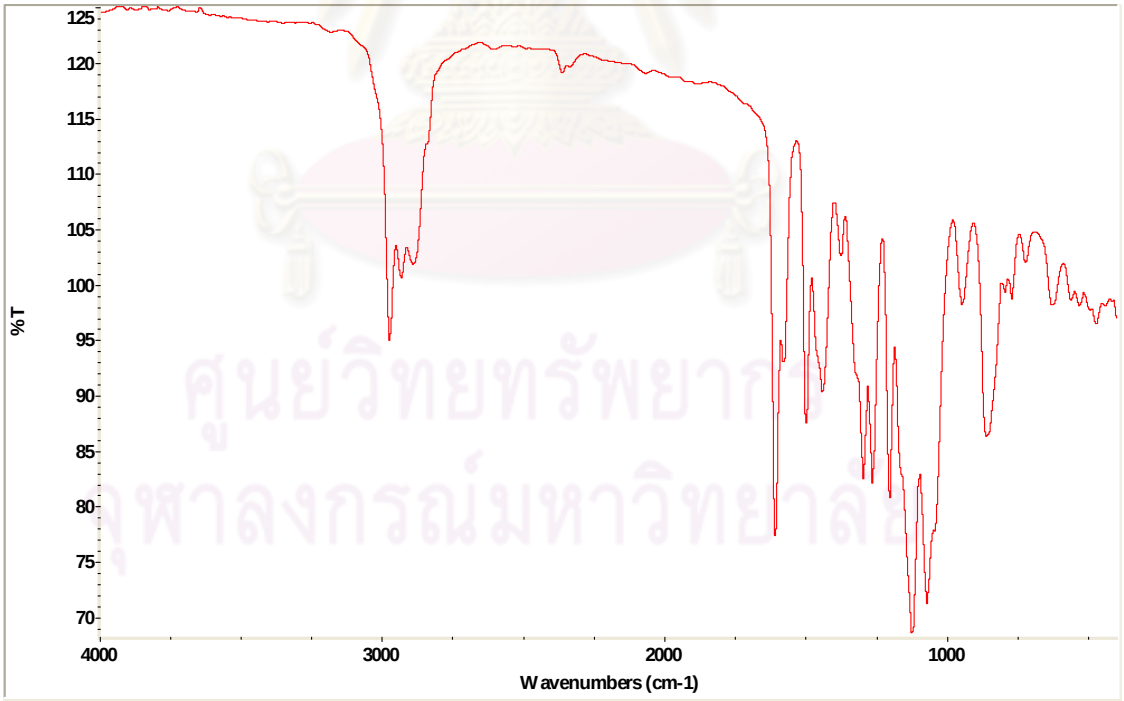

Figure 139 IR spectra of compound **165**

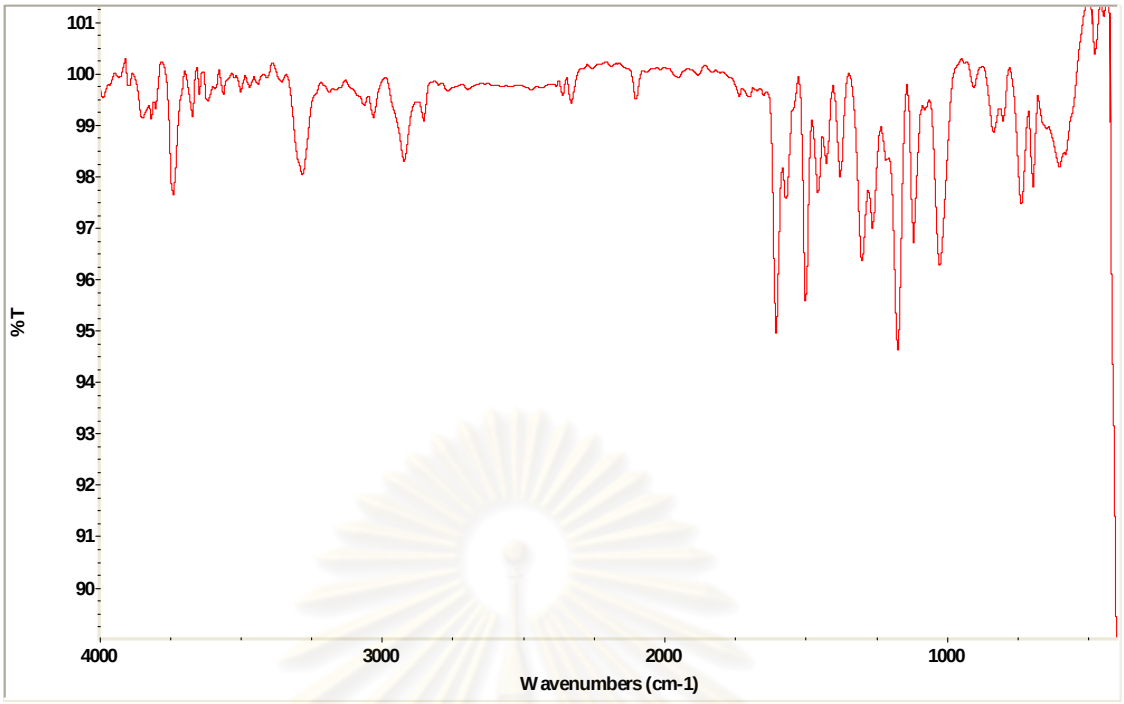

Figure 140 IR spectra of compound **166**

Figure 141 IR spectra of compound **167**

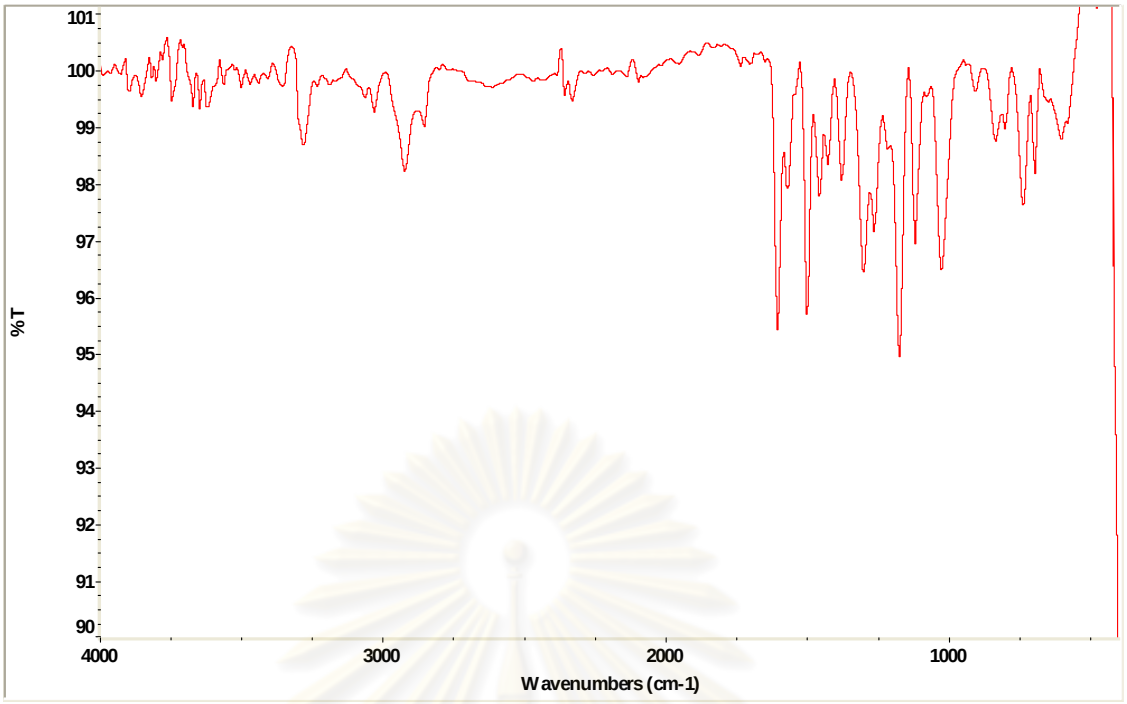

Figure 142 IR spectra of compound **168**

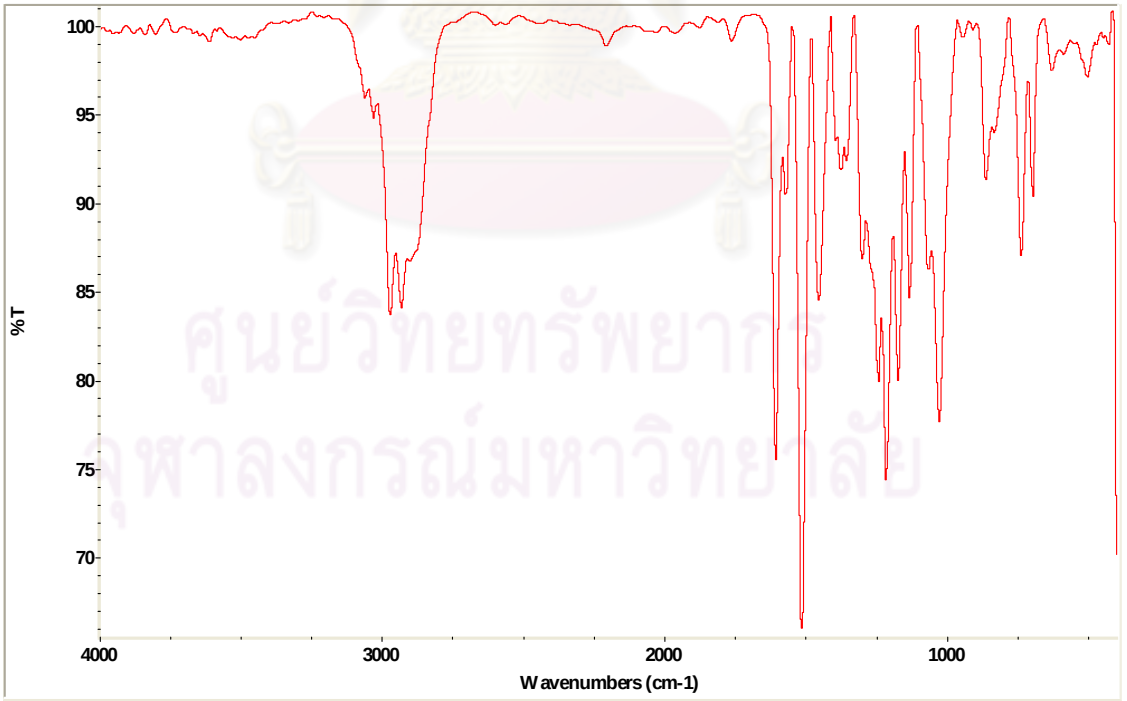

Figure 143 IR spectra of compound **169**

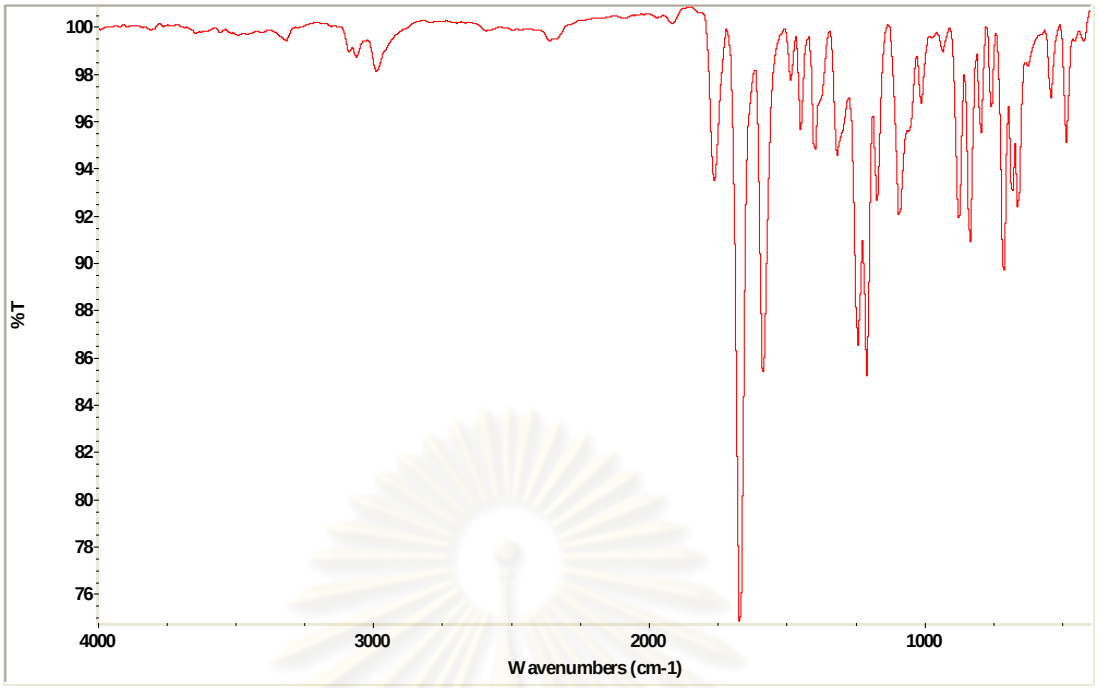

Figure 144 IR spectra of compound **170**

Figure 145 IR spectra of compound **171**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

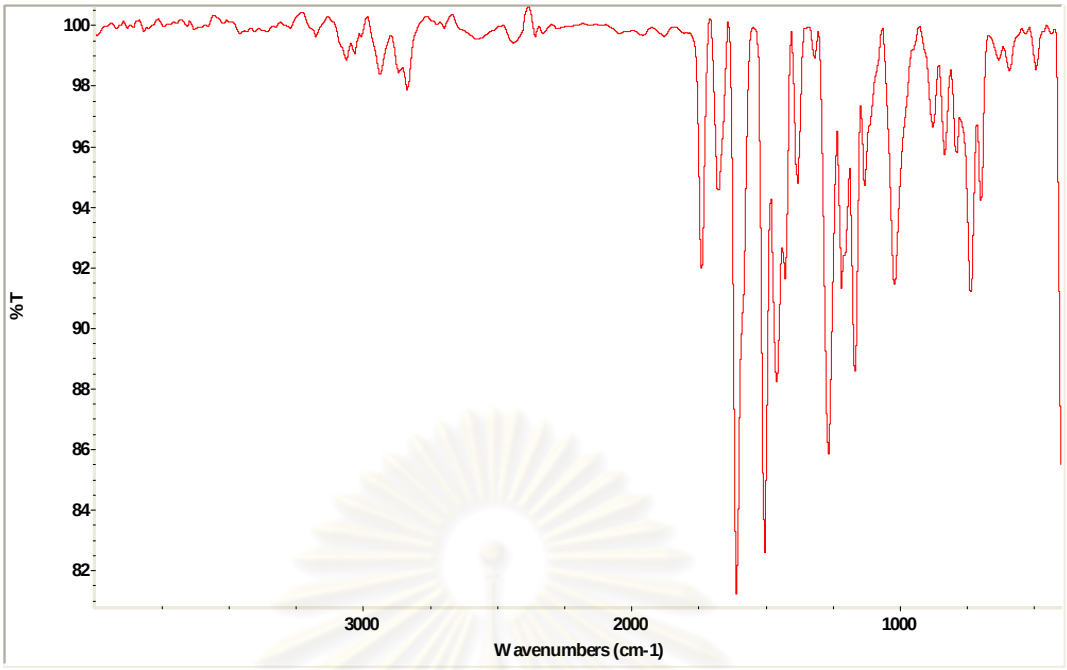

Figure 146 IR spectra of compound **172**

Figure 147 IR spectra of compound **176a**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

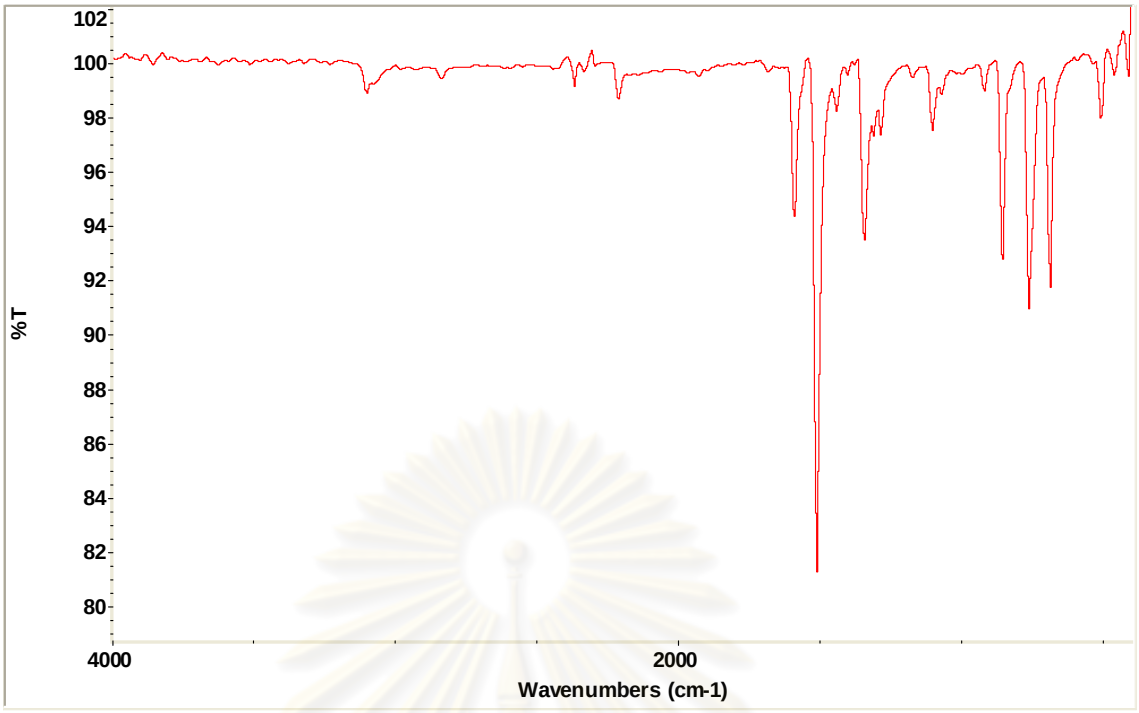

Figure 148 IR spectra of compound **176b**

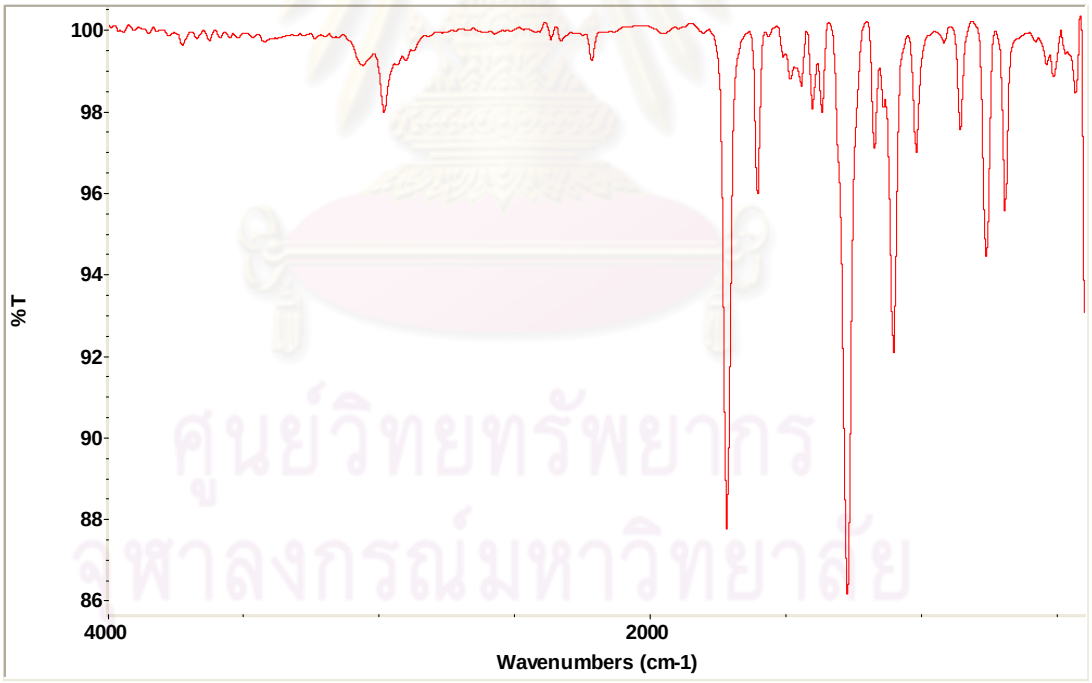

Figure 149 IR spectra of compound **176c**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

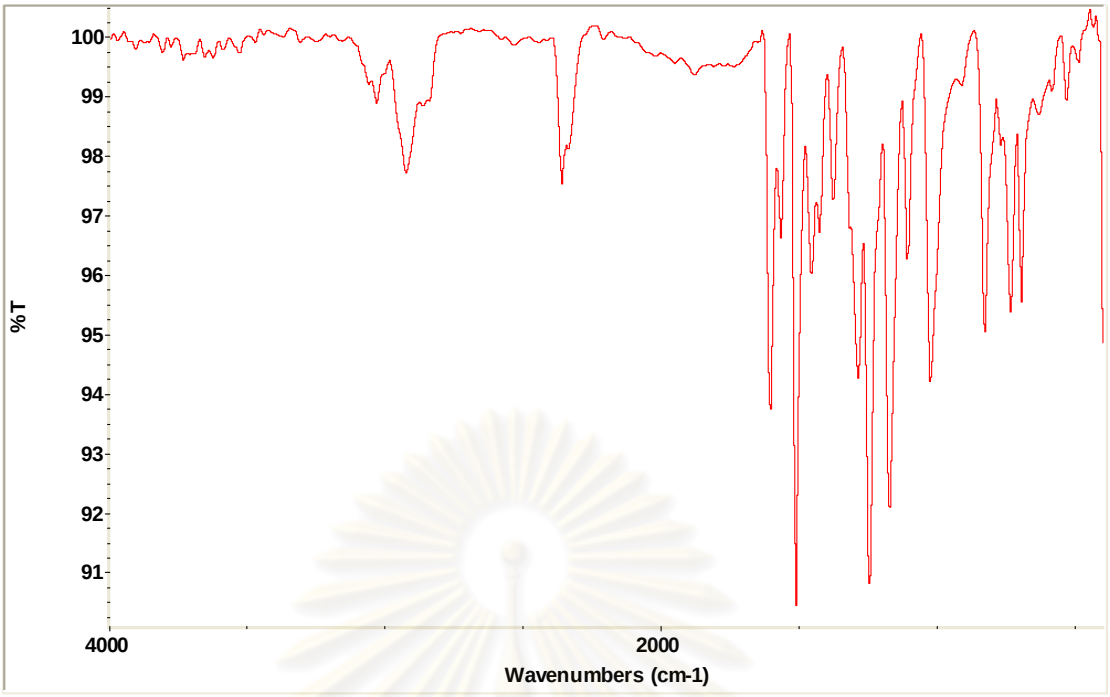

Figure 150 IR spectra of compound **176d**

Figure 151 IR spectra of compound **176e**

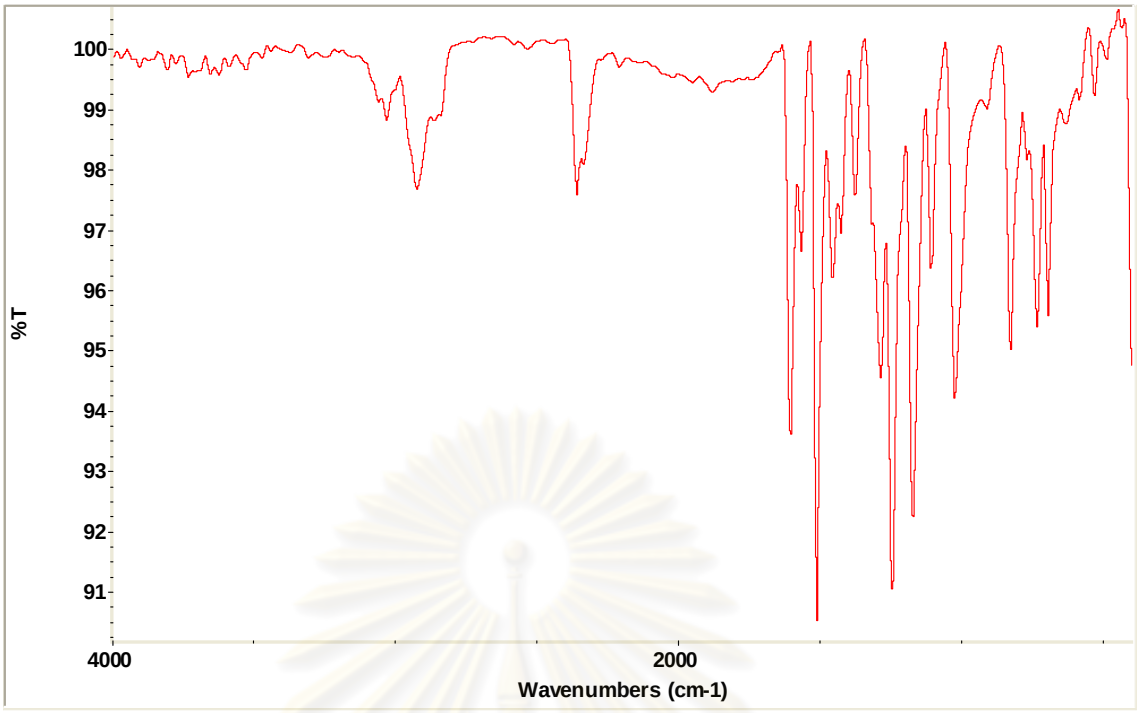

Figure 152 IR spectra of compound **176f**

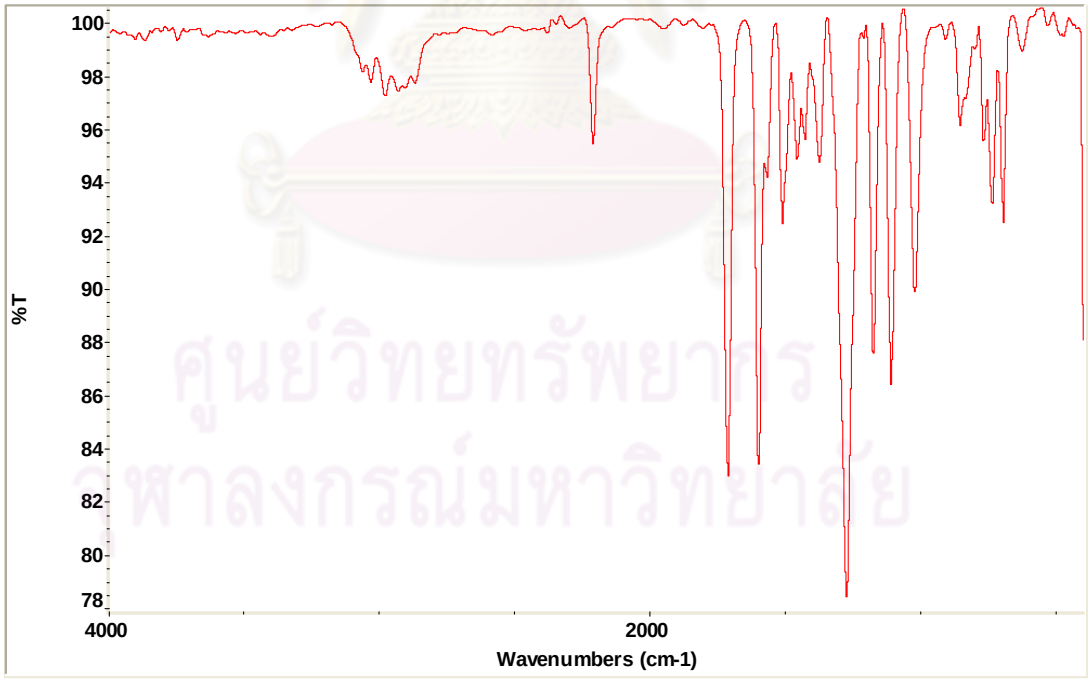

Figure 153 IR spectra of compound **176g**

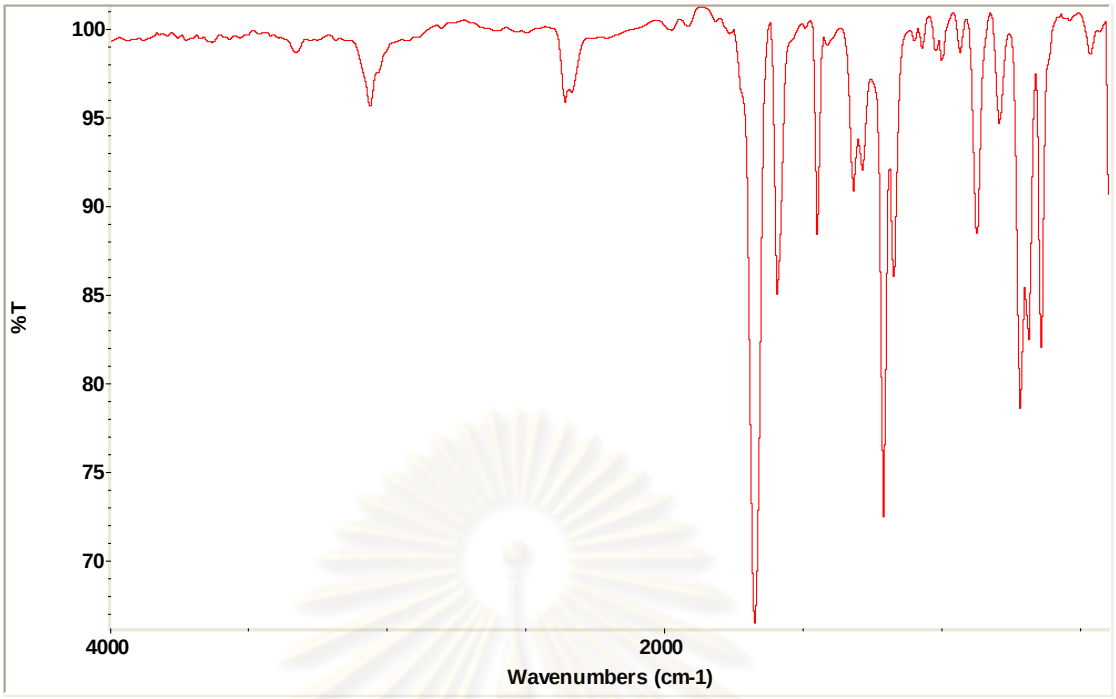

Figure 154 IR spectra of compound **177a**

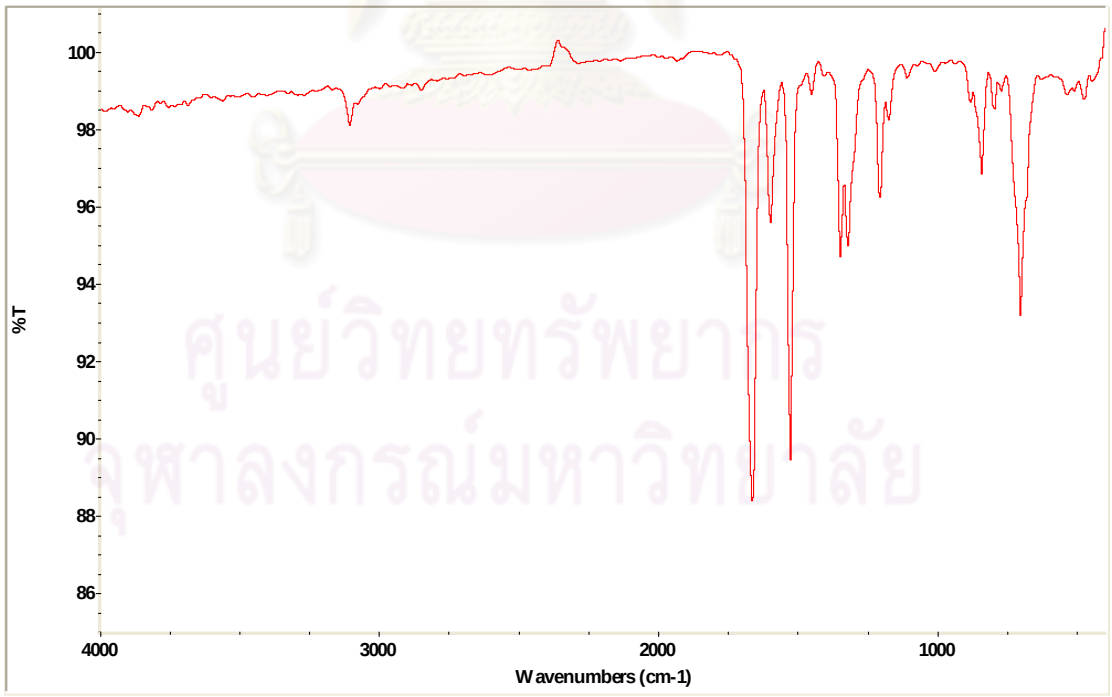

Figure 155 IR spectra of compound **177b**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Figure 156 IR spectra of compound **177c**

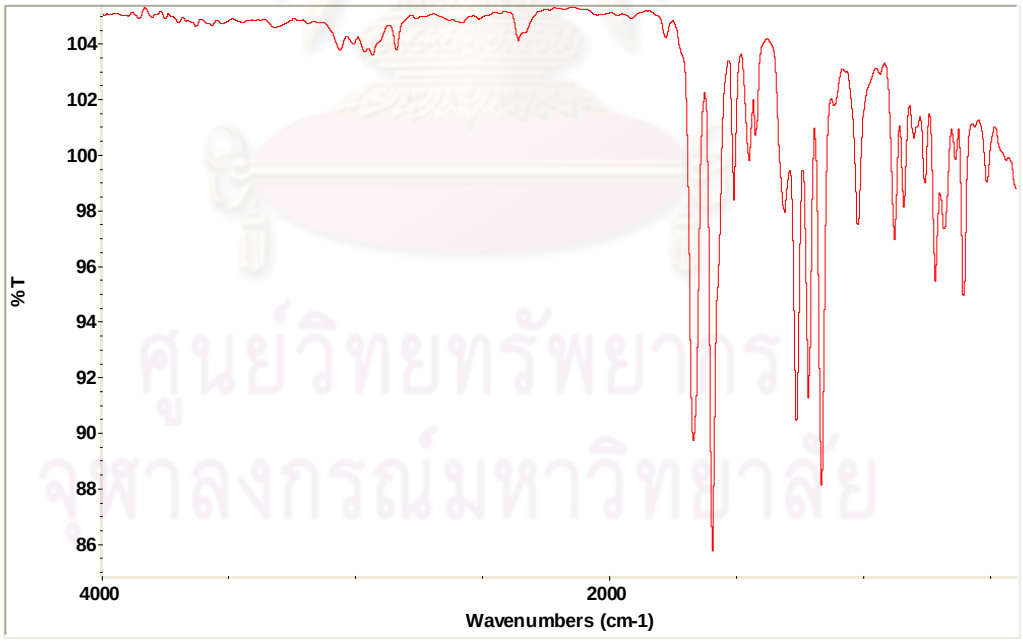

Figure 157 IR spectra of compound **177d**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

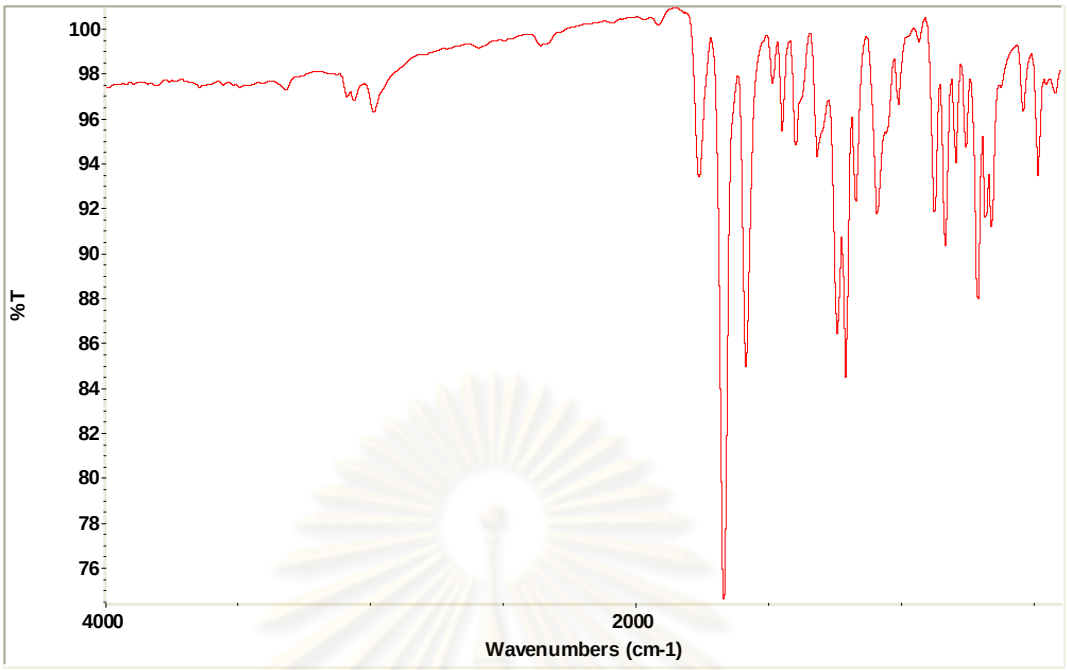

Figure 158 IR spectra of compound **177e**

Figure 159 IR spectra of compound **177f**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

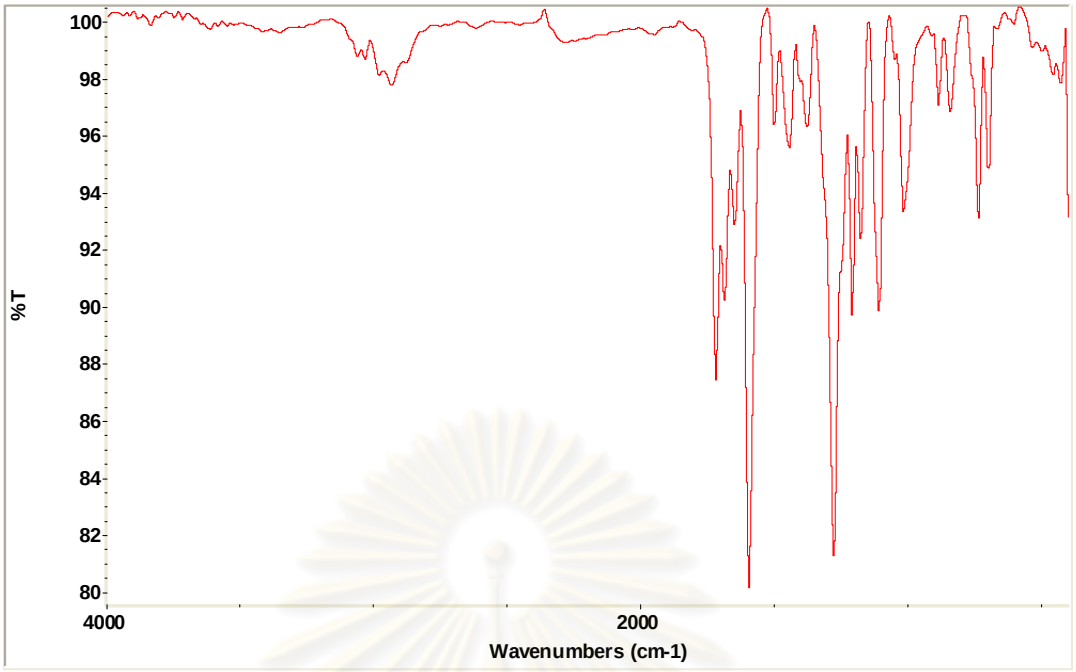

Figure 160 IR spectra of compound **177g**

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

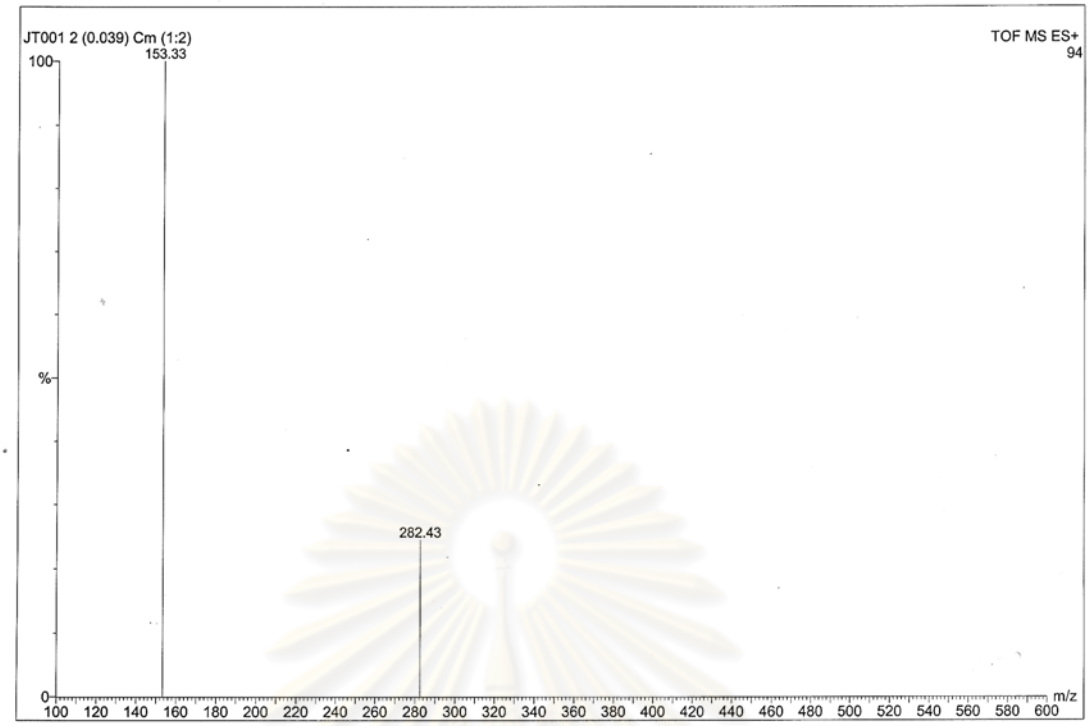

Figure 161 Mass spectra of compound **146**

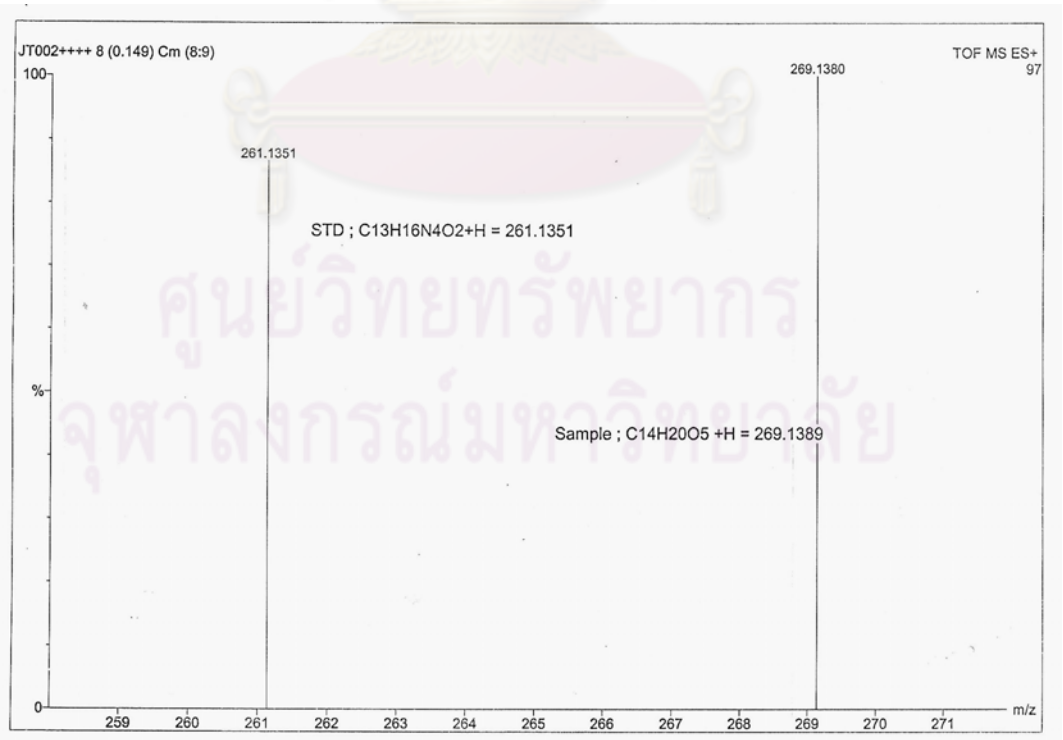

Figure 162 Mass spectra of compound **147**

Figure 163 Mass spectra of compound **148**

Figure 164 Mass spectra of compound **20**

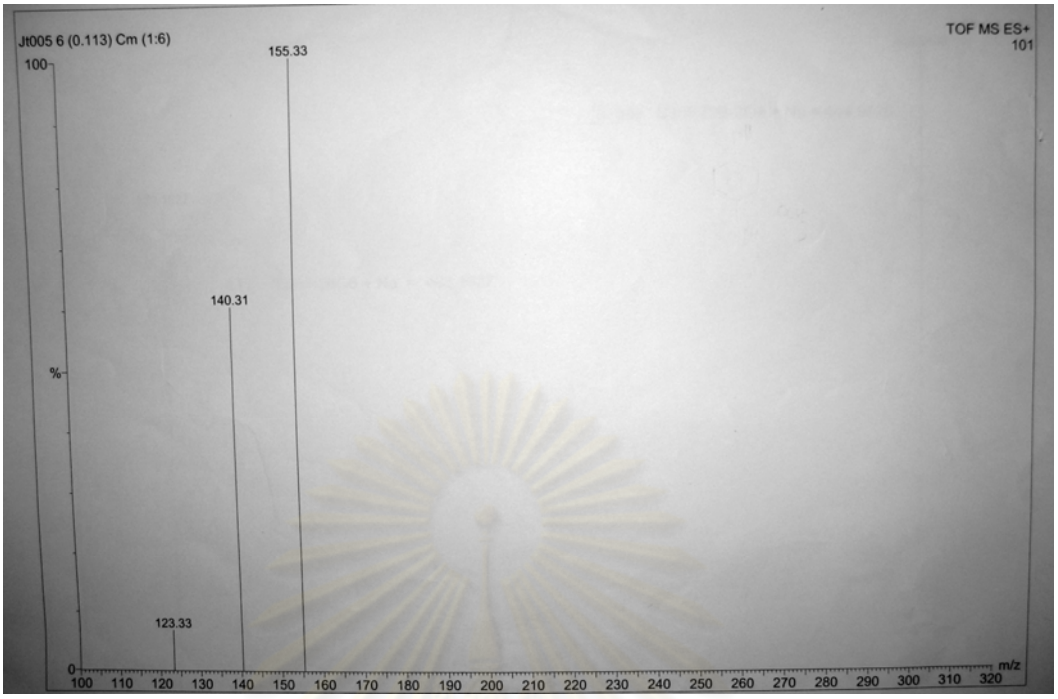

Figure 165 Mass spectra of compound **150**

Figure 166 Mass spectra of compound **151**

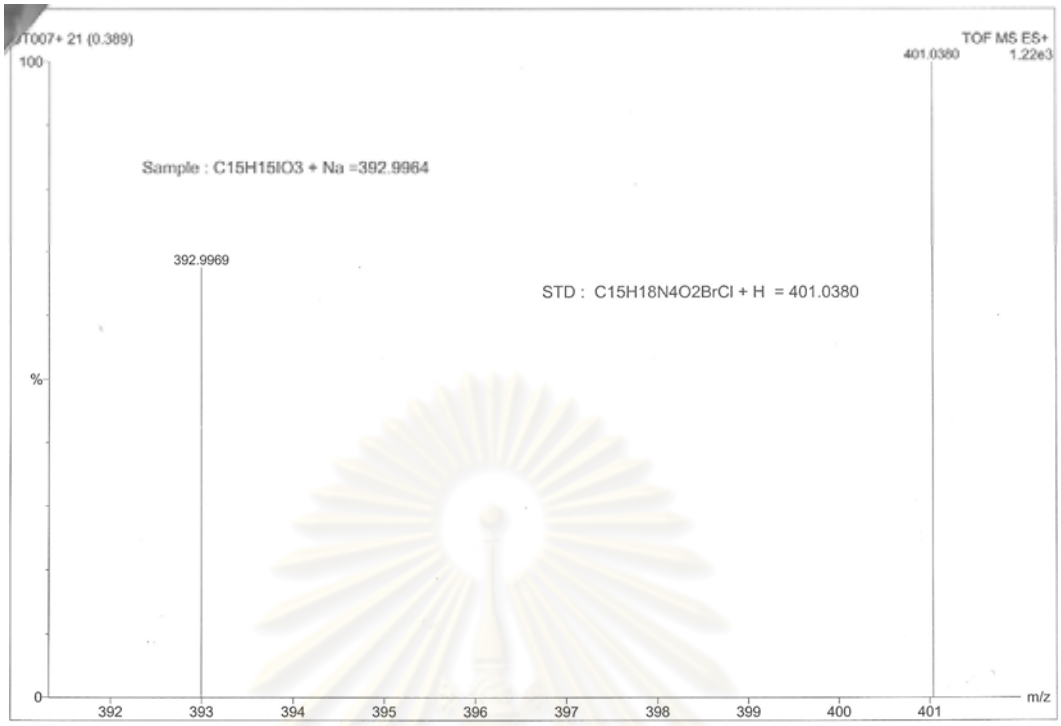

Figure 167 Mass spectra of compound **21**

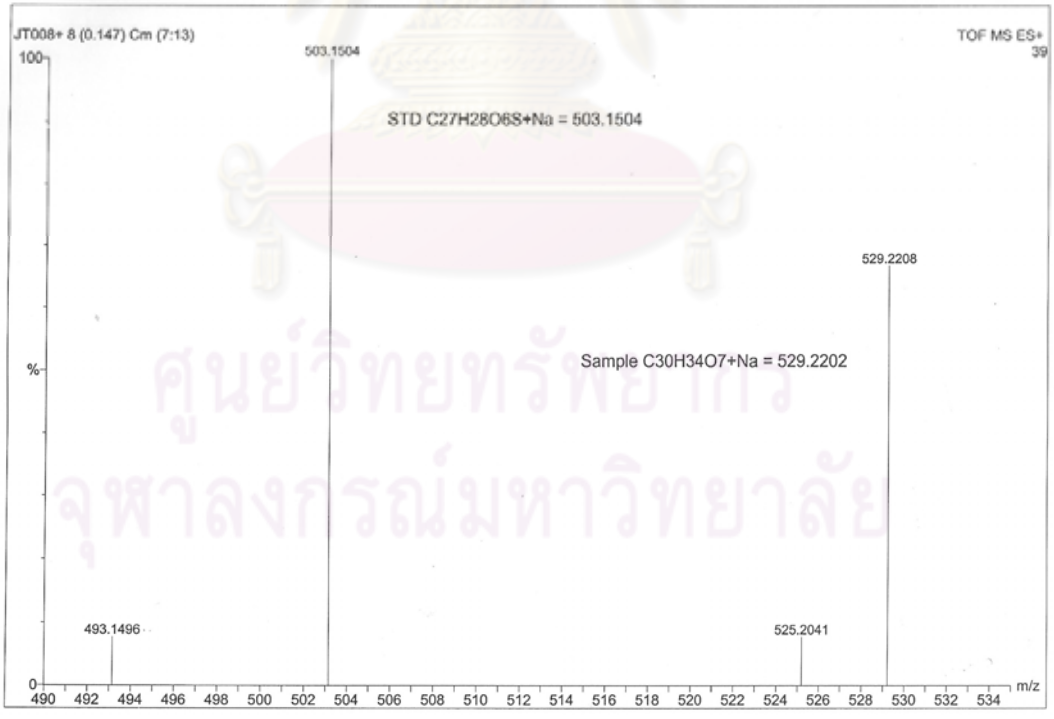

Figure 168 Mass spectra of compound **152**

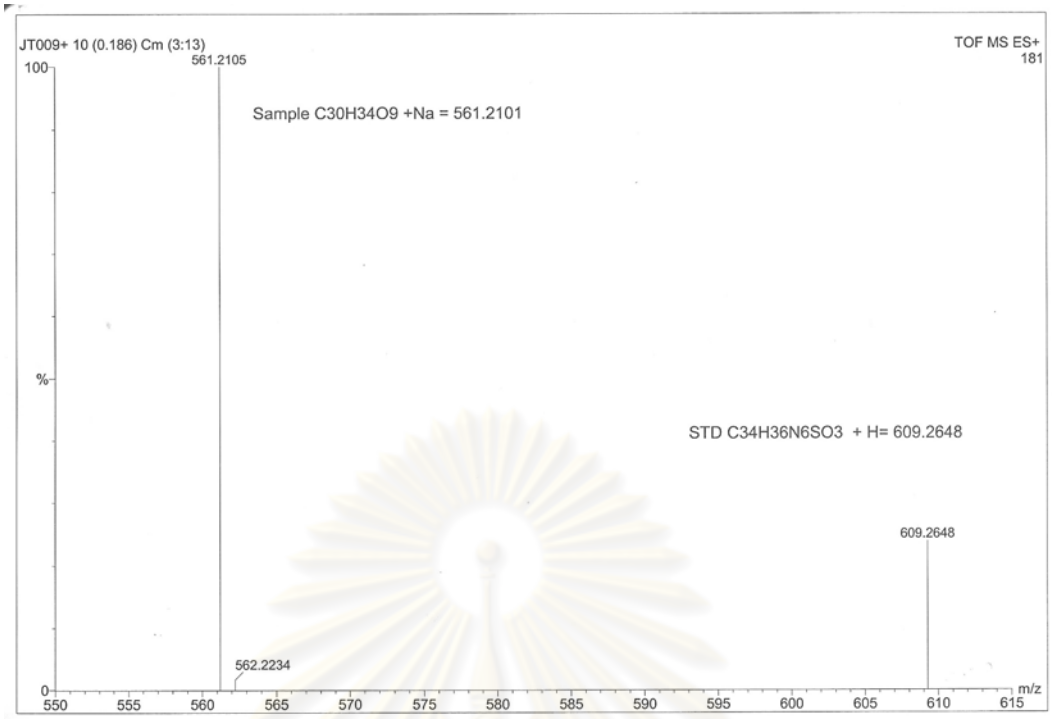

Figure 169 Mass spectra of compound **19**

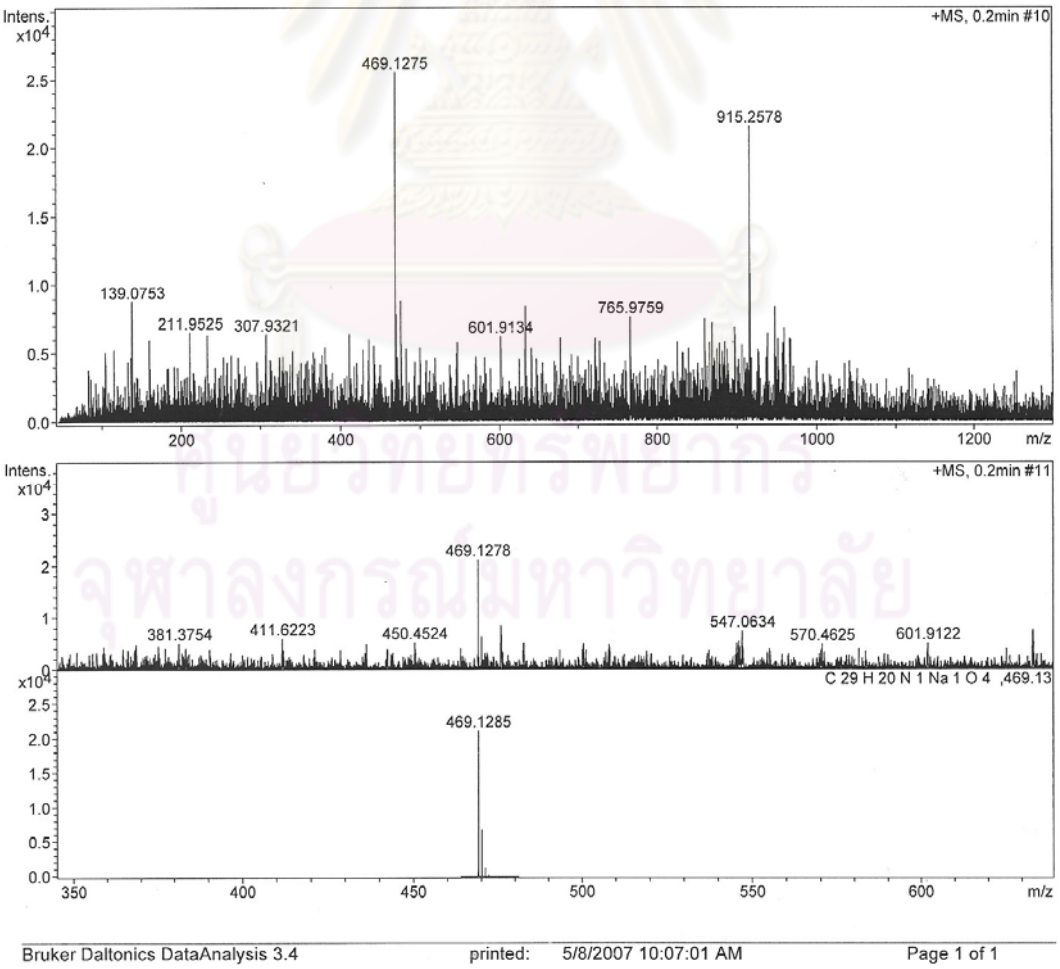

Figure 170 Mass spectra of compound **153**

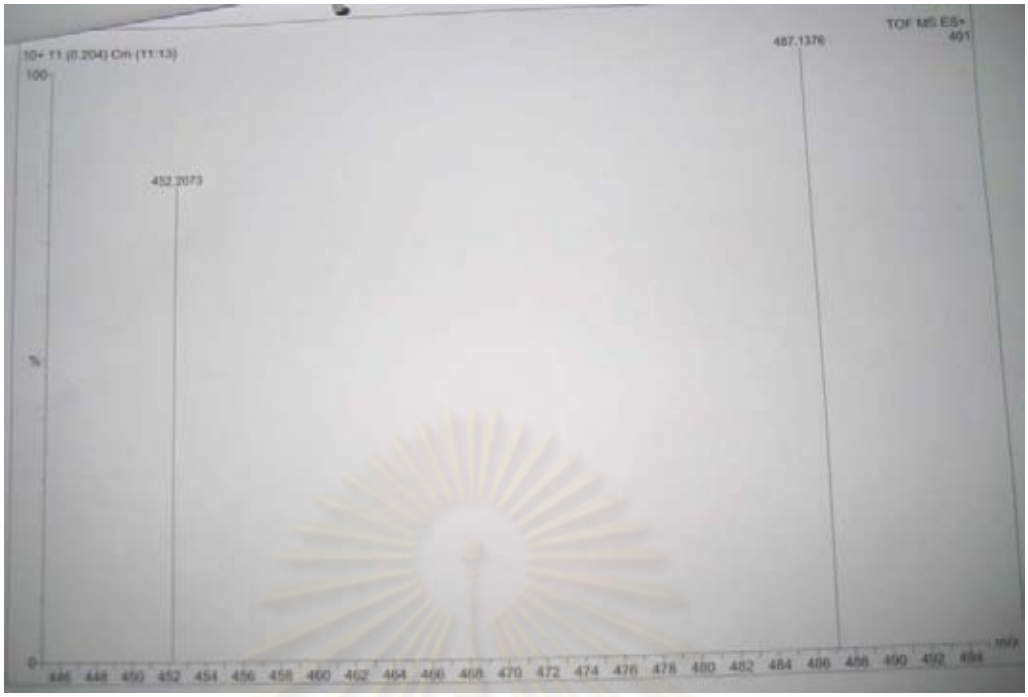

Figure 171 Mass spectra of compound **154**

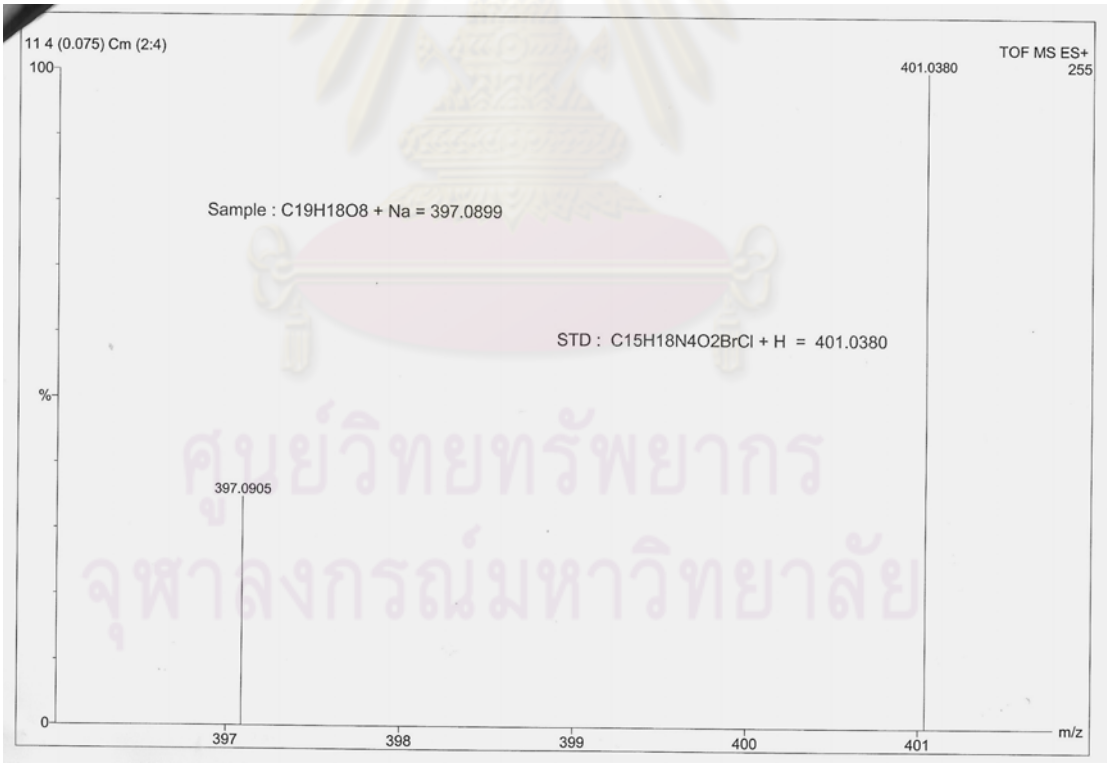

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Figure 172 Mass spectra of compound **155**

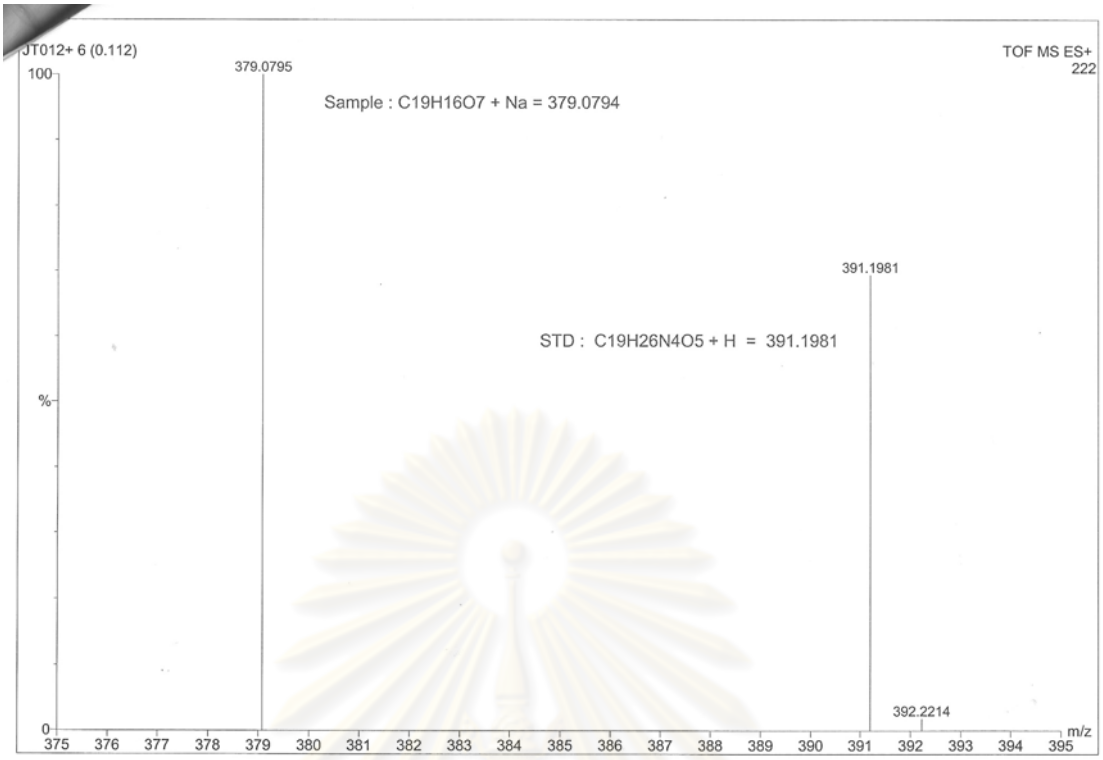

Figure 173 Mass spectra of compound **1**

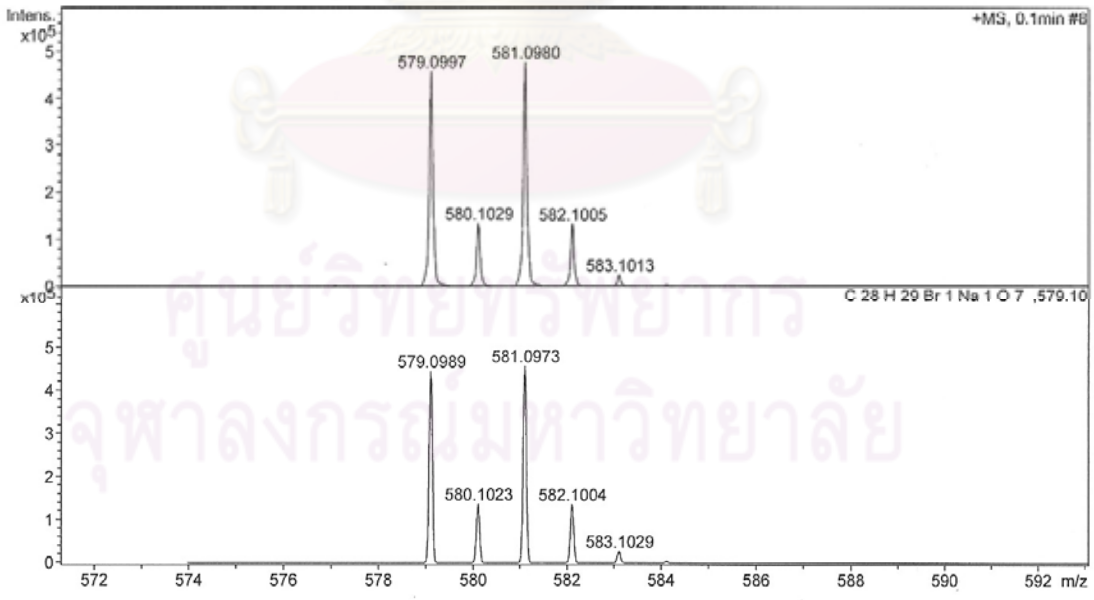

Figure 174 Mass spectra of compound **160**

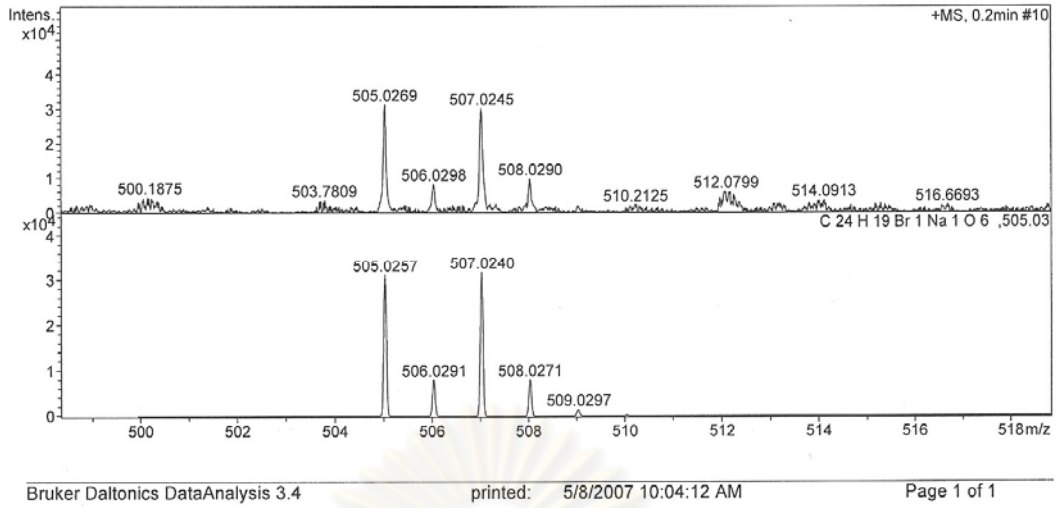

Figure 175 Mass spectra of compound **161**

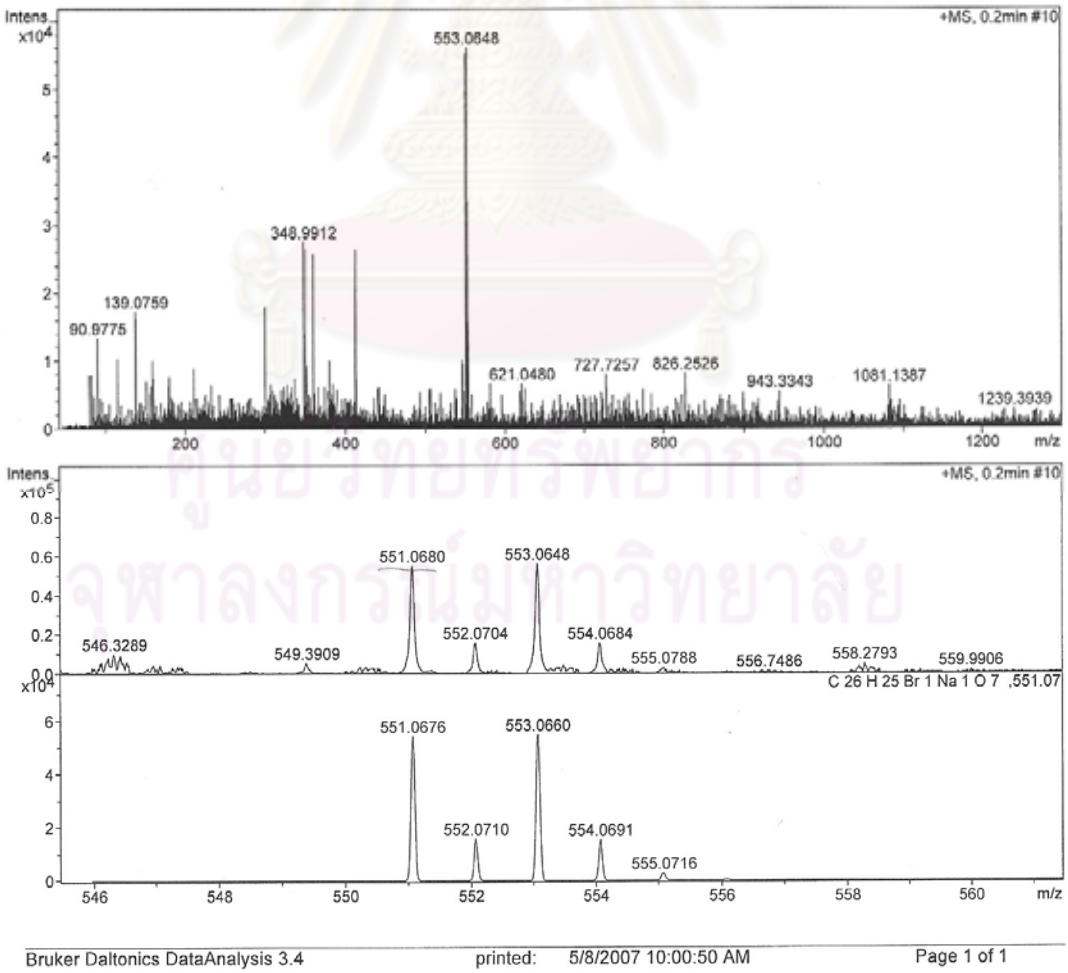

Figure 176 Mass spectra of compound **162** and **163**

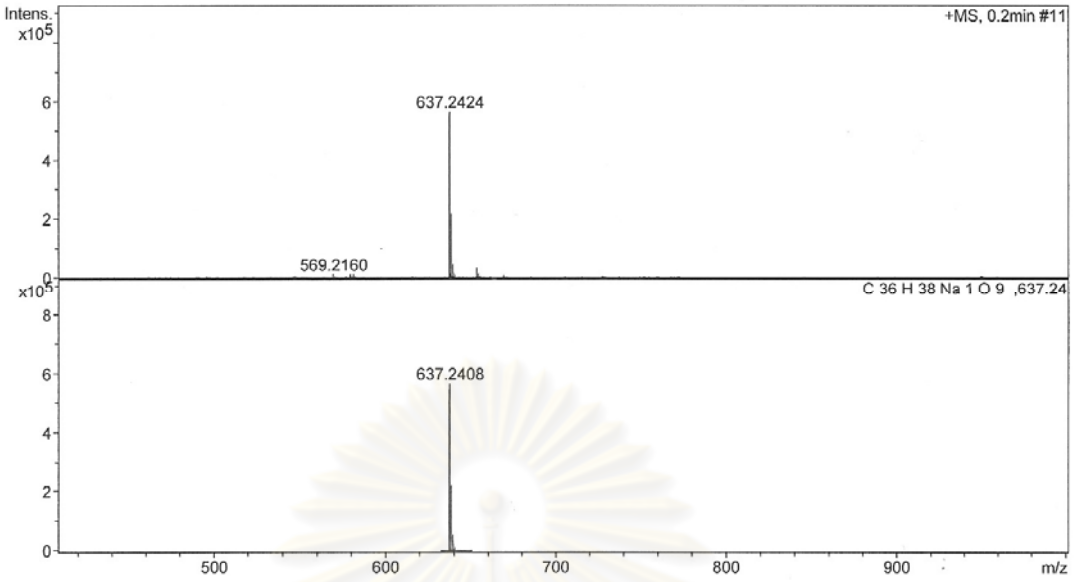

Figure 177 Mass spectra of compound **170**

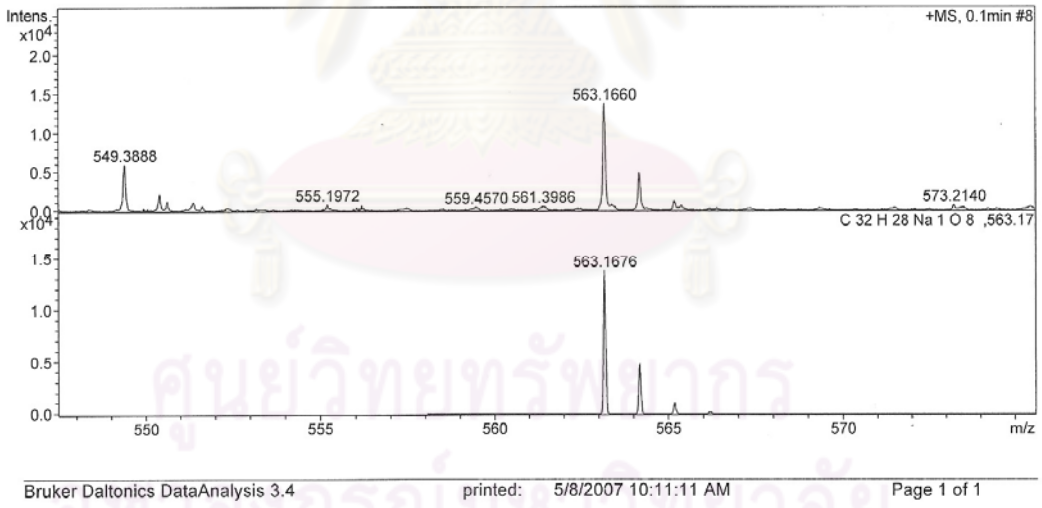

Figure 178 Mass spectra of compound **171**

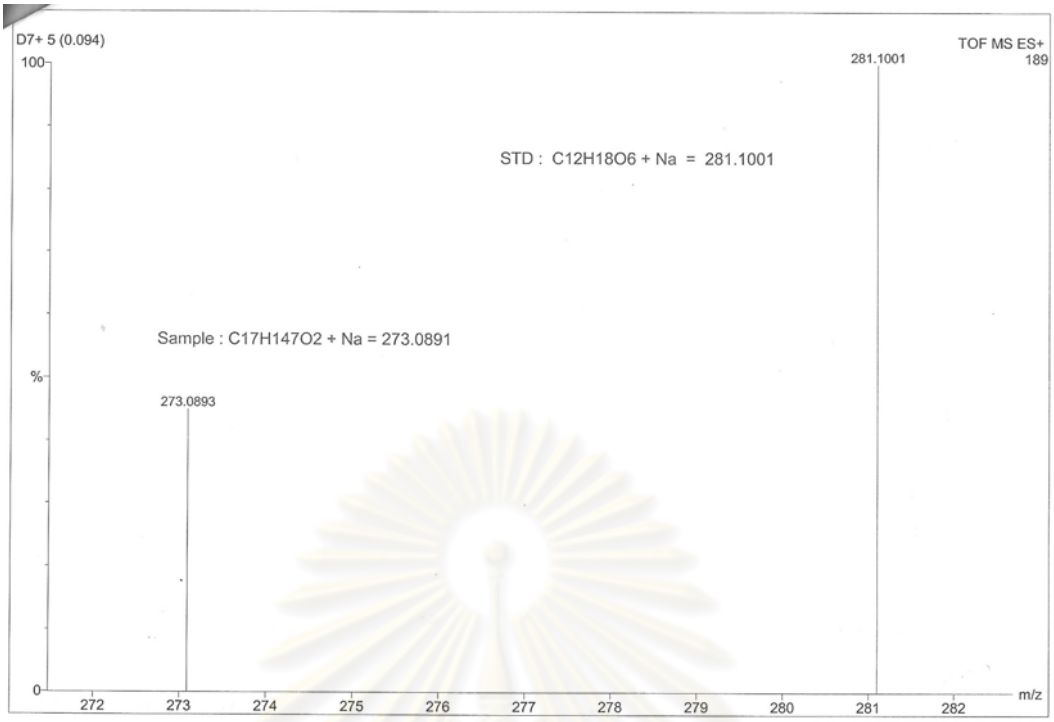

Figure 179 Mass spectra of compound **176d**

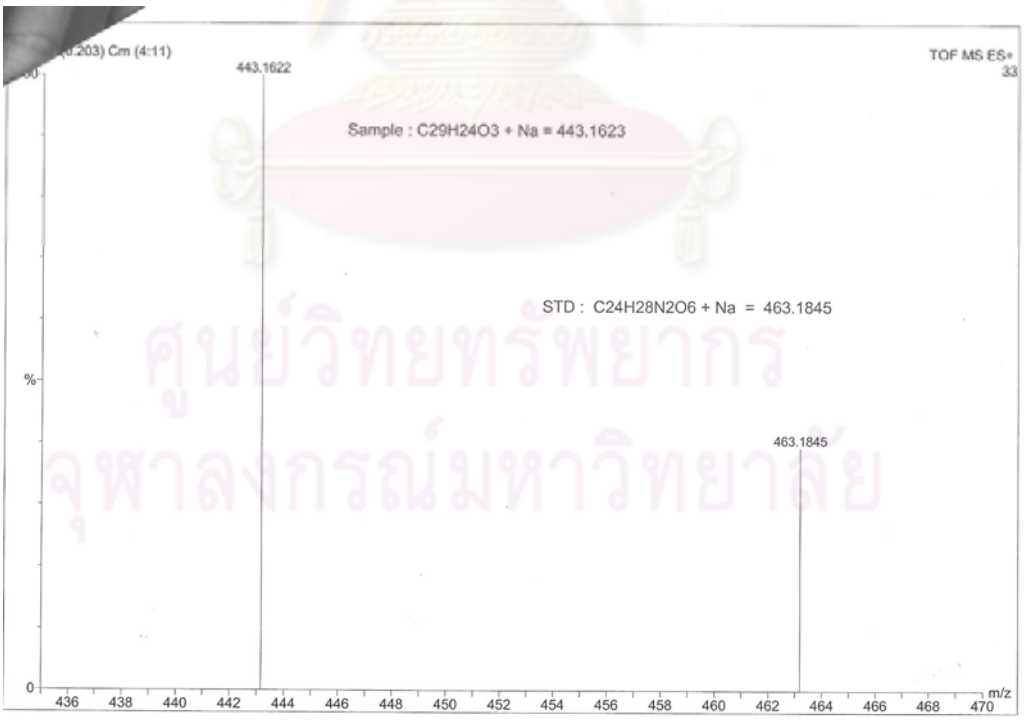

Figure 180 Mass spectra of compound **176f**

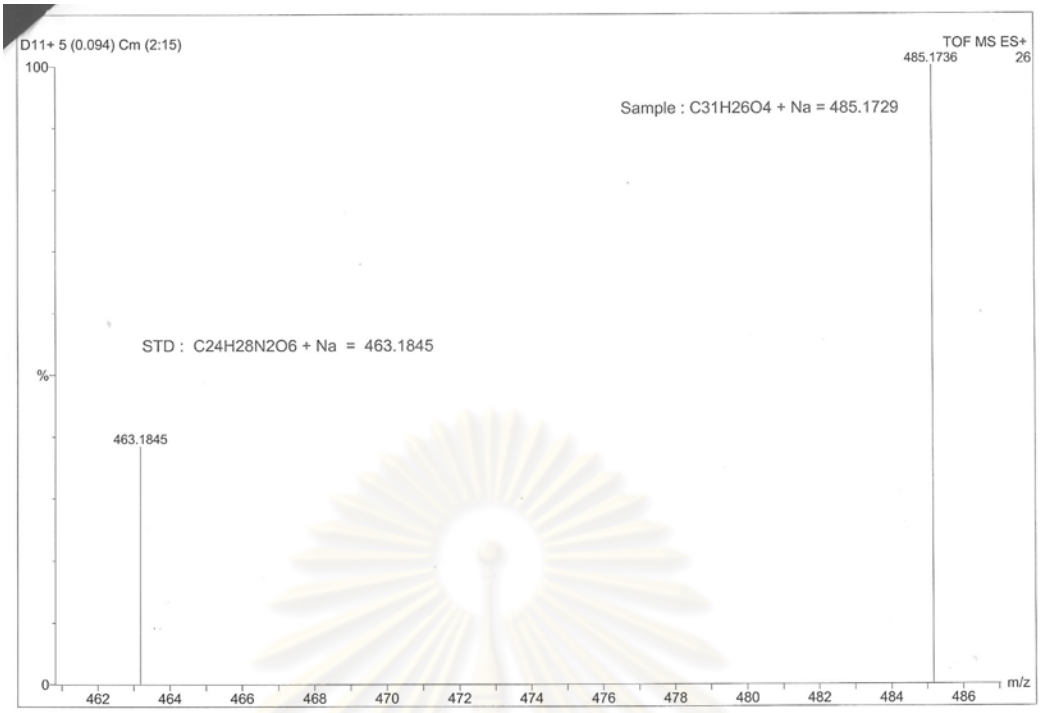

Figure 181 Mass spectra of compound **176g**

Figure 182 Mass spectra of compound **177a**

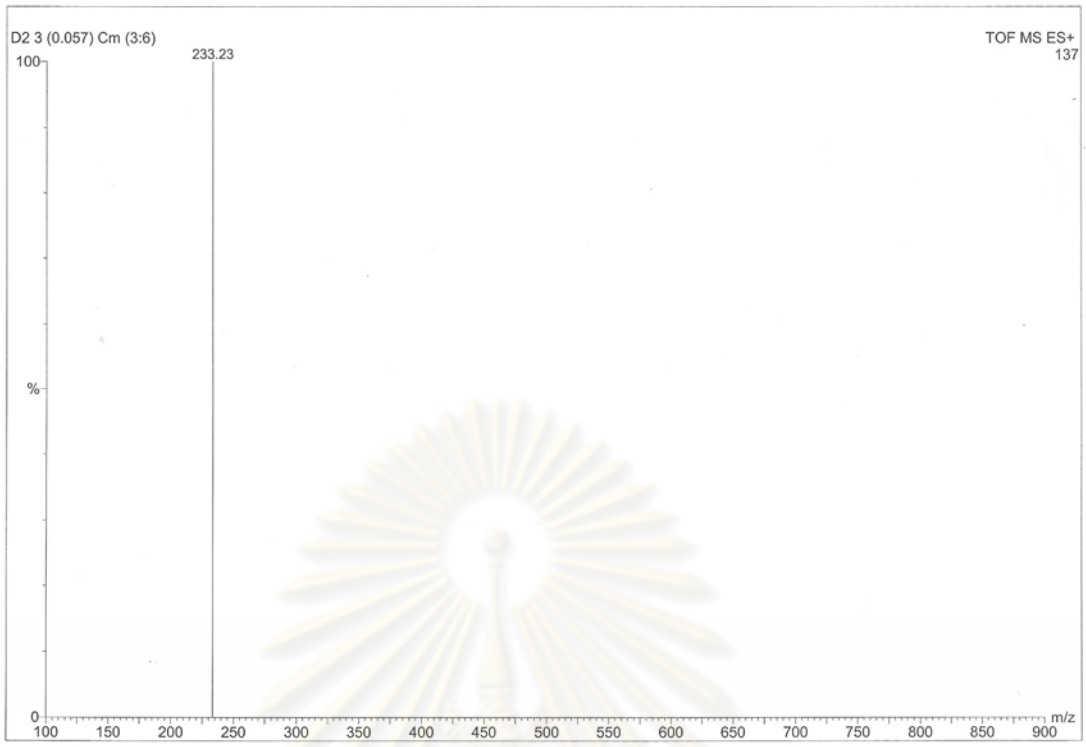

Figure 183 Mass spectra of compound **177b**

Figure 184 Mass spectra of compound **177d**

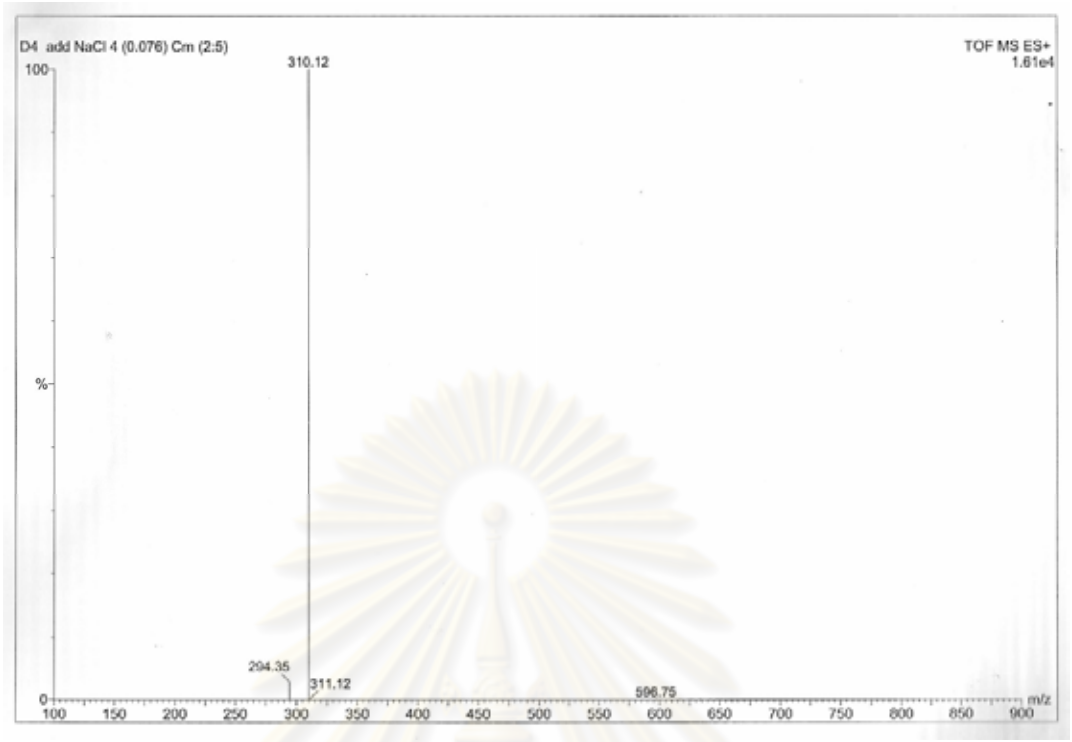

Figure 185 Mass spectra of compound **177e**

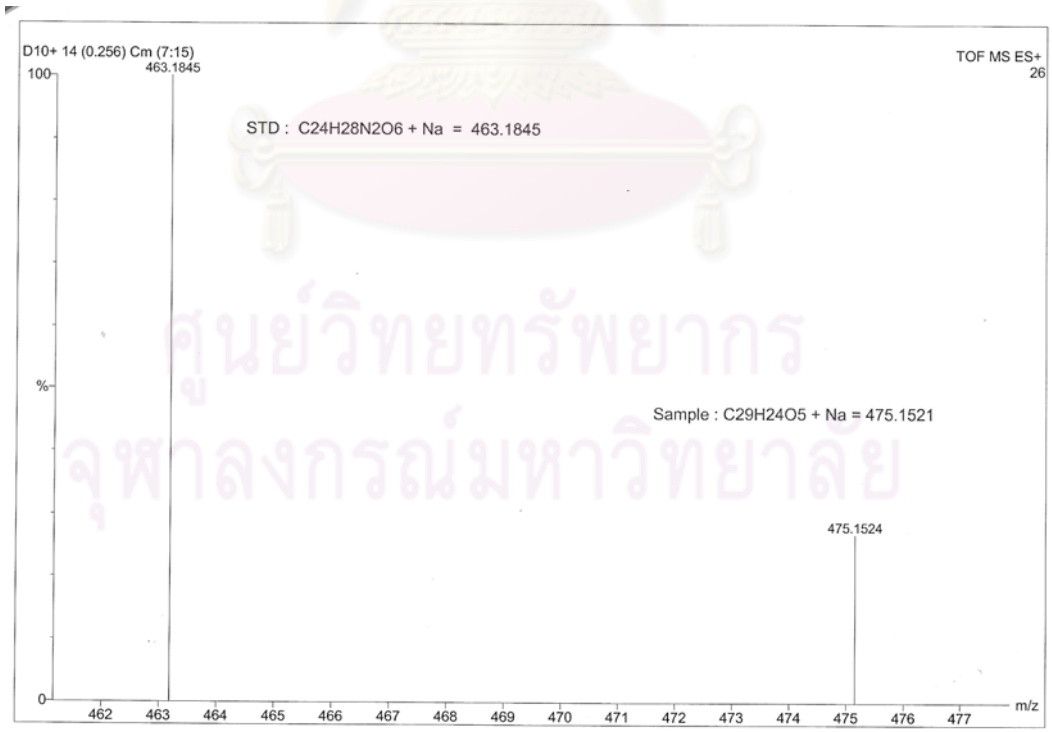

Figure 186 Mass spectra of compound **177f**

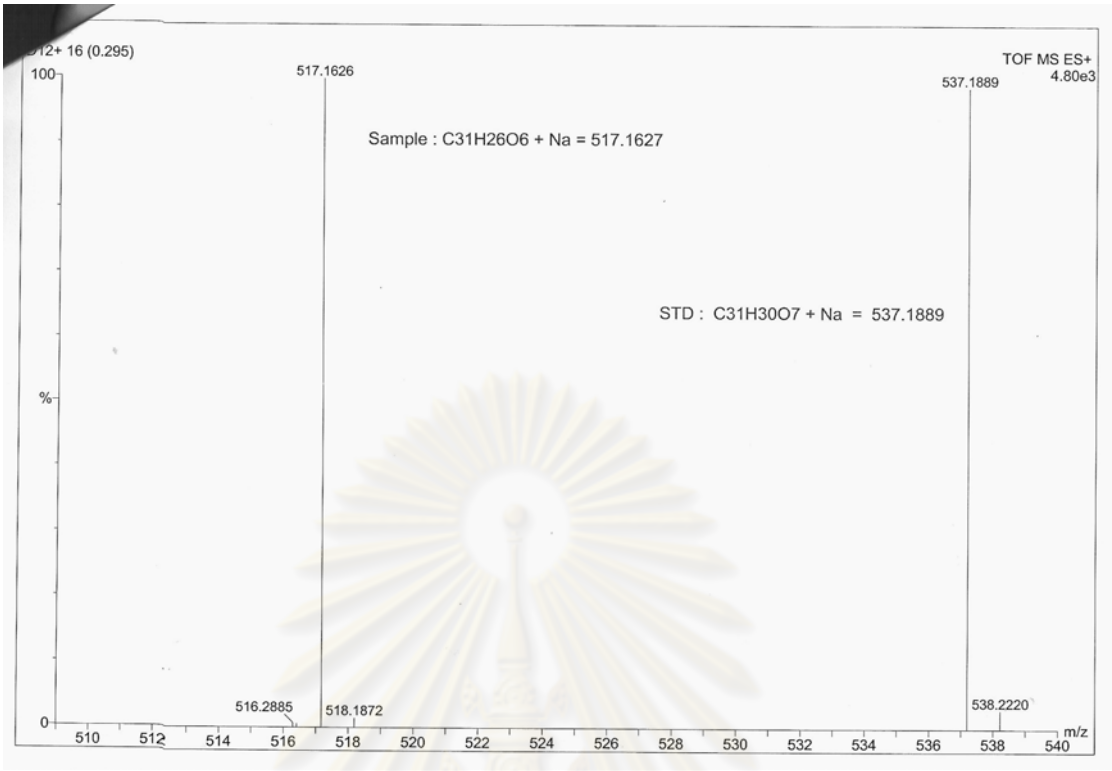

Figure 187 Mass spectra of compound **177g**

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จุฬาลงกรณ์มหาวิทยาลัย

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2006- 2008 The Royal Golden Jubilee, Thailand Research Fund for Ph.D. program

Publications:

1. **Tummatorn, J.**; Wanno, B.; Roengsumran, S.; Ruangpornvisuti, V. “Theoretical study of the diastereoselective reaction of proline-catalyzed intramolecular aldol cyclization of aldehyde derivative” 2008, submitted.
2. **Tummatorn, J.**; Dudley, G.B. “Ring-opening / fragmentation of dihydropyrones for the synthesis of homopropargyl alcohols” *J. Am. Chem. Soc.* **2008**, *130*, 5050-5051.
3. **Tummatorn, J.**; Albiniak, P.A.; Dudley, G.B. “Synthesis of benzyl esters using 2-benzyloxy-1-methylpyridinium triflate” *J. Org. Chem.* **2007**, *72*, 8962-8964.
4. **Tummatorn, J.**; Khorphueng, P.; Petsom, A.; Muangsin, N.; Chaichit, N.; Roengsumran, S. “Convenient synthetic route to a dehydorotenoid via selective intramolecular aldol condensation of 1,2-diaryl diketone” *Tetrahedron* **2007**, *63*, 11878-11885.
5. Khorphueng, P.; **Tummatorn, J.**; Petsom, A.; Taylor, R.J.K.; Roengsumran, S. “The total synthesis of 6-deoxyclitoriacetal isolated from *Stemona collinase* Craib.” *Tetrahedron Lett*. **2006**, *47*, 5989-5991.
6. Khaokum, L.; Sawasdipuksa, N.; Khumthong, N.; **Tummatorn, J.**; and Roengsumran, S. “Cardanol polysulfide as a vulcanizing agent for natural rubber” *J. Sci. Res*. **2005**, *30*, 24-40.

Presentations:

1. Iodine-catalyzed *C*-glycosidation of silylacetylene with glucal, ***Poster presentation*** in the 28th Congress on Science and Thechnology of Thailand, 24-26 October, 2002, Queen Sirikit National Convention Center Bangkok.
2. Ring-opening C-C bond cleavage of 5,6-dihydro-2-pyrones for the synthesis of homopropargyl alcohols. ***Oral-presentation*** in the 235th American Chemical Society National Meeting & Exposition, April 6-10, 2008, New Orleans, Louisiana.