การสังเคราะห์ฟิวโรฟิวแรนลิกแนนชนิดใหม่ผ่านการแทนที่ด้วยนิวคลีโอไฟล์ของซามิน

นางสาวนันทพร สุรชัยธนวัฒน์

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SYNTHESIS OF NEW FUROFURAN LIGNANS THROUGH NUCLEOPHILIC SUBSTITUTION OF SAMIN

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Field of Study	Chemistry
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นันทพร สุรชัยธนวัฒน์ : การสังเคราะห์ฟิวโรฟิวแรนลิกแนนชนิดใหม่ผ่านการแทนที่ด้วยนิวคลีโอไฟล์ของซามิน (SYNTHESIS OF NEW FUROFURAN LIGNANS THROUGH NUCLEOPHILIC SUBSTITUTION OF SAMIN) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร.ปรีชา ภูวไพรศิริศาล, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: รศ. ดร.วิวัฒน์ วชิรวงศ์กวิน, 137 หน้า.

การสังเคราะห์แบบ semi-synthesis ของ furofuran lignan ที่มีสูตรโครงสร้างแบบ [3.3.0]ไบไซคลิก เกือบ 50 อนุพันธ์เริ่มต้นจากสารที่พบได้ในธรรมชาติ sesamolin ถูกอธิบาย วิธีการสังเคราะห์เกี่ยวข้องกับการ protonation ของ samin เพื่อให้เกิดเป็นสารมัธยันตร์ oxocarbenium ion ตามด้วยการเข้าทำปฏิกิริยาของ nucleophile ที่แตกต่างกัน 3 ชนิด ได้แก่ ฟีนอลิค ไทออล และแอลกอฮอล์ วิธีการนี้ให้ผลิตภัณฑ์ที่เป็นคู่ diastereomer ยกเว้นจากการสังเคราะห์ด้วย samin กับแอลกอฮอล์ กลไกการเกิดปฏิกิริยาแบบ steroselective ถูกตรวจสอบโดยการติดตามปฏิกิริยาด้วย ^{1}H NMR และการคำนวณทางคอมพิวเตอร์ ผลการทดลองแสดงให้เห็นว่า ผลิตภัณฑ์ที่ได้น่าจะเกิดผ่านกลไกปฏิกิริยาแบบ S_N1-like โดยการ protonation ของหมู่ hemiacetal ของ samin เพื่อเกิดเป็นสารมัธยันตร์ oxocarbenium ion ตามด้วยทำปฏิกิริยากับแอลกอฮอล์ เกิดผลิตภัณฑ์ *exo,exo*-alkoxysamin ทั้งโดยตรง หรือจากการ protonation ของ *endo,exo*-alkoxysamin ผ่าน S_N2-like transition state

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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NANTAPORN SURACHAITANAWAT: SYNTHESIS OF NEW FUROFURAN LIGNANS THROUGH NUCLEOPHILIC SUBSTITUTION OF SAMIN. ADVISOR: ASSOC. PROF. PREECHA PHUWAPRAISIRISAN, Ph.D., CO-ADVISOR: ASSOC. PROF. VIWAT VCHIRAWONGKWIN, Ph.D., 137 pp.

The semi-synthesis of fifty furofuran lignans having a bicyclo[3.3.0]octane skeleton starting from the naturally available sesamolin is described. Our methodology involved protonation of samin to generate oxocarbenium ion followed by the attack of three different nucleophiles, namely, phenolics (ArOH), thiols (RSH) and alcohols (ROH). This synthesis strategy provided diastereomeric products except for those synthesized from samin and alcohols. The mechanism of stereoselective formation was investigated by ^{1}H NMR monitoring technique and computational calculation. The results revealed that the products were presumably formed through S_N1-like mechanism by protonation of the hemiacetal center of samin to generate the corresponding oxocarbenium ion as the intermediate. Subsequent reaction of this oxocarbenium ion with the alcohols then led to the observed *exo,exo*-alkoxysamin either directly, or alternatively, by protonation of the *endo,exo*-alkoxysamin through the S_N2-like transition state.

Department:	Chemistry	Student's Signature	.....
Field of Study:	Chemistry	Advisor's Signature	.....
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List of Abrevations

^{13}C NMR	carbon-13 nuclear magnetic resonance
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
d	doublet (NMR)
dd	doublet of doublet (NMR)
2D NMR	two dimensional nuclear magnetic resonance
ESIMS	electroscopy ionization mass spectrometry
eq	equivalent (s)
g	gram (s)
^{1}H NMR	proton nuclear magnetic resonance
HMBC	heteronuclear multiple bond correlation experiment
Hz	hertz
HRESIMS	high resolution electrospray ionization mass spectrum
h	hour (s)
J	coupling constant
mg	milligram (s)
mL	milliliter (s)
mmol	millimole (s)
m/z	mass per charge
m	multiplet (NMR)
M.W.	molecular weight
M	molar
NOESY	nuclear overhauser enhancement spectroscopy
rt	room temperature
s	singlet (NMR)

TFA-d	deuterated-trifluoroacetic acid (CF_3CO_2D)
TLC	thin layer chromatography
UV	ultraviolet
δ	chemical shift
°C	degree Celsius
%yield	percentage yield

CHAPTER I

INTRODUCTION

Furofurans are one of major subclasses of lignan family which originated from shikimic acid pathway followed by dimerization of phenyl propanoids (C_6-C_3) at center carbon (C-8) (Figure 1.1) [1]. Since their structures contain 2,6-diaryl substituted on 3,7-dioxabicyclo[3.3.0]octane skeleton, furofurans can be divided into three types; *endo-endo*, *endo-exo* and *exo-exo*, based on stereochemistry of substituents related to head bridge hydrogen (Figure 1.1)

Figure 1.1 Structure of phenyl propanoid and three subgroups of furofuran lignans

According to variety of their structures, furofuran lignans are responsible for a wide range of bioactive compounds, such as antitumoral of syringaresinol (**1.1**) [2], antioxidant of sesamolin (**1.2**) [3] and reducing serum and liver cholesterol levels in rat of sesamin (**1.3**) [4]. This has inspired organic chemists to develop synthetic methodologies for synthesis of this class of bioactive compounds and improve their chemical and pharmaceutical profiles.

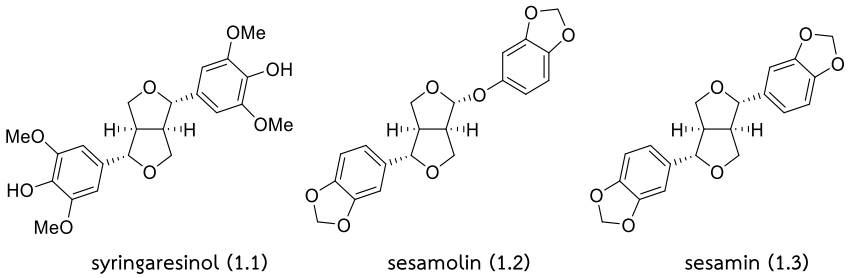
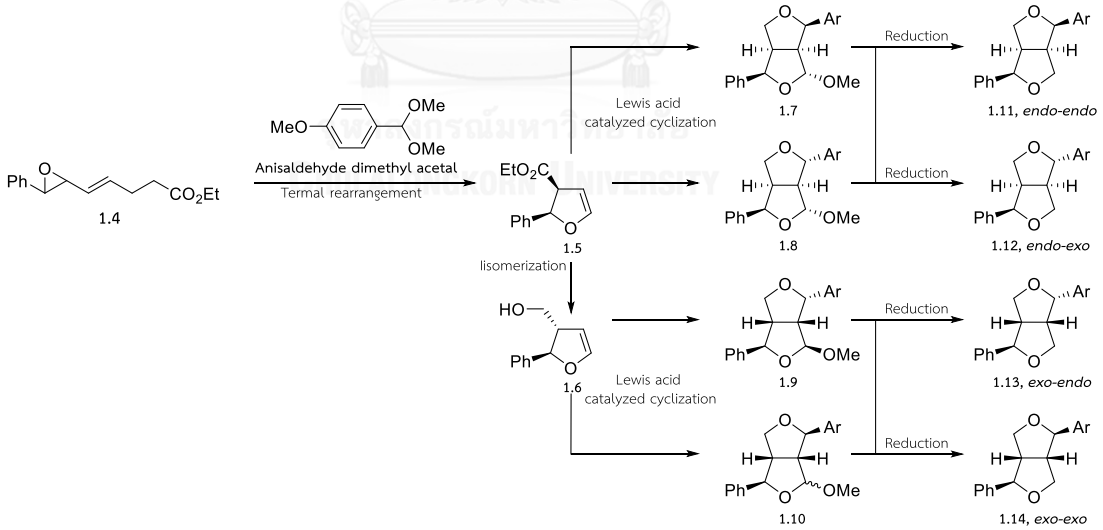


Figure 1.2 Structure of bioactive furofuran lignans.

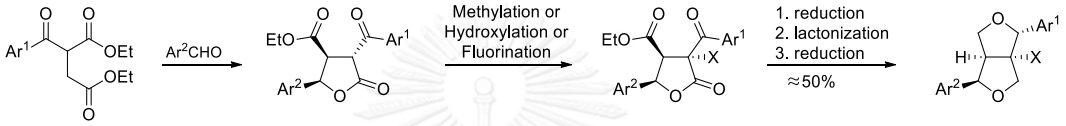
For instance in 2003, David [5] reported diastereoselective synthesis of furofuran lignans. Single vinyl epoxide (**1.4**) was used as a starting material followed by thermal rearrangement afforded *cis*-disubstituted dihydrofuryl ester (**1.5**)**.** Subsequent lewis acid catalyzed cyclization gave either the *endo-endo* (**1.7**) or *endo-exo* furofuran acetal (**1.8**) depending on reaction temperatures. Then, isomerization of **1.5** provided the alternative *exo-endo* and *exo-exo* isomers (**1.9** and **1.10** respectively). Finally, acetal group was reduced to cyclic ether to complete the synthesis furofuran skeleton (**1.11**-**1.14**), as shown in Scheme 1.1.



Scheme 1.1 Synthesis of 1-fluoro-*endo,exo*-furofurans **1.11-1.14**

As well in 2005, Pohmakotr [6] synthesized 1-substitued *endo,exo*-2,6-diaryl-3,7-dioabicyclo[3.3.0]octanes (**1.18-1.24**) and (±)-gmelinol (**1.25-1.26**). Their investigation began with the synthesis of (2,3-trans)-(4,5-cis)- α-aroylparaconic esters

(**1.16**) by reacting vicinal dianions derived from the corresponding α-aroylsuccinic esters (**1.15**) with aromatic aldehydes. Subsequently, methylation or hydroxylation at carbon position 1 was carried out to produce 1-substitued lactone as core structure. They next achieved synthesis of furofurans **1.18-1.26** by three steps involving reductions and lactonization as shown in Scheme 1.1. Similarly in 2015, Punirun [7] reported the synthesis of 1-fluorine-substituted *exo,exo*-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes (**1.27-1.32**) using aforementioned procedure (**Scheme 1.2**).



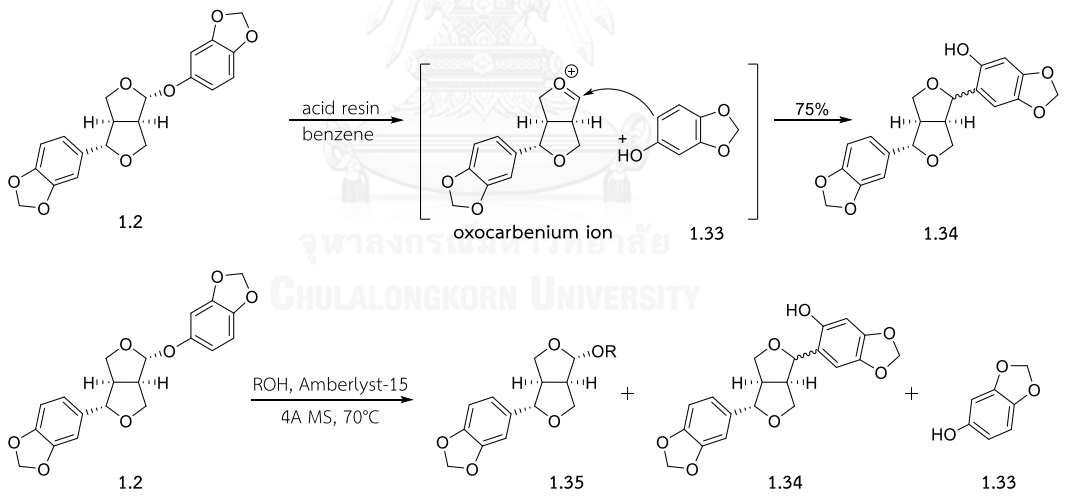
1.15 **1.16** **1.17** **1.18-1.32**

1.18	Ar^1=3,4-$(CH_3O)_2C_6H_3$,	Ar^2=3-HO-4-$CH_3C_6H_3$,	X=OH	1.26	Ar^1=C_6H_5,	Ar^2=C_6H_5,	X=F
1.19	Ar^1=3-HO-4-$CH_3OC_6H_3$,	Ar^2=3-CH_3O-4-HOC_6H_3,	X=OH	1.27	Ar^1=C_6H_5,	Ar^2=4-$CH_3OC_6H_4$,	X=F
1.20	Ar^1,Ar^2=4-HO-3-$CH_3OC_6H_3$,		X=OH	1.28	Ar^1=4-$CH_3OC_6H_4$,	Ar^2=C_6H_5,	X=F
1.21	Ar^1=3,4-$(CH_3O)_2C_6H_3$,	Ar^2=3-HO-4-$CH_3C_6H_3$,	X=CH_3	1.29	Ar^1=4-$CH_3OC_6H_4$,	Ar^2=4-$CH_3OC_6H_4$,	X=F
1.22	Ar^1=3-HO-4-$CH_3C_6H_3$,	Ar^2=3-CH_3O-4-HOC_6H_3,	X=CH_3	1.30	Ar^1=4-$CH_3C_6H_4$,	Ar^2=4-$CH_3C_6H_4$,	X=F
1.23	Ar^1,Ar2=4-HO-3-$CH_3OC_6H_3$,		X=CH_3	1.31	Ar^1=4-Br-3-$CH_3OC_6H_3$,	Ar^2=4-$CH_3C_6H_4$,	X=F
1.24	Ar^1,Ar^2=3,4-$(CH_3O)_2C_6H_3$,		X=OH	1.32	Ar^1=4-Br-3-$CH_3OC_6H_3$,	Ar^2=4-$CH_3OC_6H_4$,	X=F
1.25	Ar^1,Ar^2=3,4-$(CH_3O)_2C_6H_3$,		X=CH_3				

Scheme 1.2 Synthesis of 1-fluoro-*endo,exo*-furofurans **1.18-1.32**

Although a number of developed synthetic methodologies and structure modifications of these bioactive compounds were explored, structural activity relationship studies (SARs) have not been reported due to the lack of a practical synthetic method of producing diverse furofuran lignans. As aforementioned synthetic strategies, furofurans were synthesized through many stepwise combinations of small building block leading to provide expected products in low yield (≈50%). Moreover, a variety of furofuran lignans was also dropped because of the limited diversity of starting material. From this reasons, we would like to optimize a new synthetic approach to easily produce a huge series of furofuran lignans.

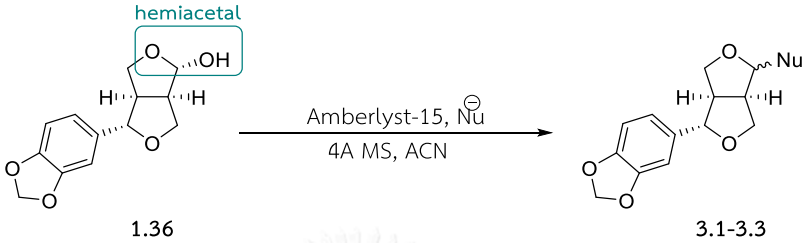
Recently, some researchers reported short route synthesis of furofuran lignans by modifying naturally available sesamolin (**1.2**) to offer its derivatives. For example in 2012 [8], Haung synthesized sesaminol (**1.34**) from **1.2** in the presence of acidic resin using benzene as aprotic nonpolar solvent. Noteworthy, the key step in aforementioned synthesis involved acid-catalyzed formation of oxocarbenium ion. Nucleophilic substitution by carbon nucleophile such as sesamol (**1.33**) afforded **1.34**. Identically in 2015, Mahamad [9] synthesized a series of alkyloxy samins (**1.35**) in one step by reaction of sesamolin (**1.2**) with various alcohols. The products were generated with retention of configuration, which were different from mechanistic presumption involving oxocarbenium ion that would result in product mixtures. Moreover, this methodology also has limitation due to the occurrence of unexpected products sesaminol (**1.34**) and sesamol (**1.33**) (Scheme 1.3).



Scheme 1.3 Semi-synthesis of sesaminol (**1.34**) and alkyloxysamins (**1.35**) from sesamolin (**1.2**)

From literature reviews, semi-synthesis seem to be a suitable approach to furnish diverse furofuran lignans. In this work, we applied above methodology using samin (**1.36**) as starter instead of **1.2** due to the fact that hemiacetal moiety in **1.36** is relatively more reactive than acetal group of **1.2** toward nucleophilic substitution.

Moreover, the released of H_2O generated upon protonation of hemiacetal could be trapped by molecular sieve readily in order to avoid regeneration of samin (**1.36**). With samin (**1.36**) in hand, we examined the wide application of this reaction with three types of nucleophiles, phenolics (C), thiols (S) and alcohols (O) as show in Scheme 1.4.



Scheme 1.4 Synthetic strategy to furofuran lignans **3.1-3.3**.

In addition, there is no research studying about mechanistic reaction of samin under acid condition; and the stereoselective outcome of previous report [9] still unclear, therefore the mechanism understanding this reaction was carefully investigated by a model reaction monitored by ^{1}H NMR and computational calculations. For computational study, the geometrical optimization and determination of product energy have been calculated using the density functional theory (DFT) with the popular hybrid method (B3LYP). The split valence with diffuse and polarization functions, 6-31+G(d,p), basis set is used in this study to propose the reaction mechanisms through minimum-energy geometry. All of these calculations will be performed by Gaussian 09 program [10]

CHAPTER II

SYNTHESYS OF SAMIN

2.1 Isolation of sesamolin

The naturally available sesamolin (**1.2**) utilized in this work was isolated from sesame seed oil which contains large amount of lignan together with sesamolin 0.5-2 % w/w. According to existing of fatty acids in sesame seed oil, the purification by column chromatography directly is challenged. Therefore, the elimination of glyceride was performed in initial step. This approach is based on the fact that fatty acids can be saponified by KOH/MeOH, to give the corresponding potassium salts whereas **1.2** and other unsaponified matterials remain unchanged. The slightly excess of KOH (~1.5 times of saponification number) was applied in order to ensure complete removal of triglyceride. After refluxed 3-5 h or completed saponification, MeOH was removed followed by liquid-liquid extraction (H_2O and EtOAc). The organic layer containing **1.2** was further purified using silica gel column chromatography, to yield sesamolin (1 %w/w) as a white solid and its identities (^1H and ^{13}C NMR) were found to be identical with those reported in the literature [11]. This isolation methodology is summarized in Figure 2.1.

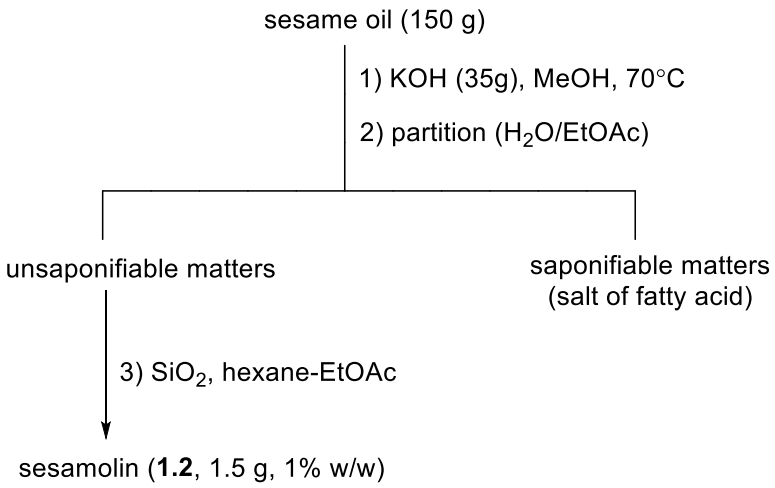
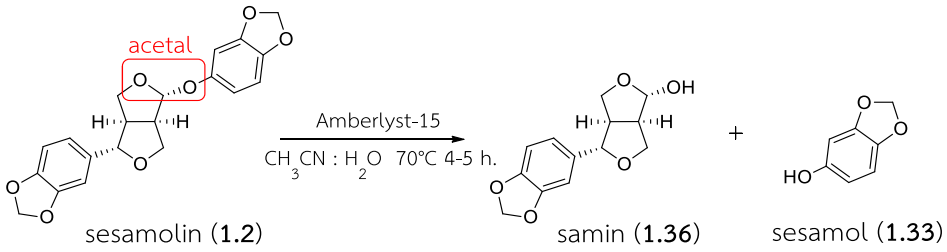


Figure 2.1 Isolation of sesamolin (**1.2**) from sesame oil.

2.2 Synthesis of samin

According to predominant potentiality of hemiacetal, samin (**1.36**) was used as a starting material. The synthesis of samin was operated with the methodology described by Reshma [12] with nominal modification. Briefly, Amberlyst-15 was used for acid-catalyzed hydrolysis of sesamolin (**1.2**) in 9:1 acetronitrile-water at 70 ℃ for 4-5 h. Sesamolin (**1.2**) was protonated on an acetal group resulting in the loss of sesamol and formation of expected samin (**1.36**) as shown in Scheme 2.1. The identification of **1.36** was investigated after purification by SiO_2 column chromatography eluting with ethyl acetate and hexane.



Scheme 2.1 Hydrolysis of sesamolin (**1.2**).

2.3 Experimental section

2.3.1 General experiment procedures

^{1}H and ^{13}C NMR were recorded ($CDCl_3$ as a solvent) at 400 and 100 MHz, respectively, Varian Mercury^{+} 400 NMR and a Bruker (Avance) 400 NMR spectrometer. The chemical shifts were reported in ppm downfield from TMS. Mass spectra were measured by HRESIMS obtaining from a micrOTOF Bruker mass spectrometer. Thin layer chromatography (TLC) was performed on pre-coated Merck silica gel 60 F_{254} plates (0.25 mm thick layer) and visualized under 254 nm UV. Silica gel 60 Merk cat. No. 7729 was used for open column chromatography.

2.3.2 Chemical

Sesame seed oils was purchased from Soun-Pana (Bangkok Thailand). All reagents were obtained from Sigma-Aldrich and used without further purification.

2.3.3 Determining of saponification number

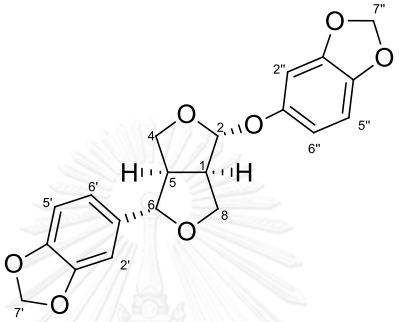
Saponification number was measured in triplicate by general procedure [13]. Briefly, a solution of 1 g sesame seed oil in 10 mL of 0.5M KOH/MeOH was stirred under 70°C for 3 h. After cooling, reaction was titrated against a standard solution of 0.5M HCl. The difference between test reaction and blank gave the volume of 0.5M HCl equivalence of KOH used in saponification 1 g sesame seed oil. Calculation of saponification number by below equation presented that sesame seed oil has S.N. around 156.6 mgKOH/oil.

$$\text{S.N. (mg KOH/oil)} = \frac{(V_{HCl,\ blank} - V_{Hcl\ test}) \times [HCl] \times 56}{W_{oil}}$$

Note : 56 is the equivalent mass of KOH. W is exact

2.3.4 Isolation of sesamolin

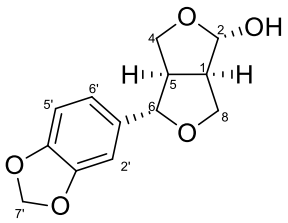
Sesame seed oil (150 g) dissolved in MeOH (150 mL) was saponified with KOH (34 g) for 5 h. After solvent removal, the resulting mixture was extracted with ethyl acetate and water. The organic layer was further purified by silica gel column chromatography using 1:9 ethylacetate/hexane to obtain sesamolin (**1.2**) (1.5 g, 1 %w/w).



Sesamolin (**1.2**) : as white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H, H-2″), 6.84 – 6.77 (m, 2H, H-5″ and H-6″), 6.71 (d, J = 8.5 Hz, 1H, H-5′), 6.62 (d, J = 2.3 Hz, 1H, H-2′), 6.50 (dd, J = 8.4, 2.4 Hz, 1H, H-6′), 5.96 (s, 2H, H-7′), 5.92 (s, 2H, H-7″), 5.50 (s, 1H, H-2), 4.47 – 4.39 (m, 2H, H-6 and H-8), 4.13 (dd, J = 9.2, 6.1 Hz, 1H, H-4), 3.96 (d, J = 9.2 Hz, 1H, H-4), 3.64 (dd, J = 9.0, 7.6 Hz, 1H, H-8), 3.31 (dd, J = 16.7, 8.7 Hz, 1H, H-1), 2.95 (dd, J = 15.4, 6.6 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8 (C-1″), 119.6 (C-6″), 108.9 (C-6′), 108.1 (C-5″), 108.0 (C-5′), 106.8 (C-2), 106.5 (C-2″), 101.2 (C-7″), 101.0 (C-7′), 100.1 (C-2′), 87.0 (C-6), 71.2 (C-8), 69.7 (C-4), 53.2 (C-1), 52.7 (C-5).

2.3.4 Synthesis of samin

To a solution of sesamolin (**1.2**) (100 g, 0.39 mmol) in a mixture of acetonitrile/H_2O (9:1, 10 mL) was treated with acidic resin Amberlyst-15 (1 mg/0.005 mmol of sesamolin (**1.2**)). After stirring at 70°C for 4-8 h, the reaction mixture was evaporated to dryness and purified by silica gel chromatography using 1:1 ethylacetate/hexane to give samin (**1.36**, 85%).



samin (**1.36**) : as brown crystal; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H, H-2′), 6.80-6.75 (m, 2H, H-5′ and H-6′), 5.94 (s, 2H, OCH_2O), 5.36 (s, 1H, H-2), 4.35 (d, J = 8.4 Hz, 2H, H-6 and H-8), 4.16 (dd, J = 9.2, 6.0 Hz, 1H, H-4), 3.89 (d, J = 9.2 Hz, 1H, H-4), 3.56 (dd, J = 8.8, 7.2 Hz, 1H, H-8), 3.25 (brs, 1H, -OH), 3.05 (m, 1H, H-1), 2.86 (m, 1H, H-5); 13C NMR ($CDCl_3$, 100 MHz) δ 148.1, 147.4, 134.7, 119.7, 108.3, 106.7, 102.4, 101.2, 87.0, 71.4, 69.5, 53.7, 52.9.

CHAPTER III

SYNTHESIS OF NEW FUROFURAN LIGNANS FROM SAMIN

3.1 General procedure for the synthesis of new furofuran lignans

The synthesis of furofuran lignans from small starting materials through multi-step strategy (total-synthesis) does not serve the need of SAR study. Due to the less variety of substrates, few of furofurans were synthesized. Consequently, a semi-synthesis seems to be efficient over total-synthesis in generating variety of new furofuran lignans.

In this work, we exhibited short and efficient synthetic strategy to synthesize diversity of new furofuran lignans using samin (**1.36**) as a lead compound. Under acidic condition, samin was protonated to produce oxocarbenium ion along with release of water which could be trapped by 4°A MS. Selected nucleophiles subsequently attacked on oxocarbenium ion yielding new furofuran lignans. Three types of nucleophile, phenolics (C), thiols (S) and alcohols (O), were used to synthesize these derivatives.

3.2 Synthesis of new furofuran lignans using phenolics as a nucleophile

Phenolics used in this experiment were classified into seven groups (**a-g**, Figure 3.1) which have the differentiation of number and orientation of electron donating groups on aromatic ring. Disappointingly, treatment of samin with anisole (**a**) failed to provide the desired furofuran lignan. The presence of one electron donating group such as OCH_3 is not enough to enhance the nucleophilicity of aromatic toward the reaction with samin. Therefore, disubstituted oxygenated benzenes (**b-d**) were introduced as stronger nucleophiles. Surprisingly, only the reactions of samin and 1,3-dioxygenated benzenes (**d** and **e**) afforded the target products **3.1d** and **3.1e** as

well as their epimers, respectively. This observation would be explained by the enhanced nucleophilicity reinforced by two electron donating groups at *meta* position. To test our hypothesis, the reaction of samin and *m*-cresol (**b**) was carried out. The products **3.1b** and ***epi*-3.1b** were obtained in moderate yields (45%). With the success of the reactions between samin and 1,3-dioxygenated benzenes, we further explored the reactions between samin and trioxygenated benzenes (**e**-**g**). The desired products were obtained in good yields (50 – 90%). Noticeably, all phenolics (**g**-**j**) used in the above reactions processed enhanced nucleophilicity caused by electron donating groups in a *meta*-relation to each other.

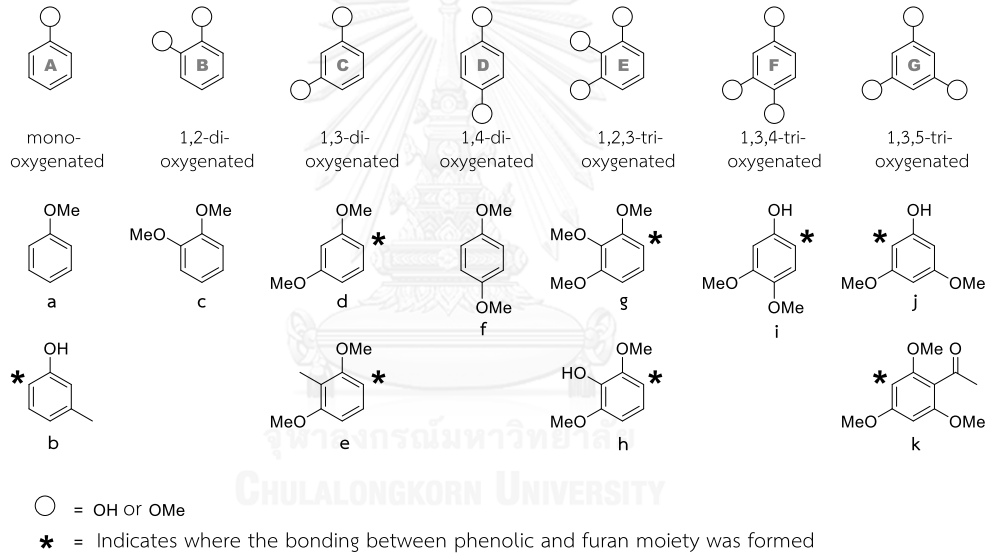
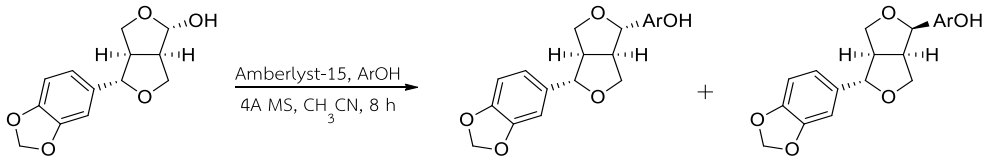


Figure 3.1. Phenolics used in synthesis strategy.

However, the presence of one electron withdrawing group such as acetyl group ($COCH_3$) decreased nucleophilicity of trioxygenated benzene **k**, resulting in lower yield (15%) of product **3.1k**. All of results are summarized in Table 3.1

Table 3.1 Synthesis of furofuran lignans from samin (**1.36**) with phenolics (**a - k**)

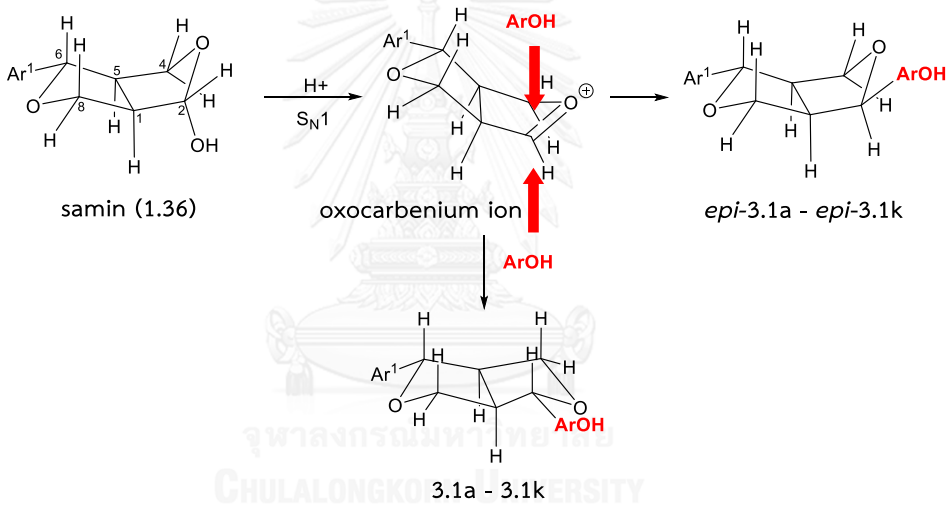


samin (1.36) **3.1** ***epi*-3.1**

Entry	ArOH	Isolated yield (%)	
		3.1	*epi*-3.1
1	a	NR	
2	b	3.1b (30 %)	*epi*-3.1b (15 %)
3	c	NR	
4	d	3.1d (55 %)	*epi*-3.1d (45 %)
5	e	3.1e (42 %)	*epi*-3.1e (31 %)
6	f	NR	
7	g	3.1g (31 %)	*epi*-3.1g (22 %)
8	h	3.1h (27 %)	*epi*-3.1h (37 %)
9	i	3.1i (68 %)	*epi*-3.1i (17 %)
10	j	3.1j (47 %)	*epi*-3.1j (51 %)
11	k	3.1k (15 %)	*epi*-3.1k (trace)

NR = no reaction

Generally, the reactions between samin and phenolics would proceed through S_N1 mechanism involving oxocarbenium ion. The hydroxyl group at anomeric center (C-2) was initially protonated by strong acid to produce oxocarbenium ion (Scheme 3.1). Phenolics as carbon nucleophiles attacked on both sides of the planar intermediate to provide diastereomeric products in equal ratio. In terms of regioselectivity, the bonding between C-2 of samin and high electron density as well as least hindrance of phenolics by *ortho* group were generally observed. The structural identification and relative stereochemistries of other products were confirmed by 2D experiments and ^{1}H NMR patterns as predicated in next section.



Scheme 3.1 Proposed mechanistic formation of **3.1a** – **3.1k** and **epi-3.1a** – ***epi*-3.1k**

3.2.1 Structural characterization of synthesized furofuran lignans (3.1 and *epi*-3.1)

Structures of all synthesized compounds were characterized mainly by ^{1}H and ^{13}C NMR, along with 2D NMR for particular compounds. The ^{1}H and ^{13}C NMR spectra of **3.1** and ***epi*-3.1** showed closely related pattern, except for some signals from H atom of core structure. For instance, H-2 and H-6 in **3.1b** showed doublet signal with comparable coupling constants ($J \approx 4.0$ Hz) whereas those in ***epi*-3.1b** displayed

significantly distinct values; 5.6 Hz for H-2 and 8.0 Hz for H-6. A more strikingly significant observation is the splitting patterns of diastereomeric H-4, which appeared as expected as doublet of doublet. However, only H-4_{eq} of ***epi*-3.1b** showed an exceptional doublet signal caused solely by germinal coupling of H-4_{eq} and H-4_{ax}. These observations would account for a nearly 90° dihedral angle between H-4_{eq} and H-5 that gave rise to $J_{H\text{-}4eq,5} \approx 0$ Hz [14] (Figure. 3.2). The above evidence could be useful in readily distinguishing the identity of other synthesized lignans **3.1** and their epimers.

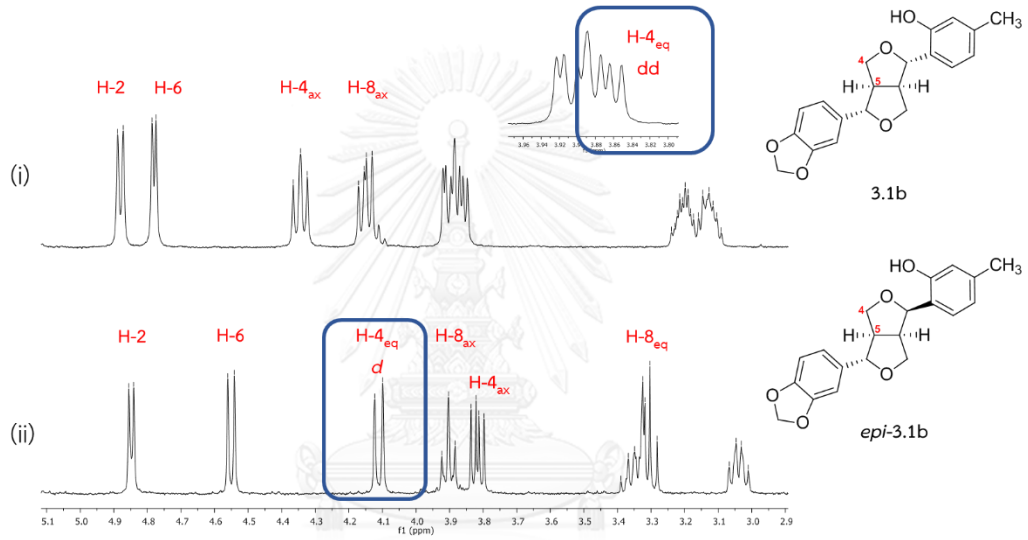


Figure 3.2. ^{1}H NMR spectra of (i) **3.1b** and (ii) ***epi*-3.1b**.

The relative configuration of **3.1b** and ***epi*-3.1b** at C-2 was further determined by NOESY data and coupling constant analysis. The NOESY spectrum of **3.1b** showed diagnostic correlations of H-2/H-8_{ax} and H-4_{ax}/H-6, suggesting that the occupation of two aryls are on the *exo-exo* face of the bicyclic core (Figure 3.2 (i)). This interpretation was corresponding with a chair-chair conformation of sesamin (**1.3**), which was verified by X-ray analysis [15]. On the other hand, ***epi*-3.1b** showed key NOESY correlations of H-2/H-4_{ax} and H-6/H-8_{ax}, which implied *endo,exo*-2,6-diarylfurofuran (Figure 3.2 (ii)). These observations correlated well with the chair-boat conformation of *epi*-sesamin or asarinin [15].

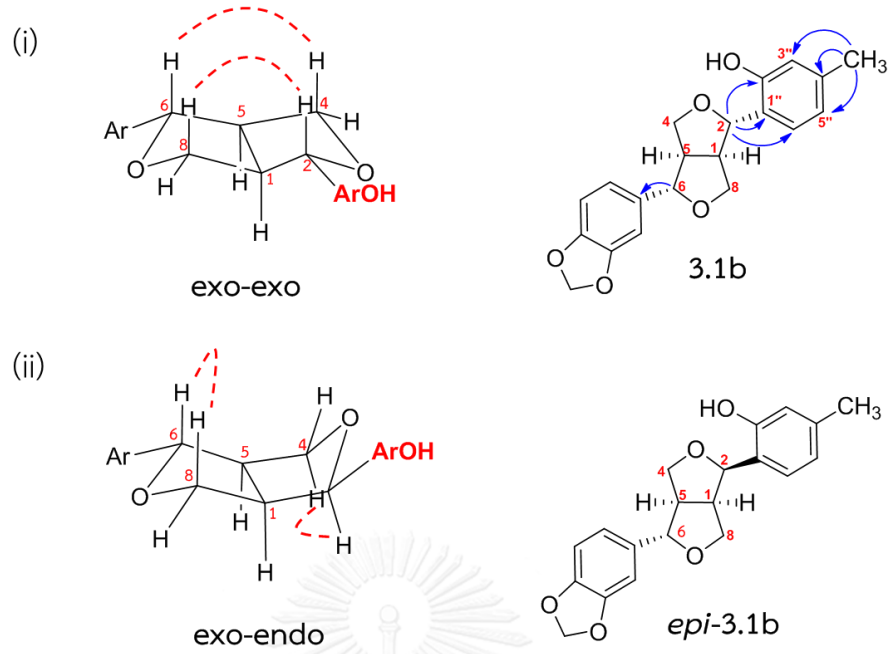


Figure 3.3 Diagnostic NOESY and HMBC correlations of (i) **3.1b** and (ii) ***epi*-3.1b**.

3.3 Synthesis of new furofuran lignans using thiols as a nucleophile

With the success in applying phenolic compounds, we further synthesized other furofuran lignans by using thiols as sulfur nucleophiles. Thiols used in this investigation are listed in Figure 3.4. They are divided into two categories; aliphatic thiols (sp^3 C–SH, **l**-**p**) and aromatic thiols (sp^2 C–SH, **q**-**z**).

A S atom is well recognized as a stronger nucleophile than C and O atoms. Therefore, the products from reaction of samin and thiols would be obtained in high to excellent yield (Table 3.2).

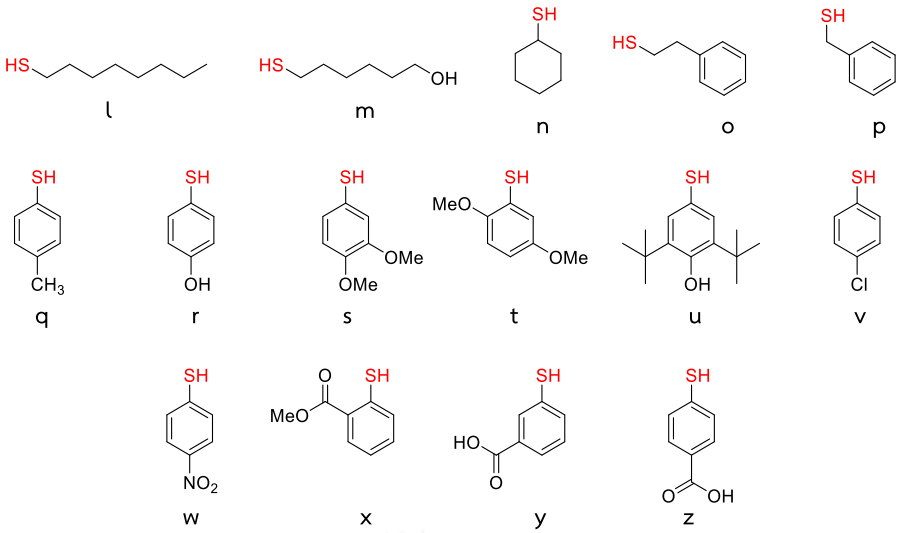
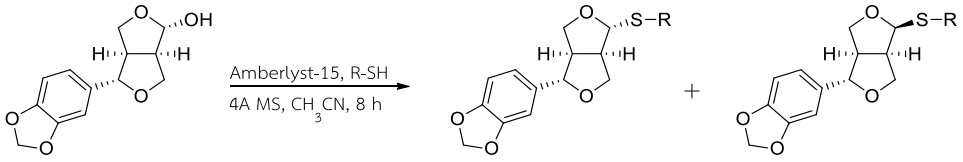


Figure 3.4 Thiols used in synthesis strategy.

Under the same reaction condition, diastereomeric furofuran lignans (**3.2** and ***epi*-3.2**) were produced after sulfur nucleophiles attacked on an oxocarbenium intermediate. The diastereomeric ratios (dr) of products synthesized from samin and aliphatic thiols (**l**-**p**) are in range of 5:1 to 7:1. On the other hand, the dr values of products synthesized from samin and aromatic thiols (**q**-**z**) varied in broader range (2:1 to 12:1). The highly diastereomeric ratios of **3.2t** : ***epi*-3.2t** and **3.2x** : ***epi*-3.2x** were possibly contributed by steric hindrance of *ortho*-substituent (**t** and **x**). These observations were supported by the lower dr values of isomeric products. For example, treatment of samin with **y** and **z**, the *meta* and *para* isomer of **x**, provided products with lower diastereomeric ratios (6:1).

Table 3.2 Synthesis of furofuran lignans from samin (**1.36**) with thiols (**l - z**)



samin (1.36) **3.2** ***epi*-3.2**

Entry	RSH	Isolated yield (%)[a]	Diastereomeric ratio[b] 3.2 : *epi*-3.2
1	l	quant	7 : 1
2	m	65 %	5 : 1
3	n	79 %	Not determine
4	o	85.2 %	6 : 1
5	p	73 %	7 : 1
6	q	97 %	3 : 1
7	r	99 %	5 : 1
8	s	69 %	3 : 1
9	t	96 %	12 : 1
10	u	69 %	2 : 1
11	v	Quant	5 : 1
12	w	73.3 %	6 : 1
13	x	67 %	12 : 1
14	y	65 %	6 : 1
15	z	77 %	6 : 1

[a] Isolated yield of diasteromeric mixture, [b] Ratios were determined by ^{1}H NMR analysis

Note: According to small amount of epimers cannot be separated purely by general technique, only pure spectra of their congeners were shown.

3.3.1 Structural characterization of synthesized furofuran lignans (3.2 and *epi*-3.2)

^{1}H NMR spectra of synthesized furofuran lignans **3.2** and ***epi*-3.2** have slightly different pattern with those obtained from samin and phenolics (**3.1a**-**3.1k**). However, careful inspection of ^{1}H NMR spectra indicated striking difference in splitting pattern of H-2. As shown in Figure 3.6, furofuran lignans **3.2** showed a singlet signal of H-2 whereas ***epi*-3.2** demonstrated doublet signal with $J \approx 6$-7 Hz. The unexpected singlet H-2 of **3.2** suggested a perpendicular dihedral angle ($\phi \approx 90°$) between H-2 and H-1 (Figure 3.6 (iii)), indicating that **3.2** adopted *exo-exo* furofuran core structure the same as samin [16].

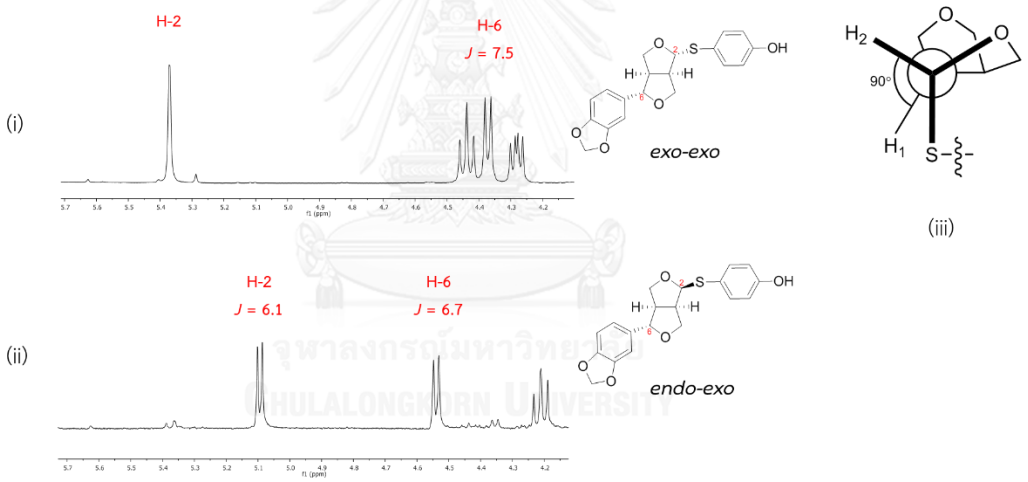


Figure 3.5 ^{1}H NMR spectra of (i) **3.2r** and (ii) ***epi*-3.2r**. Note that (iii) Newman projection of **3.2r** demonstrates dihedral angle nearly 90° between H-1 and H-2, thus resulting in singlet (s) signal rather than expected doublet (d).

Since furofuran lignans containing a S atom have never been reported, their structures were fully characterized by 2D NMR and X-ray analysis. All ^{1}H and ^{13}C signals of the representative lignans **3.2r** and ***epi*-3.2r** were first confirmed by HSQC and HMBC data, and selected HMBC correlations are shown in Figure 3.6.

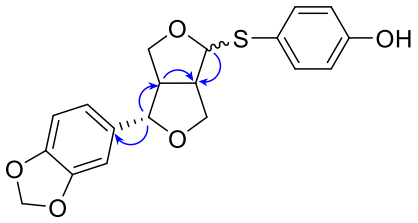
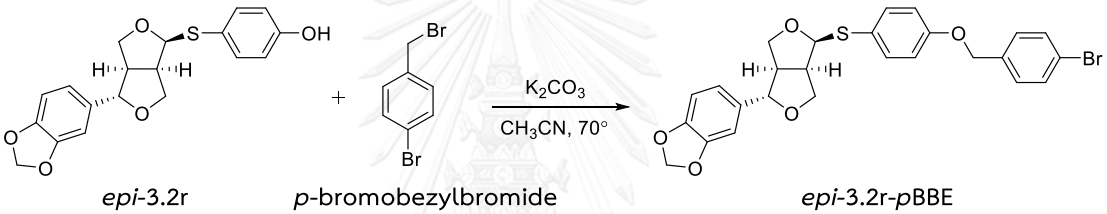


Figure 3.6 Selected HMBC correlations of **3.2r** and ***epi*-3.2r**.

To unambiguously elucidate furofuran core structure and orientation of the thiol moiety, X-ray crystallographic analysis was performed. Because a good single crystal of ***epi*-3.2r** could not be obtained, its *p*-bromobenzylether (*p*BBE) derivative (***epi*-3.2r-*p*BBE**) was prepared (Scheme 3.2).



Scheme 3.2 Preparation of ***epi*-3.2r-*p*BBE**.

Crystal structures of the two isomers are shown in Figure 3.7. Thiol substituted at C-2 of **3.2r** was located at the *exo* position, and dihedral angle between H-1 and H-2 was approximately 96.14°, resulting in singlet signal of H-2 (J = 0 Hz). On the other hand, the thiol substituent at C-2 of ***epi*-3.2r-*p*BBE** was located at *endo* position, and dihedral angle between H-1 and H-2 was approximately 28.01° (J = 6.1 Hz).

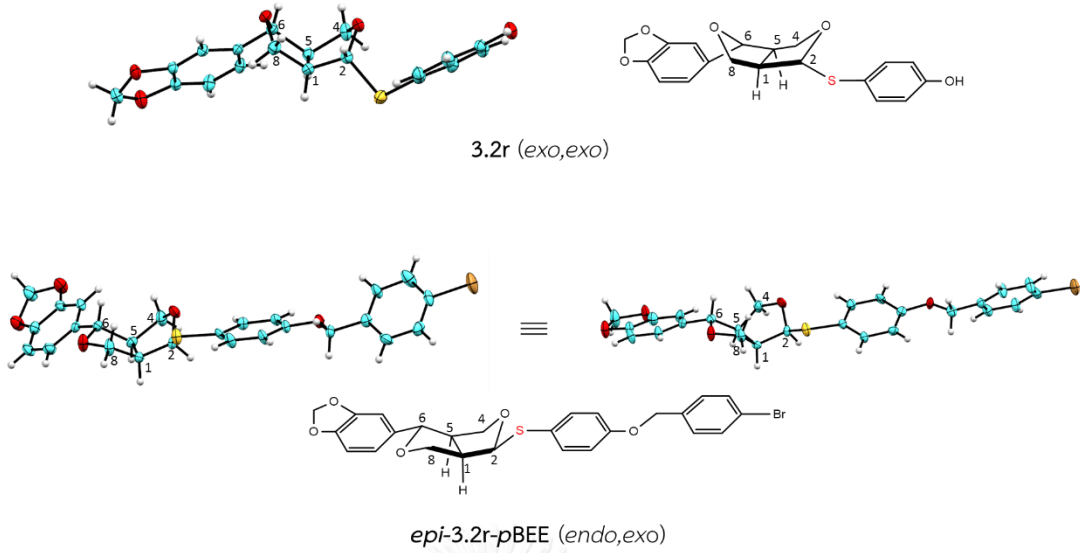


Figure 3.7 ORTEP plots (20% probability level) of **3.2r** and ***epi-3.2r-p*BBE** (color codes: C = cyan, S = yellow, Br = orange, O = red, H= white).

3.4 Synthesis of new furofuran lignans using alcohols as a nucleophile

A wide range of alcohols were also applied to demonstrate a usability of our designed synthetic method. Selected alcohols are varied in less steric alcohols (**A**-**F**), high steric alcohols (**G**-**J**) and allylic alcohols (**K**-**N**) (Figure 3.8).

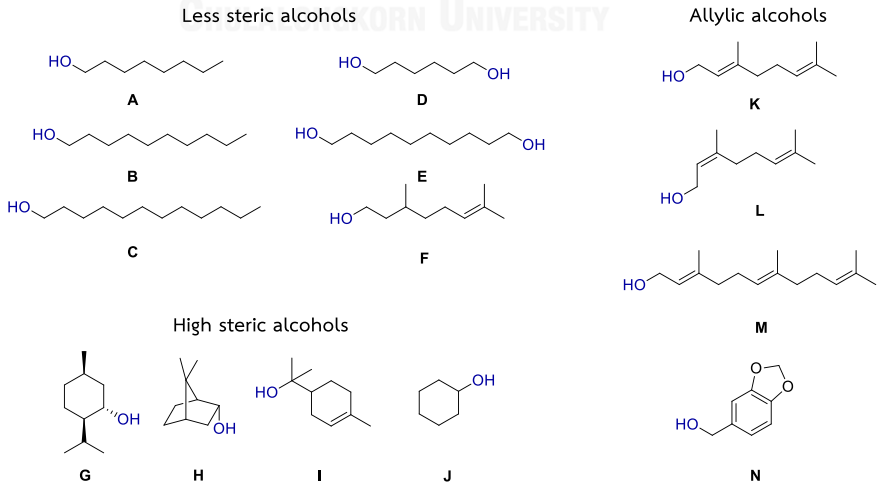
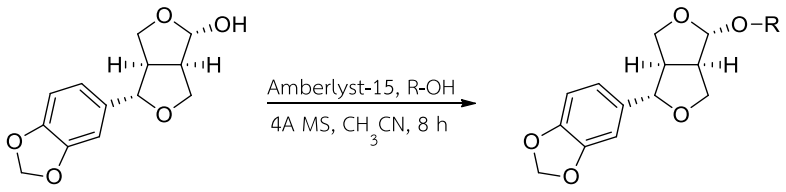


Figure 3.8 Alcohols used in synthesis strategy.

From this experiment, fourteen new furofuran lignans (**3.3A**-**3.3N**) were able to synthesize in high yield (69 % – quant, Table 3.3) although bulky or naturally allylic alcohols were used as nucleophiles. These results indicated that our methodology is compatible to all kinds of alcohols despite of alcohols **N**, which was susceptible to dehydration under strong acidic condition. Therefore, reaction between samin and **N** provided **3.3N** in moderated yield together with the byproduct generated from self-condensation of benzylic alcohol **N**.

Unexpectedly, each reaction provided single stereomeric products (**3.3A** – **3.3N**) instead of mixture of two diastereomers as previously described in the reactions between samin and phenolics as well as thiols. The stereochemistry of **3.3** proved to be retention of configuration, which were elaborated in section 3.4.1.

Table 3.3 Synthesis of furofuran lignans from samin with alcohols (**A - N**)



samin (1.36) **3.3**

Entry	ROH	Isolated yield (%)
1	A	3.3A (78 %)
2	B	3.3B (quant)
3	C	3.3C (quant)
4	D	3.3D (quant)
5	E	3.3E (quant)
6	F	3.3F (88 %)
7	G	3.3G (quant)
8	H	3.3H (75 %)
9	I	3.3I (81 %)
10	J	3.3J (93 %)
11	K	3.3K (69 %)
12	L	3.3L (82 %)
13	M	3.3M (84 %)
14	N	3.3N (44.8 %)

3.4.1 Structural characterization of synthesized furofuran lignans (3.3 and *epi*-3.3)

Compounds **3.3A**-**3.3N** showed singlet signals of H-2 similar to those of **3.2**. For instant, **3.3A** and **3.2l** exhibited sharp singlet signal around 4-5.5 ppm. These observations indicated that their conformation adopted *exo-exo* furofuran type.

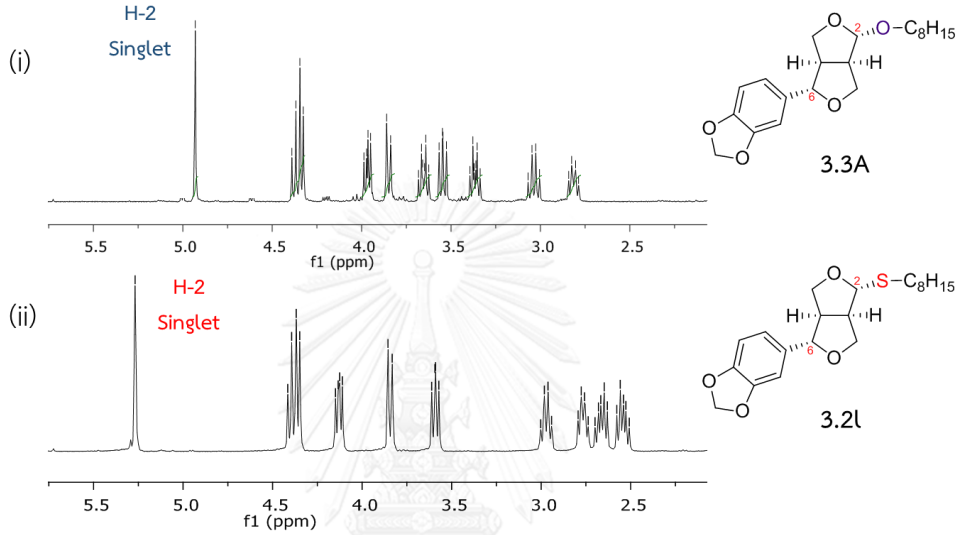


Figure 3.9 ^{1}H NMR spectra of (i) **3.3A** and (ii) **3.2l**

3.5 Experimental section

3.5.1 General experiment procedures

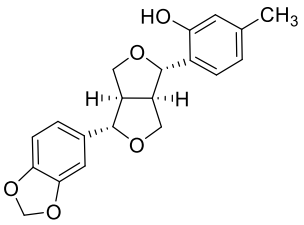
^{1}H and ^{13}C NMR were recorded ($CDCl_3$ as a solvent) at 400 and 100 MHz, respectively, Varian Mercury^{+} 400 NMR and a Bruker (Avance) 400 NMR spectrometer. The chemical shifts were reported in ppm downfield from TMS. Mass spectra were measured by HRESIMS obtaining from a micrOTOF Bruker mass spectrometer. Thin layer chromatography (TLC) and Preparative thin Layer Chromatography (Prep TLC) were operated on pre-coated Merck silica gel 60 F_{254} plates (0.25 and 0.50 mm thick layer, respectively) and visualized under 254 nm UV. Silica gel 60 Merk cat. No. 7729 was applied for open column chromatography.

3.5.2 Chemical

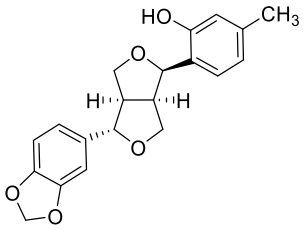
All reagents were obtained from Sigma-Aldrich and used without further purification.

3.5.3 General procedure for synthesis of new furofuran lignans

To a solution of samin (1 eq) in acetonitrile (1.0 mL/0.1 mmol of samin) was treated with selected nucleophile (2 eq), acidic resin amberlyst-15 (1 mg/0.005 mmol of samin) and molecular sieve, 4 Å. After stirring at 60°C for 8 h, the reaction mixture was evaporated to dryness and load onto silica gel column chromatography followed by Prep TLC in order to obtain purely desired products.



(*1R, 2R, 5S, 6S*)-2-(2-hydroxy-4-methylphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1b)

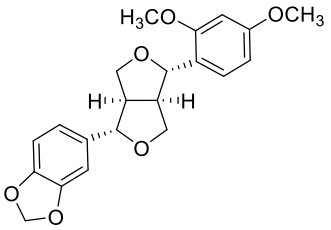


(*1R, 2S, 5S, 6S*)-2-(2-hydroxy-4-methylphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1b)

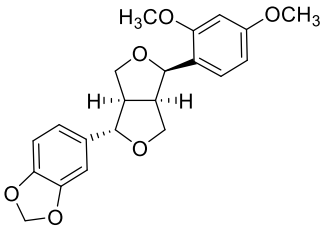
Following the general procedure, reaction of **1.36** (64.5 mg, 0.26 mmol), *m*-cresol (40 µL, 0.39 mmol) in acetonitrile (2 mL) after 8 h yielded **3.1b** (27 mg, 30%) and ***epi*-3.1b** (13 mg, 15%) as white powder.

3.1b: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (brs, 1H, -OH), 6.92 (d, *J* = 7.6 Hz, 1H, H-6″), 6.83-6.78 (m, 3H, H-2', H-5', and H-6'), 6.71 (s, 1H, H-3″), 6.67 (d, *J* = 7.6 Hz, 1H, H-5″), 5.95 (s, 2H, H-7'), 4.87 (d, *J* = 6.5 Hz, 1H, H-2), 4.78 (d, *J* = 4.4 Hz, 1H, H-6), 4.34 (dd, *J* = 9.2, 7.6 Hz, 1H, H-4), 4.15 (dd, *J* = 9.2, 6.8 Hz, 1H, H-8), 3.92-3.85 (m, 2H, H-4 and H-8), 3.21 (m, 1H, H-1), 3.14 (m, 1H, H-5), 2.29 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 155.5, 148.2, 147.4, 139.8, 134.8, 126.8, 120.9, 120.9, 119.5, 117.9, 108.4, 106.7, 101.3, 86.7, 85.6, 72.5, 70.9, 53.6, 53.1, 21.2; HRMS m/z 363.1212 $[M+Na]^+$ (calcd for $C_{20}H_{20}NaO_5$, 363.1208).

***epi*-3.1b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (brs, 1H, -OH), 6.92 (d, *J* = 7.6 Hz, 1H, H-6″), 6.86-6.80 (m, 3H, H-2', H-5', and H-6'), 6.71 (s, 1H, H-3″), 6.67 (d, *J* = 7.6 Hz, 1H, H-5″), 5.97 (s, 2H, H-7'), 4.85 (d, *J* = 5.6 Hz, 1H, H-6), 4.55 (d, *J* = 7.9 Hz, 1H, H-2), 4.11 (d, *J* = 9.6 Hz, 1H, H-8), 3.90 (dd, *J* = 8.4, 7.6 Hz, 1H, H-4), 3.82 (dd, *J* = 9.6, 6.0 Hz, 1H, H-8), 3.38-3.28 (m, 2H, H-1 and H-4), 3.04 (m, 1H, H-5), 2.29 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 155.5, 147.9, 146.9, 139.8, 132.0, 126.9, 121.2, 120.8, 118.8, 118.0, 108.4, 106.5, 101.2, 88.6, 82.0, 70.7, 70.2, 53.4, 49.9, 21.3; HRMS m/z 363.1213 $[M+Na]^+$ (calcd for $C_{20}H_{20}NaO_5$, 363.1208).



(*1R, 2R, 5S, 6S*)-2-(1,4-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1d)

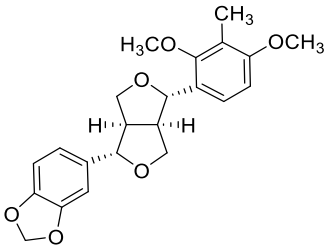


(*1R, 2S, 5S, 6S*)-2-(1,4-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1d)

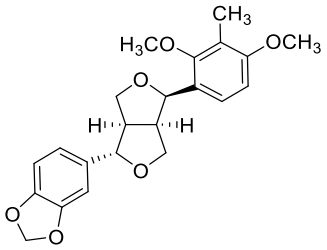
Following the general procedure, reaction of **1.36** (12.5 mg, 0.05 mmol), 1,3-dimethoxybenzene (12 mg, 0.075 mmol) in acetonitrile (0.5 mL) after 8 h yielded **3.1d** (10 mg, 55%) and ***epi*-3.1d** (8.2 mg, 45%) as colorless oil.

3.1d: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (dd, *J* = 8.0, 2.8 Hz, 1H), 6.84 (s, 1H), 6.81-6.74 (m, 2H), 6.45 (d, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 5.92 (s, 2H), 5.03 (d, *J* = 4.8 Hz, 1H), 4.64 (d, *J* = 5.6 Hz, 1H), 4.30 (dd, *J* = 9.2, 7.6 Hz, 1H), 4.19 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.98 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.90 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.80 (s, 3H, -OCH_3), 3.79 (s, 3H, -OCH_3), 3.01 (m, 1H), 2.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 160.2, 157.4, 147.9, 147.1, 135.4, 126.1, 122.8, 119.5, 108.1, 106.6, 103.8, 101.0, 98.6, 85.5, 82.0, 73.3, 71.2, 55.4, 55.3, 54.7, 53.7; HRMS m/z 393.1310 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_6$, 393.1314).

***epi*-3.1d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.81-6.76 (m, 2H), 6.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.44 (s, 1H), 5.94 (s, 2H), 4.91 (d, *J* = 6.0 Hz, 1H, H-6), 4.36 (d, *J* = 8.0 Hz, 1H, H-2), 4.09 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 3.78-3.74 (m, 2H), 3.47 (m, 1H), 3.22 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 160.2, 156.6, 148.1, 147.3, 135.6, 127.3, 127.3, 119.7, 108.3, 106.8, 103.9, 101.1, 98.3, 87.6, 78.6, 70.5, 69.9, 55.5, 55.4, 54.9, 48.7; HRMS m/z 393.1310 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_6$, 393.1314).



(*1R, 2R, 5S, 6S*)-2-(2,4-dimethoxy-3-methylphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1e)

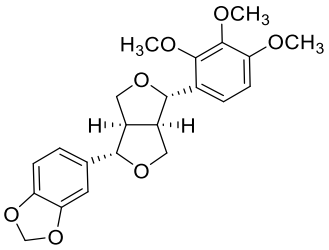


(*1R, 2S, 5S, 6S*)-2-(2,4-dimethoxy-3-methylphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1e)

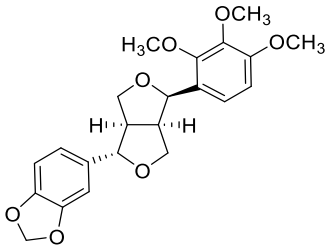
Following the general procedure, reaction of **1.36** (63.0 mg, 0.25 mmol), 2,6-dimethoxytoluene (74 µL, 0.5 mmol) in acetonitrile (2 mL) after 8 h yielded **3.1e** (40 mg, 42%) and ***epi*-3.1e** (30 mg, 31%) as yellow oil.

3.1e: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (d, *J* = 8.5 Hz, 1H), 6.90–6.72 (m, 3H), 6.63 (d, *J* = 8.5 Hz, 1H), 5.95 (s, 2H), 5.06 (d, *J* = 4.0 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 1H), 4.30 (t, *J* = 8.2 Hz, 1H), 4.26–4.13 (m, 1H), 3.98 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.90 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.82 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 3.10 (m, 1H), 3.00 (m, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 158.6, 157.0, 148.1, 147.2, 135.5, 127.0, 123.8, 120.1, 119.6, 108.3, 106.7, 106.0, 101.2, 85.7, 82.3, 73.1, 71.5, 60.9, 55.8, 54.8, 54.1, 9.2; HRMS m/z 407.1469 $[M+Na]^+$ (calcd for $C_{22}H_{24}NaO_6$, 407.1471).

***epi*-3.1e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, *J* = 8.6 Hz, 1H), 6.90 – 6.74 (m, 3H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.94 (s, 2H), 4.96 (d, *J* = 6.2 Hz, 1H, H-6), 4.38 (d, *J* = 7.4 Hz, 1H, H-2), 4.10 (d, *J* = 9.3 Hz, 1H), 3.83 (m, 4H), 3.74 (m, 4H), 3.46 (m, 1H), 3.24 (t, *J* = 8.6 Hz, 1H), 2.87 (m, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 158.3, 155.7, 148.1, 147.3, 135.6, 124.5, 124.2, 123.6, 119.8, 108.3, 106.78, 105.9, 101.2, 87.7, 78.8, 70.6, 69.9, 60.6, 55.8, 55.0, 49.3, 9.3; HRMS m/z 407.1470 $[M+Na]^+$ (calcd for $C_{22}H_{24}NaO_6$, 407.1471).



(*1R, 2R, 5S, 6S*)-2-(2,3,4-trimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1g)

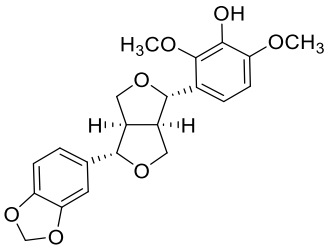


(*1R, 2S, 5S, 6S*)-2-(2,3,4-trimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1g)

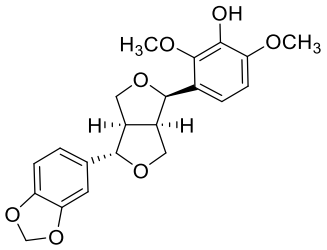
Following the general procedure, reaction of **1.36** (100 mg, 0.39 mmol), 1,2,3-trimethoxybenzene (70.3 mg, 0.58 mmol) in acetonitrile (4 mL) after 8 h yielded **3.1g** (73.3 mg, 31%) and ***epi*-3.1g** (51.7 mg, 22%) as brown oil.

3.1g: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, *J* = 8.6 Hz, 1H), 6.90 – 6.73 (m, 3H), 6.64 (d, *J* = 8.6 Hz, 1H), 5.95 (s, 2H), 5.03 (d, *J* = 4.0 Hz, 1H), 4.67 (d, *J* = 4.0 Hz, 1H), 4.33 (dd, *J* = 8.9, 7.5 Hz, 1H), 4.21 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.99 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.92 (s, 3H, -OCH_3), 3.89 (m, 1H), 3.87 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 3.05 (m, 1H), 2.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 153.4, 151.2, 148.1, 147.3, 142.4, 135.4, 128.0, 120.3, 119.6, 108.3, 107.1, 106.7, 101.2, 85.6, 82.4, 73.2, 71.5, 60.9, 60.9, 56.2, 54.8, 54.2; HRMS m/z 423.1431 $[M+Na]^+$ (calcd for $C_{22}H_{24}NaO_7$, 423.1420).

***epi*-3.1g**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, *J* = 8.6 Hz, 1H), 6.87-6.76 (m, 3H, H-2', H-5', and H-6'), 6.67 (d, *J* = 8.6 Hz, 1H), 5.94 (s, 2H, H-7'), 4.93 (d, *J* = 5.6 Hz, 1H, H-6), 4.37 (d, *J* = 8.0 Hz, 1H, H-2), 4.09 (d, *J* = 9.2 Hz, 1H, H-8), 3.92 (s, 3H, -OCH_3), 3.86 (s, 6H, -OCH_3 (x2)), 3.83-3.77 (m, 2H), 3.43 (m, 1H), 3.24 (m, 1H), 2.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 153.2, 150.0, 148.1, 147.3, 141.8, 135.5, 124.4, 121.2, 119.7, 108.3, 107.0, 106.8, 101.2, 87.7, 78.6, 70.6, 69.9, 60.9, 60.8, 56.1, 55.0, 49.2; HRMS m/z 423.1431 $[M+Na]^+$ (calcd for $C_{22}H_{24}NaO_7$, 423.1420).



(*1R, 2R, 5S, 6S*)-2-(3-hydroxy-2,4-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1h)

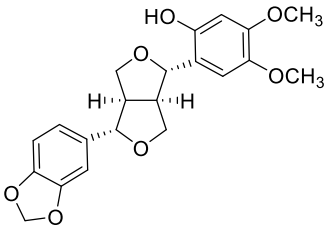


(*1R, 2S, 5S, 6S*)-2-(3-hydroxy-2,4-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1h)

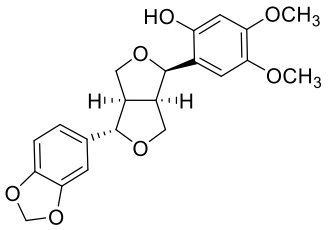
Following the general procedure, reaction of **1.36** (36.0 mg, 0.14 mmol), 2,6-dimethoxyphenol (43 mg, 0.28 mmol) in acetonitrile (2 mL) after 8 h yielded **3.1h** (15 mg, 27%) and ***epi*-3.1h** (20 mg, 37%) as yellow oil.

3.1h: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 – 6.73 (m, 4H), 6.62 (d, *J* = 8.6 Hz, 1H), 5.94 (s, 2H), 5.05 (d, *J* = 4.0 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 1H), 4.31 (dd, *J* = 9.1, 7.3 Hz, 1H), 4.22 (dd, *J* = 9.1, 6.6 Hz, 1H), 4.01 (dd, *J* = 9.2, 4.7 Hz, 1H), 3.92 (d, *J* = 4.3 Hz, 4H), 3.89 (d, *J* = 7.1 Hz, 4H), 3.10 – 3.02 (m, 1H), 3.01 – 2.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 144.6, 138.7, 135.4, 128.3, 119.6, 115.9, 108.3, 106.7, 105.9, 101.2, 85.6, 82.4, 73.1, 71.6, 60.6, 56.4, 54.8, 54.2; HRMS m/z 409.1260 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_7$, 409.1263).

***epi*-3.1h**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (d, *J* = 8.5 Hz, 1H), 6.89–6.73 (m, 3H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.95 (s, 2H), 4.95 (d, *J* = 5.9 Hz, 1H, H-6), 4.36 (d, *J* = 8.0 Hz, 1H, H-2), 4.09 (d, *J* = 9.4 Hz, 1H), 3.97–3.84 (m, 7H), 3.86–3.74 (m, 2H), 3.51–3.40 (m, 1H), 3.24 (t, *J* = 8.6 Hz, 1H), 2.86 (dd, *J* = 15.4, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.3, 147.2, 138.2, 135.5, 129.9, 124.6, 119.7, 116.8, 108.3, 106.8, 105.8, 101.2, 87.7, 78.7, 70.6, 69.9, 60.3, 56.4, 54.9, 49.2; HRMS m/z 409.1261 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_7$, 409.1263).



(*1R, 2R, 5S, 6S*)-2-(2-hydroxy-4,5-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1i)

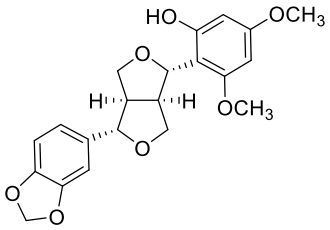


(*1R, 2S, 5S, 6S*)-2-(2-hydroxy-4,5-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1i)

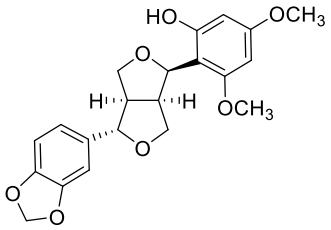
Following the general procedure, reaction of **1.36** (46.8 mg, 0.19 mmol), 3,4-dimethoxyphenol (58 mg, 0.37 mmol) in acetonitrile (2 mL) after 8 h yielded **3.1i** (49 mg, 68%) and ***epi*-3.1i** (15 mg, 17%) as white powder.

3.1i: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (brs, 1H, -OH), 6.84-6.79 (m, 3H), 6.54 (s, 1H), 6.49 (s, 1H), 5.96 (s, 2H), 4.82 (d, *J* = 4.0 Hz, 1H), 4.78 (d, *J* = 4.0 Hz, 1H), 4.36 (dd, *J* = 8.8, 7.2 Hz, 1H), 4.16 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.92-3.86 (m, 2H), 3.84 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 3.21-3.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.3, 150.1, 148.2, 147.4, 142.6, 134.8, 125.2, 119.5, 111.2, 108.4, 106.7, 102.1, 101.3, 86.7, 85.6, 72.6, 70.8, 57.2, 56.1, 53.6, 53.2; HRMS m/z 409.1286 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_7$, 409.1263).

***epi*-3.1i**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (brs, 1H, -OH), 6.87-6.77 (m, 3H), 6.46 (s, 1H), 6.42 (s, 1H), 5.95 (s, 2H), 5.01 (d, *J* = 8.0 Hz, 1H), 4.44 (d, *J* = 6.8 Hz, 1H), 4.19 (d, *J* = 9.6 Hz, 1H), 3.98 (t, *J* = 8.8 Hz, 1H), 3.88 (m, 1H), 3.85 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.49 (dd, *J* = 8.4, 9.2 Hz, 1H), 3.40 (m, 1H), 2.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.1, 149.8, 148.2, 147.5, 142.7, 134.8, 125.2, 119.8, 110.5, 108.4, 106.7, 101.9, 101.2, 87.7, 84.6, 71.9, 70.1, 57.0, 56.0, 53.7, 50.8; HRMS m/z 409.1275 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_7$, 409.1263).



(*1R, 2R, 5S, 6S*)-2-(2-hydroxy-4,6-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1j)

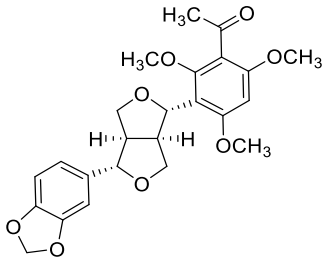


(*1R, 2S, 5S, 6S*)-2-(2-hydroxy-4,6-dimethoxyphenyl)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (*epi*-3.1j)

Following the general procedure, reaction of **1.36** (56.5 mg, 0.22 mmol), 3,5-dimethoxyphenol (52 mg, 0.34 mmol) in acetonitrile (2 mL) after 8 h yielded **3.1j** (41 mg, 47%) and ***epi*-3.1j** (44 mg, 51%) as white powder.

3.1j: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (brs, 1H, -OH), 6.82-6.77 (m, 3H), 6.06 (d, *J* = 2.4 Hz, 1H), 6.01 (d, *J* = 2.4 Hz, 1H), 5.95 (s, 2H), 5.21 (d, *J* = 4.8 Hz, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.47 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.13 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.03 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.79 (m, 1H), 3.76 (s, 6H, -OCH_3 (x2)), 3.19 (m, 1H), 3.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 161.0, 158.0, 157.6, 148.2, 147.3, 134.9, 119.5, 108.3, 106.7, 105.0, 101.2, 94.6, 91.0, 84.2, 84.2, 72.7, 71.0, 55.5, 55.5, 54.8, 53.7; HRMS m/z 387.1449 $[M+H]^+$ (calcd for $C_{21}H_{23}O_7$, 387.1444).

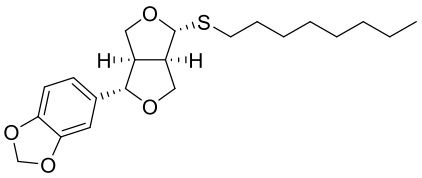
***epi*-3.1j**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (brs, 1H, -OH), 6.87-6.77 (m, 3H), 6.07 (d, *J* = 2.0 Hz, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 5.95 (s, 2H), 5.17 (d, *J* = 8.0 Hz, 1H, H-2), 4.40 (d, *J* = 6.8 Hz, 1H, H-6), 4.17 (d, *J* = 10.0 Hz, 1H), 3.91 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.81 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.77 (s, 3H, -OCH_3), 3.76 (s, 3H, -OCH_3), 3.51-3.42 (m, 2H), 2.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 160.9, 158.1, 157.4, 148.2, 147.5, 134.9, 119.8, 108.3, 106.8, 101.7, 101.2, 94.3, 90.8, 87.5, 81.9, 71.4, 70.3, 55.7, 55.4, 53.7, 49.6; HRMS m/z 409.1273 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_7$, 409.1263).



(*1R, 2R, 5S, 6S*)-2-(3-acetyl-2,4,6-trimethoxyphenyl)-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.1k)

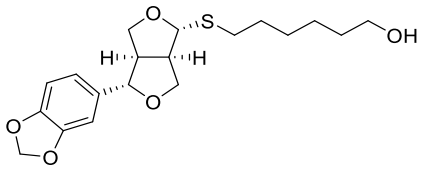
3.1k: Following the general procedure, reaction of **1.36** (100 mg, 0.39 mmol), 2,4,6-trimethoxyacetophenone (116.7 mg, 0.58 mmol) in acetonitrile (4 mL) after 8 h yielded **3.1k** (25.8 mg, 15%) as white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (m, 3H), 6.27 (s, 1H), 5.95 (s, 2H), 5.23 (d, *J* = 6.0 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.31 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.13 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.92-3.90 (m, 2H), 3.85 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3), 3.44 (m, 1H) 3.12 (m, 1H), 2.49 (s, 3H, -CH3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 202.0, 160.6, 158.1, 157.8, 148.1, 147.2, 135.7, 119.7, 119.5, 108.3, 106.7, 101.2, 101.2, 92.0, 85.3, 79.1, 72.8, 72.6, 64.4, 56.0, 56.0, 55.9, 51.5, 29.8; HRMS m/z 465.1538 $[M+Na]^+$ (calcd for $C_{24}H_{26}NaO_8$, 465.1525).



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl)-

2-(octylsulfanyl)-3,7-dioxabicyclo[3.3.0]octane (3.2l)

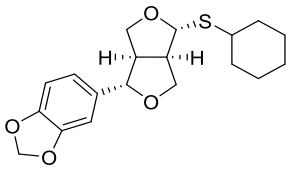
3.2l: Following the general procedure, reaction of **1.36** (80 mg, 0.32 mmol), 1-octanethiol (166 µL, 0.96 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2l** (107.52 mg, 89%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 – 6.75 (m, 3H, H-2′, H-5′ and H-6′), 5.95 (s, 2H, H-7′), 5.38 (s, 1H, H-2), 4.38 (m, 2H, H-6 and H-8), 4.15 (dd, *J* = 9.3, 5.9 Hz, 1H, H-4), 3.83 (d, *J* = 9.4 Hz, 1H, H-4), 3.60 (m, 1H, H-8), 2.96 (m, 1H, H-1), 2.77 (m, 1H, H-5), 2.75 (m, 1H, H-1″), 2.55 (m, 1H, H-1″), 1.62 – 1.27 (m, 12H, H-CH_2), 0.88 (t, 3H, H-CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.0, 147.3, 134.6, 119.6, 108.2, 106.6, 101.1, 89.0, 86.9, 73.4, 68.3, 53.3, 53.2, 31.8, 31.1, 29.8, 29.2, 29.1, 29.0, 22.6, 14.0; HRMS m/z 401.1759 $[M+Na]^+$ (calcd for $C_{21}H_{30}NaO_4S$, 401.1763).



(*1R, 2R, 5S, 6S*)- 2-[(6-hydroxy)hexylsulfanyl]-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2m)

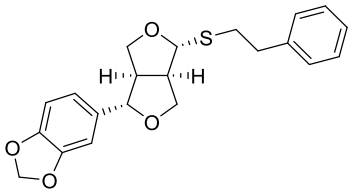
3.2m: Following the general procedure, reaction of **1.36** (43 mg, 0.172 mmol), 6-mercapto-1-hexanol (70 µL, 0.515 mmol) in acetonitrile (2 mL) after 8 h yielded **3.2m** (40.90 mg, 65%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 – 6.75 (m, 3H), 5.94 (s, 2H), 5.26 (s, 1H), 4.42 – 4.32 (m, 2H), 4.12 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.84 (d, *J* = 9.4 Hz, 1H), 3.65 – 3.52 (m, 3H), 2.97 (m, 1H), 2.81 – 2.73 (m, 1H), 2.67 (m, 1H), 2.55 (m, 1H), 1.70 – 1.25 (m, 8H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.0, 147.3, 134.5, 119.6, 108.2, 106.6, 101.1, 89.0, 86.9, 73.4, 68.3, 62.9, 53.3, 53.2, 32.6, 31.0, 29.7, 28.6, 25.3; HRMS *m/z* 389.1395 $[M+Na]^+$ (calcd for $C_{19}H_{26}NaO_5S$, 389.1399)



(*1R, 2R, 5S, 6S*)- 2-(cyclohexylsulfanyl)-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2n)

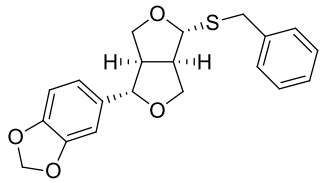
3.2n: Following the general procedure, reaction of **1.36** (20 mg, 0.08 mmol), cyclohexanethiol (29 µL, 0.24 mmol) in acetonitrile (1 mL) after 8 h yielded **3.2n** (22 mg, 79%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 – 6.75 (m, 3H), 5.95 (s, 2H), 5.38 (s, 1H), 4.42 – 4.35 (m, 2H), 4.15 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.83 (d, *J* = 9.4 Hz, 1H), 3.60 (m, 1H), 2.96 (m, 1H), 2.76 (m, 1H), 2.12 – 1.17 (m, 11H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.0, 147.3, 134.6, 119.6, 108.8, 106.6, 101.1, 87.9, 86.9, 73.5, 68.2, 53.4, 53.3, 43.4, 34.0, 33.8, 26.1, 26.0, 25.8; HRMS *m/z* 371.1297 $[M+Na]^+$ (calcd for $C_{19}H_{24}NaO_4S$, 371.1293).



(*1R, 2R, 5S, 6S*)- 6-(3,4-methylenedioxyphenyl-

2-[(2-phenylethyl)sulfanyl]-3,7-dioxabicyclo[3.3.0]octane (3.2o)

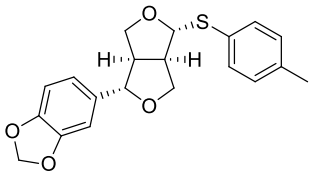
3.2o: Following the general procedure, reaction of **1.36** (65 mg, 0.26 mmol), phenylethylmercaptan (72 mg, 0.52 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2o** (72.1 mg, 75%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.20 (m, 5H), 6.87 – 6.76 (m, 3H), 5.95 (s, 2H), 5.23 (s, 1H), 4.40 – 4.35 (m, 2H), 4.12 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.85 (d, *J* = 9.4 Hz, 1H), 3.56 (m, 1H), 3.01 – 2.73 (m, 5H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.2, 147.5, 140.6, 134.7, 128.7, 128.6, 126.5, 119.8, 108.3, 106.7, 101.2, 89.3, 87.0, 73.6, 68.4, 53.5, 53.3, 36.6, 32.6; HRMS m/z 393.1149 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_4S$, 393.1136).



(*1R, 2R, 5S, 6S*)- 2-benzylsulfanyl-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2p)

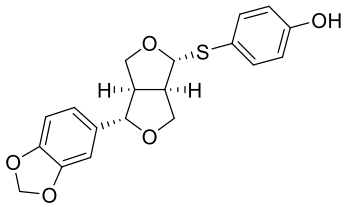
3.2p: Following the general procedure, reaction of **1.36** (68.8 mg, 0.27 mmol), benzylmercaptan (100 mg, 0.81 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2p** (47.97 mg, 50%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.24 (m, 5H), 6.86 – 6.76 (m, 3H), 5.95 (s, 2H), 5.12 (s, 1H), 4.37 – 4.31 (m, 2H), 4.18 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.91 – 3.85 (m, 2H), 3.71 (d, *J* = 13.5 Hz, 1H), 3.51 (dd, *J* = 8.9, 7.4 Hz, 1H), 2.96 (m, 1H), 2.79 (m, 1H); 13C NMR ($CDCl_3$, 400 MHz) δ 148.0, 147.4, 138.2, 134.5, 128.9, 128.6, 127.0, 119.6, 108.2, 106.6, 101.1, 87.5, 86.9, 73.4, 68.4, 53.3, 52.8, 34.8; HRMS m/z 379.0974 $[M+Na]^+$ (calcd for $C_{20}H_{20}NaO_4S$, 379.0980).



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl)-

2-(4-methylthiophenoxy)-3,7-dioxabicyclo[3.3.0]octane (3.2q)

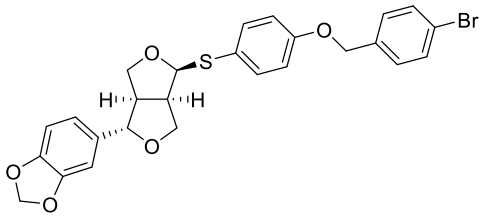
3.2q: Following the general procedure, reaction of **1.36** (50.8 mg, 0.203 mmol), 4-methylthiophenol (76 µL, 0.609 mmol) in acetonitrile (2 mL) after 8 h yielded **3.2q** (50.53 mg, 69.8%) as a white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.88 – 6.76 (m, 3H), 5.96 (s, 2H), 5.47 (s, 1H), 4.44 (t, *J* = 8.7 Hz, 1H), 4.36 (d, *J* = 7.5 Hz, 1H), 4.26 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.92 (d, *J* = 9.5 Hz, 1H), 3.61 (m, 1H), 3.12 (m, 1H), 2.83 (m, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.2, 147.5, 137.7, 134.6, 132.3, 131.2, 129.8, 119.8, 108.3, 106.7, 101.2, 92.5, 87.0, 73.5, 68.7, 53.4, 53.3, 21.2; HRMS m/z 379.0987 $[M+Na]^+$ (calcd for $C_{20}H_{20}NaO_4S$, 379.0980).



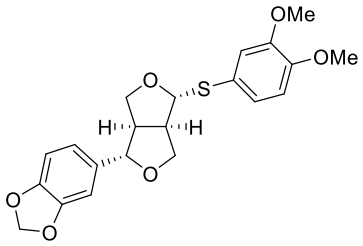
(*1R, 2R, 5S, 6S*)-2-(4-hydroxythiophenoxy)-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2r)

3.2r: Following the general procedure, reaction of **1.36** (70 mg, 0.28 mmol), 4-Hydroxythiophenol (71 mg, 0.56 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2r** (71.65 mg, 71.4%) as a white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, *J* = 8.5 Hz, 2H), 6.87 – 6.71 (m, 5H), 5.95 (s, 2H), 5.37 (s, 1H), 4.44 (t, *J* = 8.7 Hz, 1H), 4.37 (d, *J* = 7.5 Hz, 1H), 4.28 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.93 (d, *J* = 9.4 Hz, 1H), 3.61 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.11 (m, 1H), 2.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 156.1, 148.2, 147.6, 135.2, 134.4, 133.1, 119.9, 116.2, 108.4, 106.7, 101.2, 93.2, 87.0, 73.5, 68.7, 53.3, 53.0; HRMS *m/z* 381.0771 $[M+Na]^+$ (calcd for $C_{19}H_{18}NaO_5S$, 381.0773).



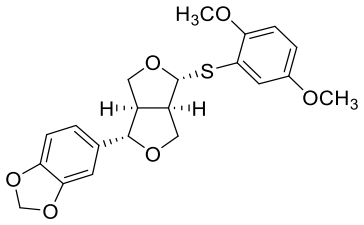
epi-3.2r-*p*BBE: Following the general procedure, reaction of **1.36** (100 mg, 0.40 mmol), 4-Hydroxythiophenol (100 mg, 0.80 mmol) in acetonitrile (4 mL) was carfully performed in room temperature for 1 h. Preparative TLC is used for purification of ***epi*-3.2r** (28.86 mg, 20%). A Solution of ***epi*-3.2r** in CH_3CN was further reacted with 4-bromobenzylbromide (30 mg, 0.12 mmol) under basic condition (K_2CO_3) for 4 h. Solvent was evaporated, water was added, and after the usual work up in EtOAc, the residue was purified by column chromatography. The white semisolid was recrystallized from MeOH to afford **epi-3.2r-*p*BBE** (50 mg, 80 %) as a white crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 11.3, 8.6 Hz, 4H, H-2‴, H-3‴, H-5‴and H-6‴) 7.29 (d, *J* = 8.2 Hz, 2H, H-2″ and H-6″) 6.91 (d, *J* = 8.7 Hz, 2H, H-3″and H-5″) 6.85 (s, 1H, H-2′) 6.82 – 6.76 (m, 2H ,H-5′and H-6′) 5.95 (s, 2H, H-7′) 5.11 (d, *J* = 6.1 Hz, 1H, H-2) 5.00 (s, 2H, H-7″) 4.54 (d, *J* = 6.7 Hz, 1H, H-6) 4.21 (t, *J* = 8.7 Hz, 1H, H-8) 4.02 (dd, *J* = 17.2, 9.7 Hz, 2H, H-4) 3.81 (dd, *J* = 9.4, 6.7 Hz, 1H, H-8) 3.38 (dd, *J* = 15.7, 8.0 Hz, 1H, H-1) 2.88 – 2.82 (m, 1H, H-5); HRMS *m/z* 549.0349, 551.0329 $[M+Na]^+$ (calcd for $C_{26}H_{23}{}^{79}BrNaO_5S$, 549.0347 and $C_{26}H_{23}{}^{81}BrNaO_5S$, 551.0327).



(*1R, 2R, 5S, 6S*)-2-(3,4- dimethoxythiophenoxy)-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2s)

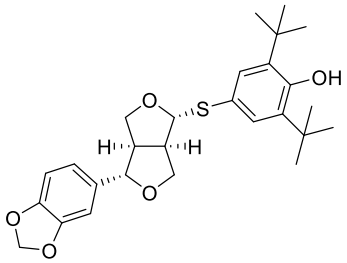
3.2s: Following the general procedure, reaction of **1.36** (107 mg, 0.427 mmol), 3,4-dimethoxythiophenol (123 µL, 0.557 mmol) in acetonitrile (4 mL) after 8 h yielded **3.2s** (86.56 mg, 50.4%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.05 (d, *J* = 1.6 Hz, 1H) 6.81 (m, 4H), 5.95 (s, 2H), 5.42 (s, 1H), 4.44 (t, *J* = 8.7 Hz, 1H), 4.37 (d, *J* = 7.5 Hz, 1H), 4.27 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.93 (d, *J* = 9.5 Hz, 1H), 3.89 (s, 3H, H-OCH_3), 3.87 (s, 3H, H-OCH_3), 3.62 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.11 (m, 1H), 2.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 149.3, 149.1, 148.0, 147.4, 134.4, 125.8, 125.5, 119.6, 116.1, 111.6, 108.2, 106.5, 101.9, 92.9, 86.8, 73.4, 68.6, 56.0, 56.0, 53.3, 53.0; HRMS m/z 425.1048 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_6S$, 425.1035).



(*1R, 2R, 5S, 6S*)-2-(2,5- dimethoxythiophenoxy)-

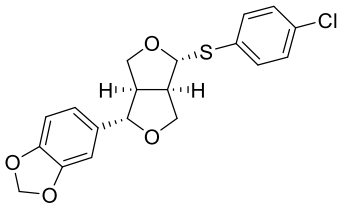
6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2t)

3.2t: Following the general procedure, reaction of **1.36** (77.7 mg, 0.310 mmol), 2,5-dimethoxythiophenol (93 µL, 0.621 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2t** (119.78 mg, 88.3%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, *J* = 2.6 Hz, 1H), 6.87 – 6.74 (m, 5H), 5.94 (s, 2H), 5.68 (s, 1H), 4.44 (t, *J* = 8.7 Hz, 1H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.23 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.91 (d, *J* = 9.5 Hz, 1H), 3.84 (s, 3H, H-OCH_3), 3.77 (s, 3H, H-OCH_3), 3.64 (dd, *J* = 8.9, 7.2 Hz, 1H), 3.17 (m, 1H), 2.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 153.9, 152.1, 148.0, 147.4, 134.4, 124.0, 119.6, 118.0, 112.9, 111.7, 108.2, 106.6, 101.1, 89.8, 86.9, 73.4, 68.8, 56.5, 55.8, 53.3, 53.2; HRMS m/z 425.1048 $[M+Na]^+$ (calcd for $C_{21}H_{22}NaO_6S$, 425.1035).



(*1R, 2R, 5S, 6S*)-2-(4-hydroxy-3,5-ditertiarybutylthiophenoxy)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2u)

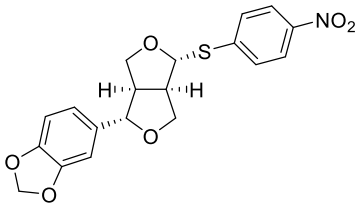
3.2u: Following the general procedure, reaction of **1.36** (50.8 mg, 0.209 mmol), 2,6-di-*tert*-butyl-4-mercaptophenol (96.78 mg, 0.406 mmol) in acetonitrile (2 mL) after 8 h yielded **3.2u** (45.9 mg, 48.3%) as a yellow oil; ^{1}1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (s, 2H), 6.87 – 6.75 (m, 3H), 5.95 (s, 2H), 5.39 (s, 1H), 4.43 (t, *J* = 8.7 Hz, 1H), 4.37 (d, *J* = 7.5 Hz, 1H), 4.29 (dd, *J* = 9.4, 5.9 Hz, 1H), 3.93 (d, *J* = 9.4 Hz, 1H), 3.61 (m, 1H), 3.11 (m, 1H), 2.81 (m, 1H), 1.43 (s, 18H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 154.2, 148.2, 147.5, 136.7, 130.4, 127.9, 119.8, 108.3, 106.7, 101.2, 93.1, 86.98, 73.5, 68.5, 53.5, 53.2, 34.5, 30.3; HRMS m/z 493.2024 $[M+Na]^+$ (calcd for $C_{27}H_{34}NaO_5S$, 493.2025).



(*1R, 2R, 5S, 6S*)-2-(4-chlorothiophenoxy)-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2v)

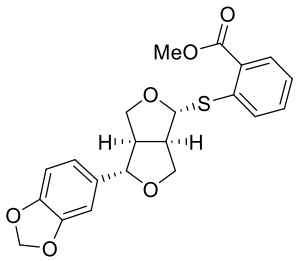
3.2v: Following the general procedure, reaction of **1.36** (28.9 mg, 0.115 mmol), 4-chlorothiophenol (50 mg, 0.35 mmol) in acetonitrile (2 mL) after 8 h yielded **3.2v** (36.27 mg, 83.7%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.84 – 6.73 (m, 3H), 5.93 (s, 2H), 5.46 (s, 1H), 4.42 (t, *J* = 8.7 Hz, 1H), 4.34 (d, *J* = 7.5 Hz, 1H), 4.21 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.91 (d, *J* = 9.6 Hz, 1H), 3.59 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.09 (m, 1H), 2.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.0, 147.4, 134.3, 133.5, 133.4, 132.8, 129.0, 119.6, 108.2, 106.5, 101.1, 92.0, 86.9, 73.3, 68.7, 53.2, 53.1.



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl))-

2-(4-nitrolthiophenoxy)-3,7-dioxabicyclo[3.3.0]octane (3.2w)

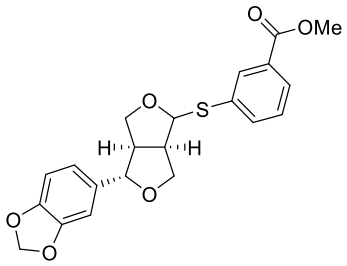
3.2w: Following the general procedure, reaction of **1.36** (65 mg, 0.26 mmol), 4-nitrothiophenol (81 mg, 0.52 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2w** (70.5 mg, 70%) as a yellow powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 6.87 – 6.75 (m, 3H), 5.95 (s, 2H), 5.73 (s, 1H), 4.48 (t, *J* = 8.8 Hz, 1H), 4.41 (d, *J* = 7.5 Hz, 1H), 4.21 (dd, *J* = 9.7, 5.8 Hz, 1H), 3.99 (d, *J* = 9.6 Hz, 1H), 3.67 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.16 (m, 1H), 2.88 (m, 1H).; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.2, 147.6, 146.2, 145.8, 134.2, 128.8, 124.0, 119.8, 108.4, 106.6, 101.3, 90.6, 87.0, 73.4, 69.2, 53.3, 53.2.



(*1R, 2R, 5S, 6S*)-2-[(2- methoxycarbonyl)thiophenoxy]-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2x)

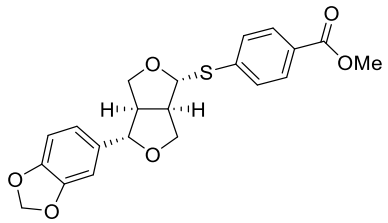
3.2x: Following the general procedure above, reaction of **1.36** (80 mg, 0.319 mmol), methylthiosalicylate (87.9 mg, 0.639 mmol) in acetonitrile (3 mL) after 8 h yielded **3.2x** (78.73 mg, 61.7%) as a white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.47 (m, 1H), 7.23 (dd, *J* = 14.2, 6.9 Hz, 1H), 6.88 – 6.75 (m, 3H), 5.95 (s, 2H), 5.68 (s, 1H), 4.48 – 4.41 (m, 2H), 4.23 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.99 – 3.89 (m, 4H), 3.70 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.24 (m, 1H), 2.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 167.0, 148.1, 147.4, 139.9, 134.3, 132.4, 130.9, 128.8, 128.4, 125.1, 119.6, 108.2, 106.5, 101.1, 89.8, 86.8, 73.5, 68.9, 53.3, 53.0, 52.2; HRMS m/z 423.0884 $[M+Na]^+$ (calcd for $C_{21}H_{20}NaO_6S$, 423.0878).



(*1R, 2R, 5S, 6S*)-2-[(3- methoxycarbonyl)thiophenoxy]-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2y)

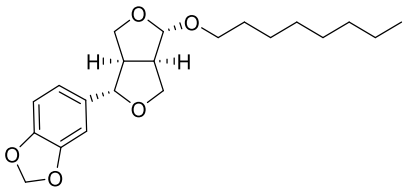
3.2y: To a solution of **1.36** (100 mg, 0.399 mmol) were treated with 3-mercatobenzoic acid (123 mg, 0.799 mmol), Amberlyst-15 (1 mg/0.005 mmol of **1.36**) and 4 Å molecular seive. After stirring at room temperature for 8 h, the reaction mixture was evaporated to dryness. The crude reaction was then metelated [17] in order to make easily to sepearate by column cromatography, yielded **3.2y** (89.3 mg, 56%) as a white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 6.88 – 6.75 (m, 3H), 5.95 (s, 2H), 5.58 (s, 1H), 4.46 (t, *J* = 8.7 Hz, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 4.26 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.92 (s, 3H), 3.64 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.14 (m, 1H), 2.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 166.5, 148.1, 147.4, 135.7, 135.5, 134.3, 132.2, 130.9, 130.8, 128.9, 128.3, 119.6, 108.2, 106.5, 101.1, 91.8, 86.8, 73.3, 68.7, 53.2, 52.2; HRMS m/z 423.0884 $[M+Na]^+$ (calcd for $C_{21}H_{20}NaO_6S$, 423.0878).



(*1R, 2R, 5S, 6S*)-2-[(4- methoxycarbonyl)thiophenoxy]-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.2z)

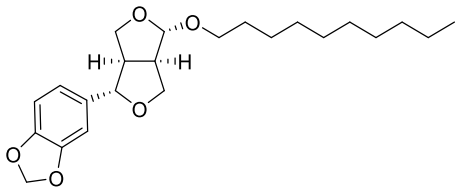
3.2z: To a solution of **1.36** (100 mg, 0.399 mmol) were treated with 4-mercatobenzoic acid (123 mg, 0.798 mmol), Amberlyst-15 (1 mg/0.005 mmol of **1.36**) and 4 Å molecular seive. After stirring at room temperature for 8 h, the reaction mixture was evaporated to dryness. The crude reaction was then metelated [17] in order to make easily to sepearate via column cromatography, yielded **3.2z** (105.8 mg, 66.2%) as a white powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.88 – 6.76 (m, 3H), 5.96 (s, 2H), 5.68 (s, 1H), 4.47 (t, *J* = 8.7 Hz, 1H), 4.40 (d, *J* = 7.5 Hz, 1H), 4.23 (m, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 3.91 (s, 3H), 3.67 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.15 (m, 1H), 2.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 166.7, 148.1, 147.5, 142.1, 134.2, 129.9, 129.0, 128.8, 119.7, 108.2, 106.5, 101.1, 90.8, 86.9, 73.4, 68.9, 53.2, 53.1, 52.1; HRMS m/z 423.0884 $[M+Na]^+$ (calcd for $C_{21}H_{20}NaO_6S$, 423.0878).



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl)-

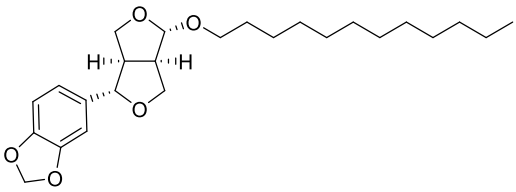
2-octyloxy-3,7-dioxabicyclo[3.3.0]octane (3.3A)

3.3A: Following the general procedure, reaction of **1.36** (16 mg, 0.06 mmol), 1-octanol (30 µL, 0.18 mmol) in acetonitrile (0.6 mL) after 8 h yielded **3.3A** (18 mg, 78%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (d, *J* = 0.8 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 2H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 1H), 3.97 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.65 (m, 1H), 3.55 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.37 (m, 1H), 3.04 (q, *J* = 8.8 Hz, 1H), 2.81 (q, *J* = 9.2 Hz, 1H), 1.59-1.54 (m, 4H), 1.27 (overlap, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 134.9, 119.8, 108.3, 107.6, 106.7, 101.2, 87.2, 71.6, 69.0, 67.6, 53.2, 52.9, 31.9, 29.8, 29.5, 29.4, 26.3, 22.8, 14.2; HRMS *m/z* 385.1997 $[M+Na]^+$ (calcd for $C_{21}H_{30}NaO_5$, 385.1991).



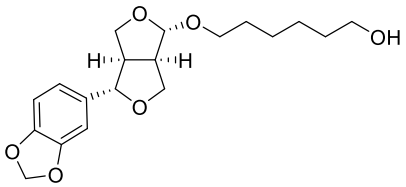
(*1R, 2R, 5S, 6S*)-2-decyloxy-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3B)

3.3B: Following the general procedure, reaction of **1.36** (11.3 mg, 0.05 mmol), 1-decanol (30 µL, 0.15 mmol) in acetonitrile (0.5 mL) after 8 h yielded **3.3B** (20.4 mg, quantitative yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (d, *J* = 1.6 Hz, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.35 (t, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 3.65 (m, 1H), 3.55 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.36 (m, 1H), 3.04 (q, *J* = 8.8 Hz, 1H), 2.81 (m, 1H), 1.60-1.52 (m, 4H), 1.26 (overlap, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 134.9, 119.8, 108.3, 107.6, 106.7, 101.2, 87.2, 71.6, 69.0, 67.6, 53.3, 52.9, 32.0, 29.8, 29.7, 29.7, 29.6, 29.4, 26.3, 22.8, 14.2; HRMS m/z 413.2306 $[M+Na]^+$ (calcd for $C_{23}H_{34}NaO_5$, 413.2304).



(*1R, 2R, 5S, 6S*)-2-dodecyloxy-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3C)

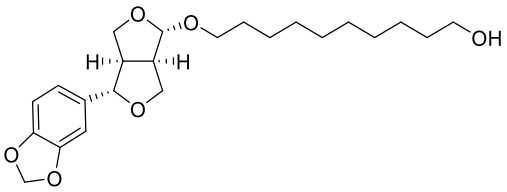
3.3C: Following the general procedure, reaction of **1.36** (13.6 mg, 0.05 mmol), 1-dodecanol (34 µL, 0.15 mmol) in acetonitrile (0.5 mL) after 8 h yielded **3.3C** (20 mg, quantitative yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (d, *J* = 1.2 Hz, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.34 (t, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.65 (m, 1H), 3.54 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.36 (m, 1H), 3.04 (q, *J* = 8.4 Hz, 1H), 2.81 (m, 1H), 1.60-1.52 (m, 4H), 1.25 (overlap, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.0, 119.8, 108.3, 107.6, 106.8, 101.2, 87.2, 71.6, 69.1, 67.6, 53.3, 53.0, 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 26.4, 22.8, 14.2; HRMS *m/z* 441.2618 $[M+Na]^+$ (calcd for $C_{25}H_{38}NaO_5$, 441.2617).



(*1R, 2R, 5S, 6S*)-2-(6-hydroxy)hexyloxy-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3D)

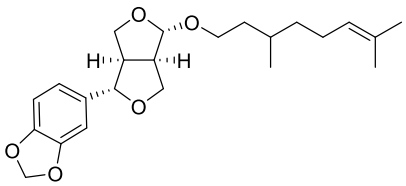
3.3D: Following the general procedure, reaction of **1.36** (6.5 mg, 0.03 mmol), 1,6-hexanediol (11 mg, 0.09 mmol) in acetonitrile (0.2 mL) after 8 h yielded **3.3D** (12 mg, quantitative yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.81-6.76 (m, 2H), 5.94 (s, 2H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.35 (t, *J* = 8.0 Hz, 1H), 3.96 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.69-3.62 (m, 3H), 3.55 (dd, *J* = 8.8, 8.0 Hz, 1H), 3.38 (m, 1H), 3.03 (q, *J* = 8.4 Hz, 1H), 2.81 (q, *J* =8.8 Hz, 1H), 1.59-1.56 (m, 2H), 1.43-1.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 134.9, 119.8, 108.3, 107.6, 106.7, 101.2, 87.2, 71.5, 69.1, 67.4, 64.6, 53.2, 52.9, 32.8, 29.7, 28.7, 25.9; HRMS *m/z* 373.1630 $[M+Na]^+$ (calcd for $C_{19}H_{26}NaO_6$, 373.1627).



(*1R, 2R, 5S, 6S*)-2-(10-hydroxy)decyloxy-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3E)

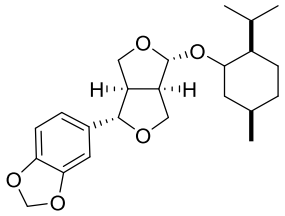
3.3E: Following the general procedure, reaction of **1.36** (7 mg, 0.03 mmol), 1,10-decanediol (16 mg, 0.09 mmol) in acetonitrile (0.3 mL) after 8 h yielded **3.3**E (13 mg, quantitative yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.35 (t, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.68-3.62 (m, 3H), 3.55 (dd, *J* = 8.8, 7.6 Hz, 1H, H-8), 3.37 (m, 1H), 3.04 (q, *J* = 8.4 Hz, 1H), 2.82 (q, *J* =8.8 Hz, 1H), 1.57-1.54 (m, 2H), 1.28-1.25 (m, 14H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 134.9, 119.8, 108.3, 107.6, 106.7, 101.2, 87.2, 71.6, 69.1, 67.6, 63.2, 53.2, 52.9, 32.9, 29.8, 29.8, 29.7, 29.6, 29.5, 26.3, 25.9; HRMS m/z 429.2261 $[M+Na]^+$ (calcd for $C_{23}H_{34}NaO_6$, 429.2253).



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl)-

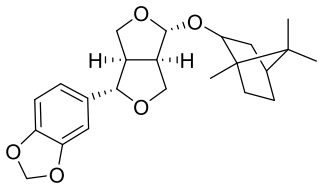
2-[3,7-dimethyloct-6-en-1-yloxy]-3,7-dioxabicyclo[3.3.0]octane (3.3F)

3.3F: Following the general procedure, reaction of **1.36** (27.8 mg, 0.11 mmol), β-citronellol (60 µL, 0.33 mmol) in acetonitrile (1 mL) after 8 h yielded **3.3**F (38 mg, 88%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.81-6.76 (m, 2H), 5.94 (s, 2H), 5.09 (t, *J* = 6.8 Hz, 1H), 4.93 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.35 (t, *J* = 7.2 Hz, 1H), 3.97 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.85 (d, *J* = 8.8 Hz, 1H), 3.70 (m, 1H), 3.55 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.40 (m, 1H), 3.03 (q, *J* = 9.2 Hz, 1H), 2.81 (q, *J* = 6.8 Hz, 1H), 2.03-1.91 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.54 (m, 1H), 1.41-1.30 (m, 3H), 1.16 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.0, 131.3, 124.9, 119.8, 108.3, 107.5, 106.7, 101.2, 87.2, 71.6, 69.1, 65.9, 53.3, 53.0, 37.4, 36.8, 29.8, 25.8, 25.6, 19.8, 17.8; HRMS m/z 411.2155 $[M+Na]^+$ (calcd for $C_{23}H_{32}NaO_5$, 411.2147).



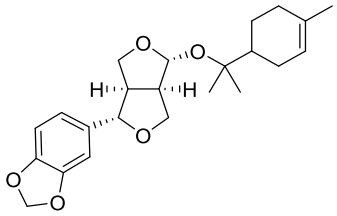
(*1R, 2R, 5S, 6S*)-2-[(*1R, 2S, 5R*)-2-isopropyl-5-methylcyclohexyloxy-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3G)

3.3G: Following the general procedure, reaction of **1.36** (12.6 mg, 0.05 mmol), menthol (23 mg, 0.15 mmol) in acetonitrile (0.5 mL) after 8 h yielded **3.3G** (20 mg, quantitative yield) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.84 (s, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 5.01 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.35 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.05 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.84 (d, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.31 (ddd, *J* = 10.4, 10.0, 4.4 Hz, 1H), 3.04 (q, *J* = 8.0 Hz, 1H), 2.83 (q, *J* = 8.8 Hz, 1H), 2.13-2.04 (m, 2H), 1.63-1.59 (m, 3H), 1.40 (m, 1H), 1.17 (m, 1H), 1.01-0.94 (m, 2H), 0.91(d, *J* = 4.8 Hz, 3H), 0.89 (d, *J* = 4.4 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.1, 119.8, 109.4, 108.3, 106.7, 101.2, 87.3, 79.7, 71.7, 69.1, 53.4, 52.9, 48.9, 43.6, 34.5, 31.9, 25.9, 23.5, 22.4, 21.3, 16.5; HRMS m/z 411.2143 $[M+Na]^+$ (calcd for $C_{23}H_{32}NaO_5$, 411.2147).



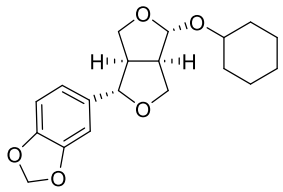
(*1R, 2R, 5S, 6S*)-2-(4,7,7-trimethylbicyclo[2.2.1]heptan-3-yloxy)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3H)

3.3H: Following the general procedure, reaction of **1.36** (20 mg, 0.08 mmol), borneol (37 mg, 0.24 mmol) in acetonitrile (0.8 mL) after 8 h yielded **3.3H** (23 mg, 75%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.82-6.76 (m, 2H), 5.95 (s, 2H), 4.95 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.34 (dd, *J* = 12.8, 8.0 Hz, 1H), 3.98 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.82 (d, *J* = 8.8 Hz, 1H), 3.76 (brd, *J* = 8.0 Hz, 1H), 3.53 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.07 (q, *J* = 8.4 Hz, 1H), 2.84 (q, *J* = 9.2 Hz, 1H), 2.22 (m, 1H), 1.89 (m, 1H), 1.68-1.58 (m, 2H), 1.22-1.15 (m, 2H), 1.01 (dd, *J* = 13.6, 3.2 Hz, 1H), 0.85 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.1, 119.8, 109.2, 108.3, 106.8, 101.2, 87.2, 84.0, 71.7, 69.0, 53.3, 53.1, 49.4, 47.5, 45.2, 37.9, 28.4, 26.9, 19.9, 18.9, 14.0; HRMS m/z 409.1992 $[M+Na]^+$ (calcd for $C_{23}H_{30}NaO_5$, 409.1991).



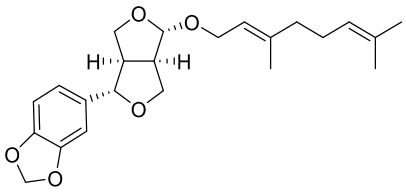
(*1R, 2R, 5S, 6S*)-2-[2-(4-methylcyclohex-3-en-1-yl)propan-2-yloxy]-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3l)

3.3l: Following the general procedure, reaction of **1.36** (48 mg, 0.19 mmol), α-terpeneol (95 µL, 0.57 mmol) in acetonitrile (2 mL) after 8 h yielded **3.3l** (60 mg, 81%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.84 (d, *J* = 1.6 Hz, 1H), 6.80-6.77 (m, 2H), 5.94 (s, 2H), 5.37 (brs, 1H), 5.24 (s, 1H), 4.36 (d, *J* = 5.6 Hz, 1H), 4.33 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.05 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.80 (d, *J* = 8.8 Hz, 1H), 3.57 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.95 (m, 1H), 2.83 (m, 1H), 2.04-1.96 (m, 4H), 1.83-1.81 (m, 3H), 1.64 (s, 3H), 1.57 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.3, 134.1, 121.0, 119.7, 108.3, 106.7, 102.3, 101.2, 87.2, 78.5, 71.8, 69.1, 54.2, 53.2, 44.2, 31.2, 26.9, 24.3, 24.0, 23.6, 23.5; HRMS m/z 409.1992 $[M+Na]^+$ (calcd for $C_{23}H_{30}NaO_5$, 409.1991).



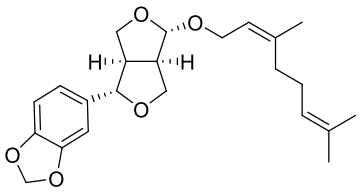
(*1R, 2R, 5S, 6S*)-2-cyclohexyloxy-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3J)

3.3J: Following the general procedure, reaction of **1.36** (12.9 mg, 0.05 mmol), cyclohexanol (16 µL, 0.15 mmol) in acetonitrile (0.5 mL) after 8 h yielded **3.3J** (16 mg, 93%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (d, *J* = 0.8 Hz, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 4.93 (s, 1H), 4.37 (d, *J* = 8.8 Hz, 1H), 4.34 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.01 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.83 (d, *J* = 8.8 Hz, 1H), 3.55 (m, 2H), 3.02 (q, *J* = 8.4 Hz, 1H), 2.83 (m, 1H), 1.89-1.52 (m, 10H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 135.0, 119.8, 108.3, 106.8, 105.6, 101.2, 87.3, 74.9, 71.6, 69.0, 53.5, 53.0, 34.0, 32.0, 25.8, 24.5, 24.4; HRMS m/z 355.1527 $[M+Na]^+$ (calcd for $C_{19}H_{24}NaO_5$, 355.1521).



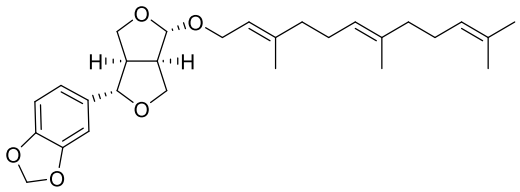
(*1R, 2R, 5S, 6S*)-2-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yloxy]-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (**3.3K**)

3.3K: Following the general procedure, reaction of **1.36** (17 mg, 0.07 mmol), geraniol (37 µL, 0.21 mmol) in acetonitrile (0.7 mL) after 8 h yielded **3.3K** (18 mg, 69%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.81-6.75 (m, 2H), 5.94 (s, 2H), 5.33 (t, *J* = 6.4 Hz, 1H), 5.09 (m, 1H), 4.99 (s, 1H), 4.38 (d, *J* = 9.2 Hz, 1H), 4.35 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.17 (dd, *J* = 12.0, 6.8 Hz, 1H), 4.02-3.97 (m, 2H), 3.87 (d, *J* = 8.8 Hz, 1H), 3.55 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.06 (m, 1H), 2.82 (m, 1H), 2.10-2.04 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 141.1, 134.9, 131.8, 124.1, 120.2, 119.8, 108.3, 106.8, 106.7, 101.2, 87.2, 71.6, 69.1, 63.6, 53.3, 53.0, 39.8, 26.5, 25.8, 17.8, 16.6; HRMS m/z 409.1992 $[M+Na]^+$ (calcd for $C_{23}H_{30}NaO_5$, 409.1991).



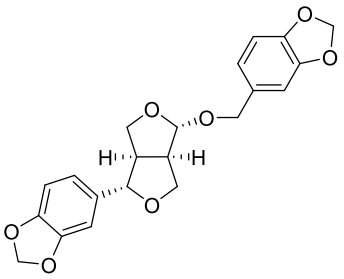
(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxyphenyl)-2-[(2*Z*)-3,7-dimethylocta-2,6-dien-1-yloxy]-3,7-dioxabicyclo[3.3.0]octane (3.3L)

3.3L: Following the general procedure, reaction of **1.36** (105.8 mg, 0.42 mmol), nerol (222 µL, 1.26 mmol) in acetonitrile (4 mL) after 8 h yielded **3.3L** (134 mg, 82%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.79-6.75 (m, 2H), 5.94 (s, 2H), 5.34 (m, 1H), 5.09 (brs, 1H), 4.98 (s, 1H), 4.38 (d, *J* = 9.2 Hz, 1H), 4.34 (dd, *J* = 12.4, 7.6 Hz, 1H), 4.16 (m, 1H), 4.01-3.94 (m, 2H), 3.86 (d, *J* = 8.8 Hz, 1H), 3.54 (m, 1H), 3.05 (m, 1H), 2.80 (m, 1H), 2.08 (brs, 4H), 1.75 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 141.4, 134.9, 132.1, 123.9, 121.1, 119.8, 108.3, 106.7, 106.7, 101.2, 87.1, 71.5, 69.1, 63.3, 53.2, 53.0, 32.3, 26.9, 25.8, 23.7, 17.8; HRMS m/z 409.1997 $[M+Na]^+$ (calcd for $C_{23}H_{30}NaO_5$, 409.1991).



(*1R, 2R, 5S, 6S*)-2-[(2*E*, 6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yloxy]-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3M)

3.3M: Following the general procedure, reaction of **1.36** (77.2 mg, 0.31 mmol), *trans*,*trans*-farnesol (235 µL, 0.93 mmol) in acetonitrile (3 mL) after 8 h yielded **3.3M** (118 mg, 84%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.79-6.75 (m, 2H), 5.94 (s, 2H), 5.33 (m, 1H), 5.10-5.07 (m, 2H), 4.98 (s, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 4.34 (dd, *J* = 9.6, 7.6 Hz, 1H), 4.18 (m, 1H), 4.01-3.98 (m, 2H), 3.86 (d, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.06 (m, 1H), 2.81 (m, 1H), 2.12-1.95 (m, 8H), 1.69 (s, 3H), 1.67 (s, 3H), 1.59 (s, 6H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.1, 147.4, 141.1, 135.5, 134.9, 131.4, 124.5, 123.9, 120.2, 119.8, 108.3, 106.7, 106.7, 101.2, 87.1, 71.5, 69.1, 63.6, 53.2, 53.0, 39.8, 39.7, 26.9, 26.4, 25.8, 17.8, 16.6, 16.1; HRMS m/z 477.2617 $[M+Na]^+$ (calcd for $C_{28}H_{38}NaO_5$, 477.2617).



(*1R, 2R, 5S,* 6S)- 2-(3,4-(methylenedioxy)benzyloxy-

6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (3.3N)

3.3N: Following the general procedure, reaction of 1.36 (63.3 mg, 0.25 mmol), Piperonyl alcohol (235 µL, 0.51 mmol) in acetonitrile (3 mL) after 8 h yielded **3.3N** (43.6 mg, 44.8%) as a whith solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (m, 6H), 5.95 (d, *J* = 1.0 Hz, 4H), 5.02 (s, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.42 – 4.31 (m, 3H), 4.03 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.90 (d, *J* = 9.0 Hz, 1H), 3.57 – 3.51 (m, 1H), 3.09 (dd, *J* = 16.9, 8.7 Hz, 1H), 2.83 (dd, *J* = 15.5, 6.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 134.8, 131.6, 121.9, 119.8, 108.9, 108.3, 106.7, 106.5, 101.2, 101.2, 87.2, 71.5, 69.3, 68.9, 53.2, 52.9.

3.5.4 X-ray Crystallographic Analysis of 3.2r and *epi*-3.2r

Single crystal X-ray diffraction data were collected at 296(2) K on a Bruker X8 PROSPECTOR KAPPA CCD diffractometer using an IμS X-ray microfocus source with multilayer mirrors, yielding intense monochromatic Cu-Kα radiation (λ = 1.54178 Å) for 3.2r and on a Bruker X8 APEX II KAPPA CCD diffractometer using graphite monochromatized Mo-Kα radiation (λ= 0.71073 Å) for epi-3.2r. The structures were solved using SHELXTL XT 2013/1 [18], expanded using difference Fourier method, and refined using full-matrix least squares on F2 with SHELXTL XLMP 2014/7 [19]. Absolute configurations of the two compounds were ambiguously determined with the estimated Flack parameters (x's) [20] that are statistically close to zero; the corresponding respective values are 0.040(19) and 0.026(12). Details of crystal data and refinement parameters are listed in Table 3.4.

Table 3.4 Crystal data and refinement parameters of compounds **3.2r** and ***epi*-3.2r.**

	3.2r	***epi*-3.2r**
Crystal habit	Thin plate, colorless	Thin plate, colorless
Crystal size (mm^3)	0.01×0.24×0.34	0.01×0.18×0.20
Empirical formula	C_{19} H_{18} O_5 S	C_{26} H_{23} Br O_5 S
FW	358.40	527.41
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$ (no. 4)	*P*1 (no. 1)
a [Å]	6.1485(2)	6.7501(13)
b [Å]	7.6475(2)	8.8663(18)
c [Å]	17.9288(4)	20.864(4)
α [°]	90	95.858(5)
β [°]	90.711(1)	94.023(5)
γ [°]	90	111.089(5)
V [$Å^3$]	842.96(4)	1151.3(4)
Z	2	2
ρ_{calcd} [Mg m^{-3}]	1.412	1.521
μ [mm^{-1}]	1.948	1.912
F(000)	376	540
Diffractometer	Bruker X8 Prospector KAPPA CCD	Bruker X8 APEX II KAPPA CCD
Radiation (λ, Å)	CuKα (1.54178)	MoKα (0.71073)
Resolution (Å)	0.83	0.83
Temperature (K)	296(2)	296(2)
$2\theta_{max}$	136.8	50.6
Completeness (%)	99.6	99.7
Reflns collected/ unique/ > 2σ(*I*)	6974 / 3010 / 2417	20477 / 8319 / 3229
R_{int}	0.0522	0.0943
Data / parameters	3010 / 227	8319 / 595
Goodness on fit	1.100	0.921
R_1, [a] *wR*2 [b][*I* > 2σ(*I*)]	0.0558, 0.1403	0.0584, 0.0827
R_1, wR_2 [all data]	0.0672, 0.1535	0.2047, 0.1200
Flack parameter (*x*)	0.040(19)	0.026(12)
$\Delta\rho$ (e $Å^{-3}$)	-0.39, 0.21	-0.28, 0.28

[a] $R = \sum ||F_o| - |F_c|| / \sum |F_o|$; [b] $wR = \sum \{w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2\}^{1/2}$.

CHAPTER IV

MECHANISTIC INVESTIGATION OF ALKOXYSAMIN (3.3) FORMATION

Generally, hemiacetals are susceptible to protonation under strong acid condition to generate oxocarbenium ion [21]. The attack of nucleophile on both sides of oxocarbenium ion would produce a mixture of two diastereomers in an equal amount. The aforementioned phenomena were observed in the reaction between samin and phenolics. However, high stereoselectivity was noticed in reaction between samin and thiols. Moreover, the reaction of samin and alcohols merely provide a single stereomeric product. Therefore, the mechanism of unexpected of alkoxysamin formations (**3.3**) were carefully investigate by a model reaction monitored by ^{1}H NMR spectroscopy and computational calculation.

4.1 Mechanistic investigation on 3.3 formation

The model reaction monitored by ^{1}H NMR was set by treatment of samin (**1.36**) with CD_3OD as a representative nucleophile in the presence of deuterated-trifluoroacetic acid (TFA-d) (Figure 4.1). During time interval observation, we found that this reaction generated both **4.1** and ***epi*-4.1** with diverse ratios. The presence of compound **4.1** could be observed by singlet signal of H-2 at 4.88 ppm while its epimer (***epi*-4.1**) showed H-2 as doublet signal at 4.95 ppm with J = 5.4 Hz. Noticeably, the depletion of starting samin could be monitored by signal integration at 5.29 ppm (Figure 4.1).

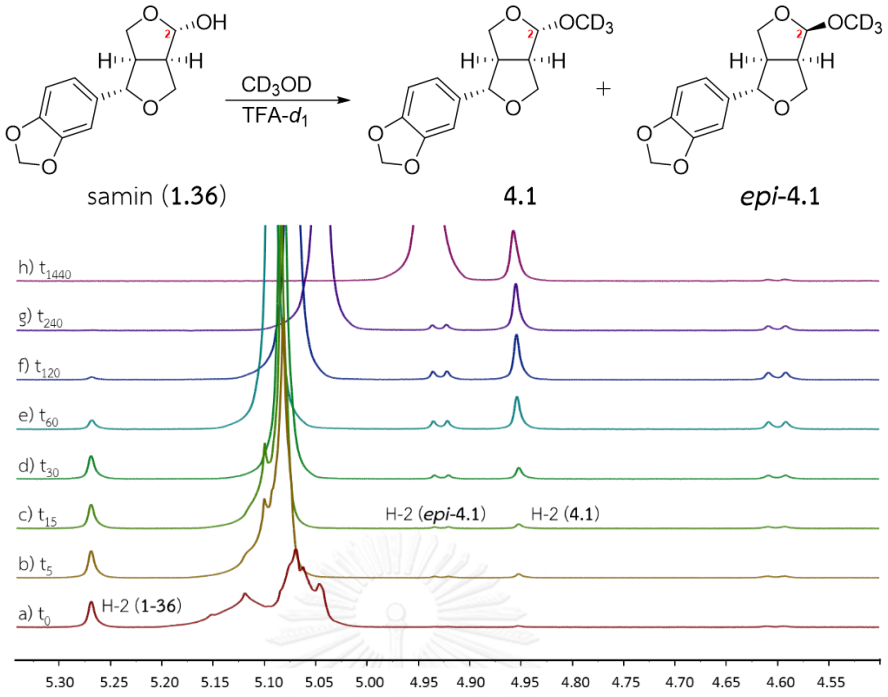


Figure 4.1 Overlaid ^{1}H NMR spectra of methoxy-d^{3} samin, **4.1** and ***epi*-4.1** (CD_3OD), occurring in the reaction, for different times.

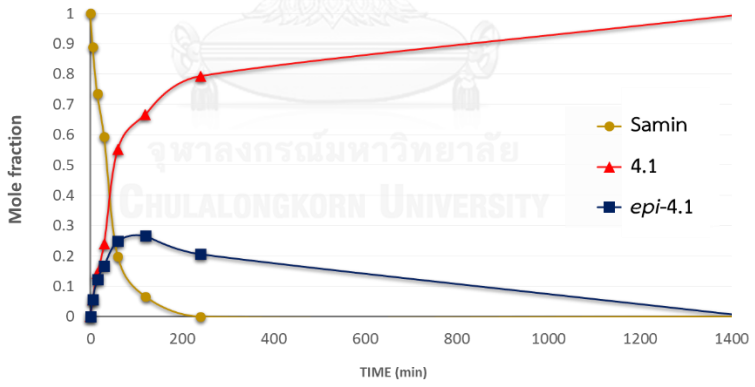
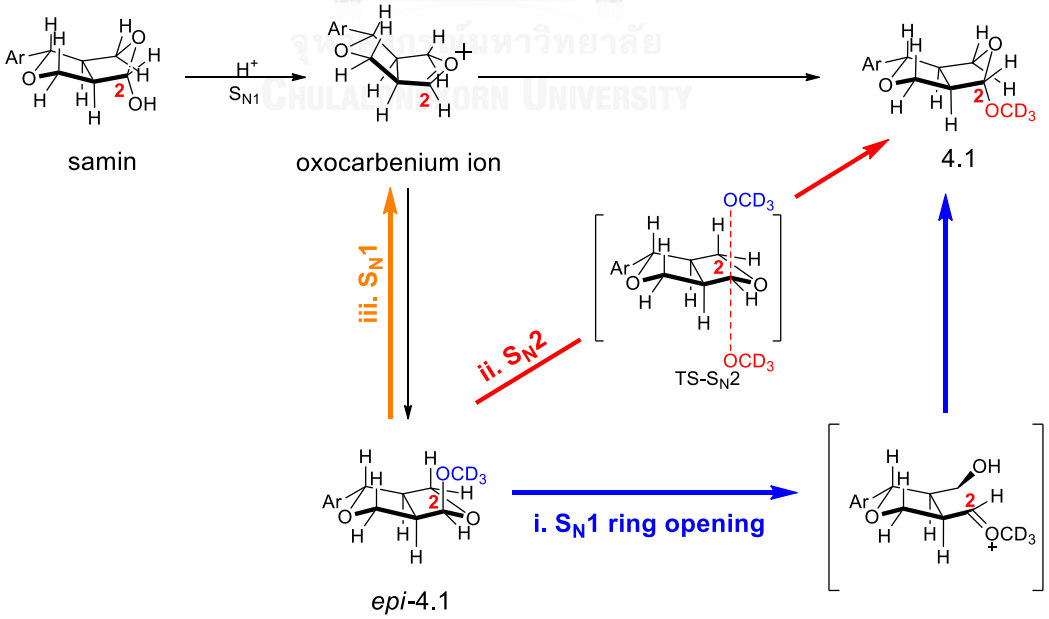


Figure 4.2 Time course of the evolution of samin (**1.36**), **4.1**, and ***epi*-4.1** in mole fraction by ^{1}H NMR spectroscopy (400 MHz).

Figure 4.2 showed time course of the evolution of **1.36**, **4.1**, and ***epi*-4.1** in mole fraction by integration of ^{1}H NMR signals. After 5 min of reaction, **4.1** and ***epi*-4.1** were first detected in the ratio of 1:1 (**4.1**:***epi*-4.1**), suggesting that the reaction proceed through S_N1-like mechanism. Noticeably, compound **4.1** was predominantly generated

after 60 min as observed in unequal ratio with ***epi*-4.1** (1.5:1 to 2:1). Although the starting samin was completely consumed after 240 min of reaction, the mole fraction of **4.1** still increased while ***epi*-4.1** gradually declined. We inevitable hypothesized that ***epi*-4.1** would be transformed to **4.1**. This result could explain the absence of *epi*-alkoxysamins from reaction between samin and alcohols (section 3.3.); however exact mechanism on transformation of ***epi*-4.1** to **4.1** remain unclear.

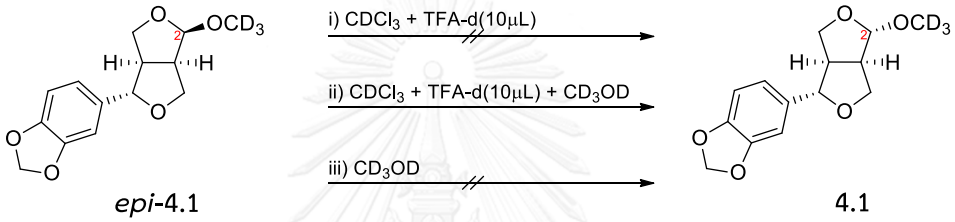
In fact, the epimerization of furofuran lignans has been rarely explained due to the complexity of their conformations. Mostly, isomerization on these compounds was claimed to occur through ring opening reaction [5, 22]. In this experiment, we proposed the mechanism for the transformation of ***epi*-4.1** to **4.1** as illustrated in Scheme 4.1. The first route involved the endocyclic C2–O cleavage facilitated by the electron-donating OCH_3 (Scheme 4.1 (i)). Alternatively, S_N2 mechanism using CD_3OD as nucleophile was also proposed (Scheme 4.1 (ii)). Lastly, compound ***epi*-4.1** might be reversed subsequently through oxocarbenium ion to form a stable compound **4.1** (Scheme 4.1 (iii)).



Scheme 4.1 Proposed mechanistic formation of **4.1** and ***epi*-4.1**

4.2 Mechanistic investigation on epimerization of alkoxysamin and *epi*-alkoxysamin

To investigate the reasonable epimerization mechanism from ***epi*-4.1** to **4.1**, we set the criteria to prove this mechanism using the diastereomeric pure ***epi*-4.1** as starting material (Scheme 4.2). After diastereomeric pure ***epi*-4.1** was gently produced and separated by high performance liquid chromatography (HPLC), it was dissolved in $CDCl_3$ in the presence of TFA-d (10μL) (Scheme 4.2).



***epi*-4.1** **4.1**

Scheme 4.2 Epimerization of ***epi*-4.1** under different conditions i) - iii).

After ^{1}H NMR acquisition, there was neither change on ***epi*-4.1** nor presence of **4.1** formation under first condition. This observation suggested that epimerization through S_N1 ring opening (Scheme 4.1, route i) is impossible, and external nucleophile is presumably required. To verify this assumption, a small amount (20μL) of CD_3OD was added into the reaction NMR tube (Scheme 4.2, condition (ii)). After shaken well and left standing at room temperature for 10 min, the doublet signal H-2 of ***epi*-4.1** was completely disappeared while singlet signal H-2 of **4.1** was clearly observed. In addition, epimerization of ***epi*-4.1** to **4.1** could not proceed without the presence of strong acid as illustrate by dissolved ***epi*-4.1** in CD_3OD, and left it overnight without any change (Scheme 4.2, condition (iii)).

We further considered possible epimerization through route ii and iii. Protonation of ***epi*-4.1** to regenerate oxocarbenium ion (Scheme 4.1, route iii), which was subsequently attacked by nucleophile to produce **4.1**, is less likely to proceed

because there was no ***epi*-4.1** remained after reaction completed. In fact, if any reaction proceed with equilibrium, both starting material (***epi*-4.1**) and product (**4.1**) would be detected in approximately equal amount.

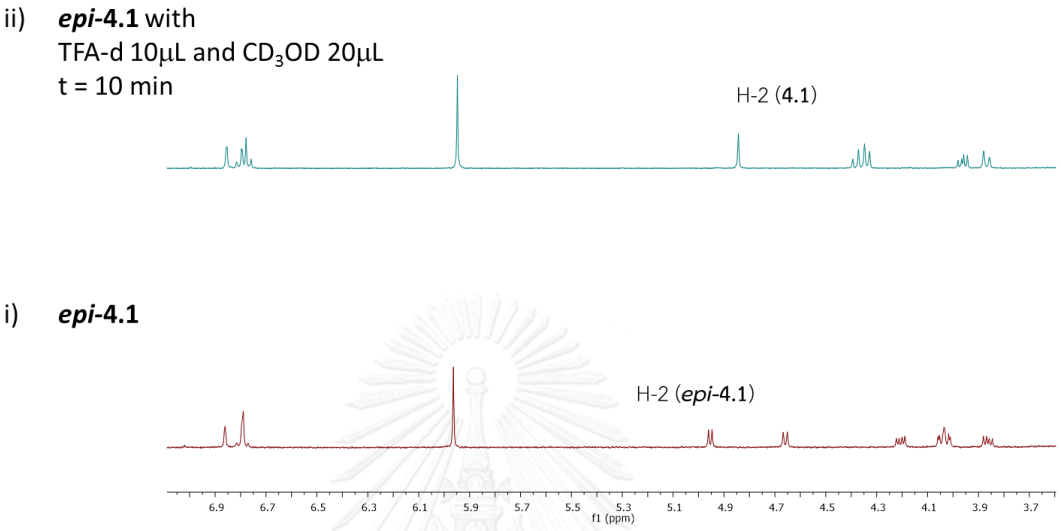
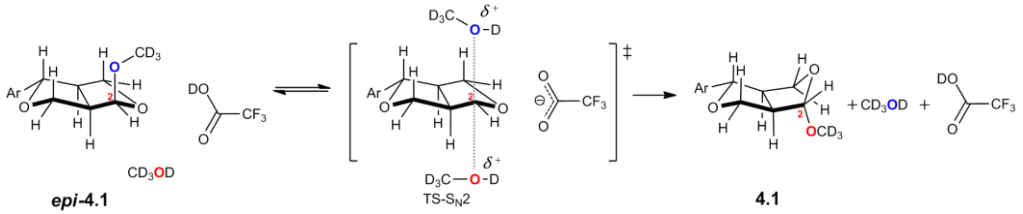


Figure 4.3 Overlaid ^{1}H NMR spectra of (i) ***epi*-4** and (ii) the treated ***epi*-4.1** with CD_3OD and TFA-d for 10 min.

From this result, the requiring of CD_3OD in the presence of TFA-d in epimerization reaction revealed that this reaction presumably undergo S_N2-like transition state contributed by acid-catalysis (Scheme 4.3).



Scheme 4.3 Proposed S_N2 reaction between ***epi*-4.1** and deuterated methanol (CD_3OD) with the present of deuterated-trifluoroacetic acid (CF_3CO_2D).

4.3 Computational calculations

The above experimental result was strikingly different with that of Johansson et al. [22], reported epimerization of furanosides by ring opening mechanism. Therefore, we then confirmed a transformational possibility of ***epi*-4.1** by bond distances observation of structures at transition state, using PCM/B3LYP/6-31+G(d,p) method to optimize the transition state structure (Figure 4.4). Table 4.1 lists major geometrical features of the transition state. Due to the nucleophile and leaving group are totally the same alcohols. C-O (breaking bond) and C-O^{b} (forming bond) bond distances at transition state were not significantly different. However, the slightly shorter new C-O^{b} (2.51 Å) bond inferred that there is more preferable bond formation than C-O bond. The short H^{a}-O bond (0.97 Å) also supported the -OCH_3 of ***epi*-4.1** prefer leaving to form free methanol molecule after receive proton from acid (TFA-d) rather than bonding with anomeric carbon (C-2). All illustrated evidences corroborated reasonably transformation of ***epi*-4.1** into **4.1** through S_N2-like transition state [10].

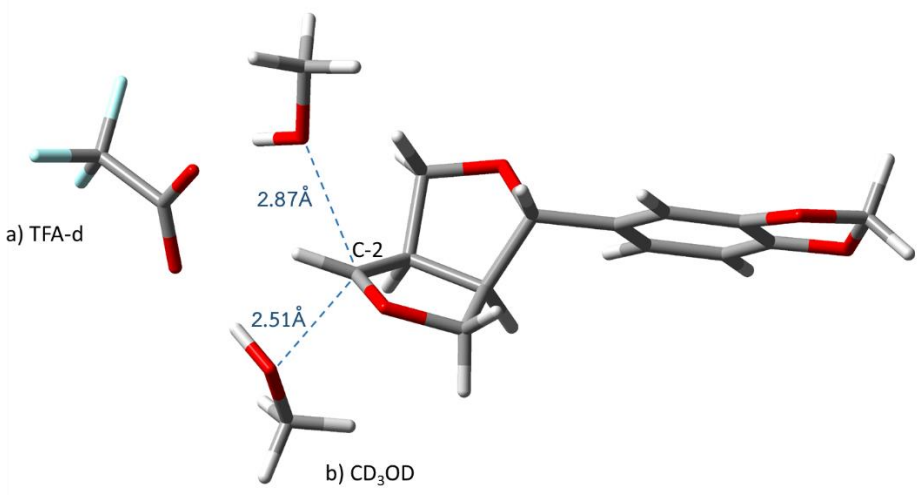


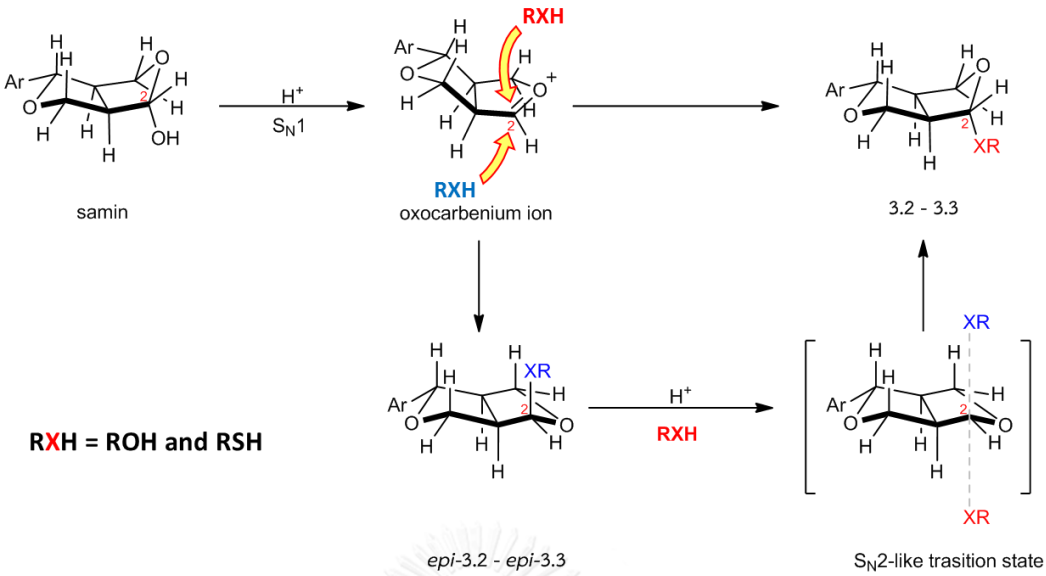
Figure 4.4 Transition-state model for the epimerization reaction of ***epi*-4.1.** (Note ^{a} Atoms of TFA-d and ^{b} Atoms of CD_3OD)

Table 4.1 Most important bond distances (in Å) and valence angle (in °) of transition state structure.

Coordinate/property			Transition state
O[a]	H[a]		1.843
H[a]	O		0.975
O	C		2.868
C	O[b]		2.517
O[b]	H[b]		0.991
H[b]	O[a]		1.715
O	C	O[b]	123.1

[a] Atoms of TFA-d [b] Atoms of CD_3OD

In summary, our stereoselective products from reaction between samin and alcohols as well as thiols were reasonably formed through S_N1-like mechanism by protonation of the hemiacetal center of samin to generate the corresponding oxocarbenium ion. Subsequent reaction of this oxocarbenium ion with the nucleophiles (**l-z** and **A-N**) then led to the observed only *exo,exo*-furofurans (**3.2-3.3**) either directly, or alternatively, by protonation of their epimers (*endo,exo*-furofurans) through the S_N2-like transition state contributed by acid-catalysis, likewise reaction sequence of model reaction monitoring which is exemplified in Scheme 4.4.



Scheme 4.4 A proposed mechanistic reaction of synthesis of stereoselective products (**3.2** and **3.3**).

4.4 Experimental section

4.4.1 Mechanistic investigation on 3.3 formation

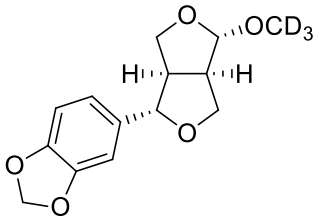
Solution of samin (7 mg, 0.027mmol), deuterated-trifluoroacetic acid (TFA-d, 20 µL) and CD_3OD were sealed in NMR tube. At time interval, NMR proton spectra were recorded. Chemical shifts of all combinations in ^1H NMR spectra obtained with Varian Mercury$^+$ 400 were 5.29 ppm (1H, s) for samin, 4.95 ppm (*J*= 5. 4, 1H, s) for ***epi*-4.1** and 4.88 ppm (1H, s) for **4.1**. Mole ratios were calculated from integration of NMR signals corresponding to samin, **4.1** and ***epi*-4.1**.

4.4.2 Mechanistic investigation on epimerization

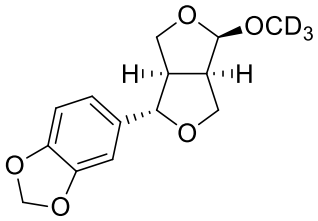
4.4.2.1 Synthesis of 4.1 and *epi*-4.1

To a solution of samin (100 mg, 0.39 mmol) in acetonitrile (4 mL) was treated with methanol (0.80 mmol), acidic resin amberlyst-15 and molecular sieve, 4 Å. After stirring at 0°C for 1 h, the reaction was suddenly quenched, and evaporated to dryness.

Reaction mixture was firstly purify by siliga gel column chromatography followed by semi-preparative HPLC (t_R = 45 min, gradient of CH_3CN/H_2O).



(*1R, 2R, 5S, 6S*)-6-(3,4-methylenedioxy-phenyl)-2-metyl-d_3-oxy-3,7-dioxabicyclo[3.3.0]octane (4.1)



(*1R, 2S, 5S, 6S*)-6-(3,4-methylenedioxy-phenyl)-2-metyl-d_3-oxy-3,7-dioxabicyclo[3.3.0]octane (*epi*-4.1)

4.1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (d, *J* = 17.9 Hz, 3H), 5.96 (s, 2H), 4.95 (s, 1H), 4.44 (dd, *J* = 21.2, 8.2 Hz, 2H), 4.02 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.95 (d, *J* = 9.1 Hz, 1H), 3.65 (dd, *J* = 9.3, 7.6 Hz, 1H), 3.11 (dd, *J* = 16.5, 8.6 Hz, 1H), 2.92 (dd, *J* = 15.3, 7.2 Hz, 1H).

***epi*-4.1**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (m, 3H), 5.94 (s, 2H), 4.93 (d, *J* = 5.5 Hz, 1H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.18 (dd, *J* = 8.9, 4.2 Hz, 1H), 4.05 – 3.97 (m, 2H), 3.86 – 3.81 (m, 1H), 3.11 (m, 1H), 2.92 (m, 1H).

4.4.2.2 ^{1}H NMR monitoring section

Solution of compound ***epi*-4.1** (14 mM), in $CDCl_3$ were treated with two conditions, namely, deuterated-trifluoroacetic acid (TFA-d 10 μL) and TFA-d 10 μL along with duterated methanol (CD_3OD, 20 μL), performed in NMR tube. ^{1}H NMR spectroscopy was applied to monitor the transformation under different condition of each compounds as well as ***epi*-4.1** in CD_3OD.

4.4.3 Computational section

The geometrical optimization and determination of product energy have been calculated using the density functional theory (DFT) with the popular hybrid method (B3LYP) with the 6-31+G(d,p) basis set. Methanol phase and the polarizable continuum model (PCM) calculations were carried out using the Gaussian09 package [23] with default convergence criteria.

CHAPTER V

CONCLUSION

Our synthesis approach is efficient to provide almost fifty furofuran lignans starting from naturally available sesamolin. Key step of our methodology involved protonation of samin to generate oxocarbenium ion, followed by nucleophilic addition. Three types of nucleophiles were used to investigate the feasibility of our designed synthetic method; namely, phenolics (ArOH), thiols (RSH), and alcohols (ROH). This synthesis strategy provided moderate to high yield of diastereomeric products except for those synthesized from samin and alcohols which was further investigated by a time-course ^{1}H NMR technique. The result revealed that the stereoselective products were presumably obtained from nucleophilic addition of oxocarbenium ion, or alternatively, via protonation of their epimers through the S_N2-like transition state which can be confirmed by structural energy and bond distances of optimized transition state structure, generated by Gaussian09.

This practical synthesis method of furofuran lignans suggested an opportunity of studying structural activity relationship would be improved. In addition, mechanistic insights make us easily controlled the producing of expected products in further research.

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APPENDIX

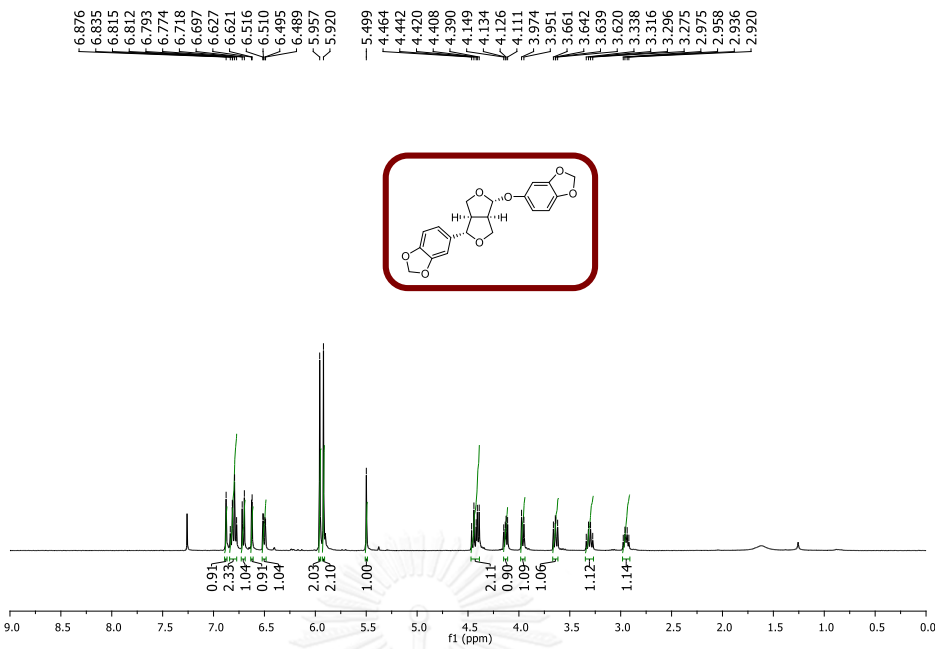

Figure 1. ^{1}H NMR spectrum of compound **1.2** in $CDCl_3$

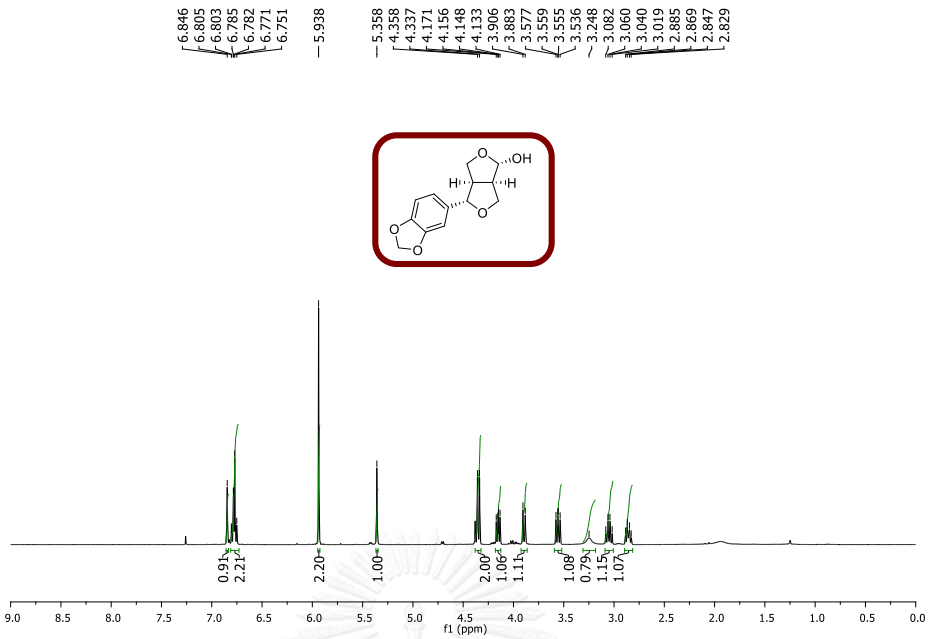

Figure 2. ^{1}H NMR spectrum of compound **1.36** in $CDCl_3$

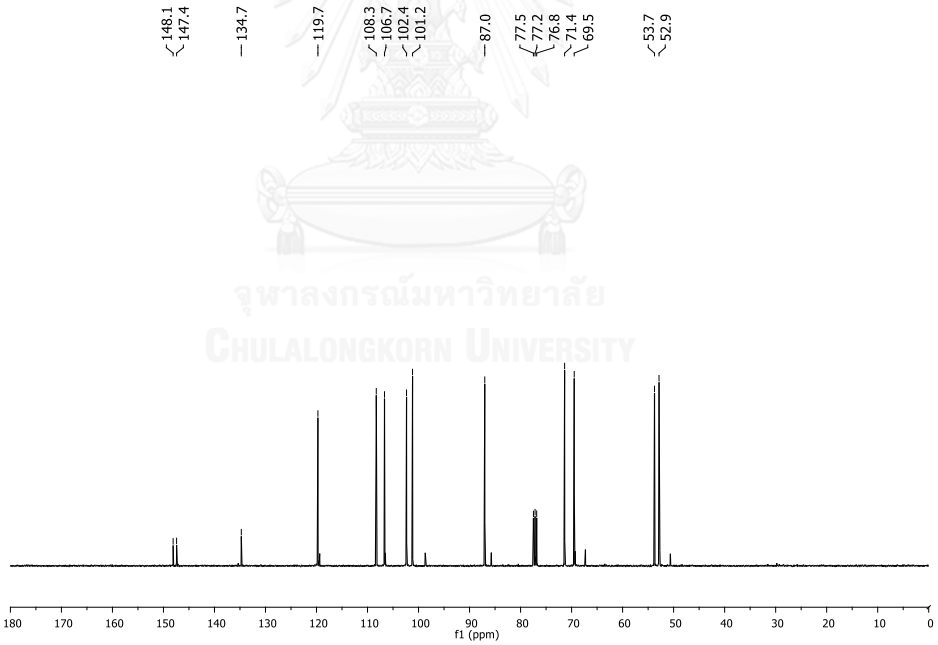

Figure 3. ^{13}C NMR spectrum of compound **1.36** in $CDCl_3$

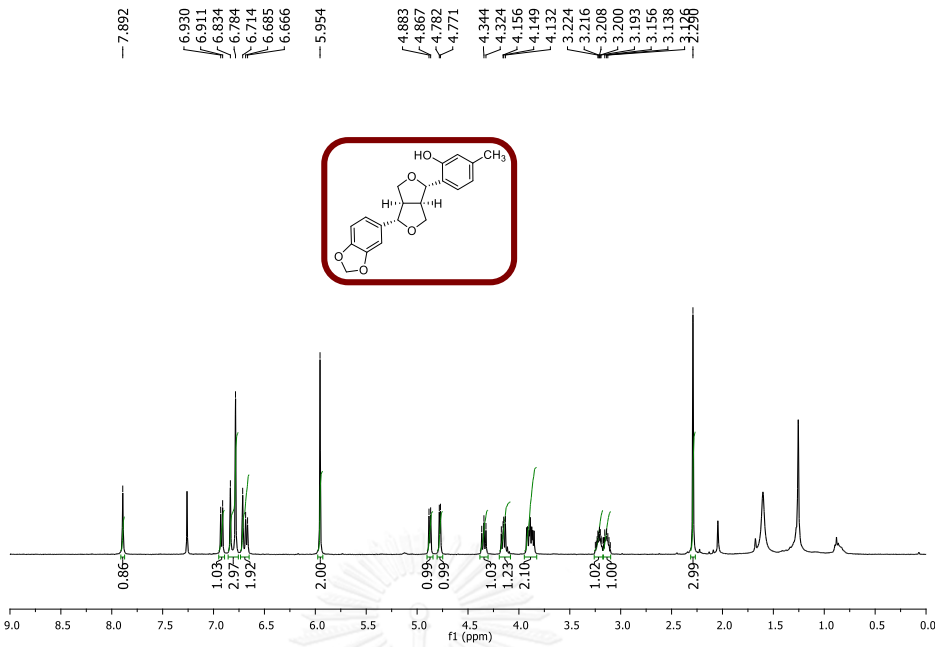

Figure 4. ^{1}H NMR spectrum of compound **3.1b** in $CDCl_3$

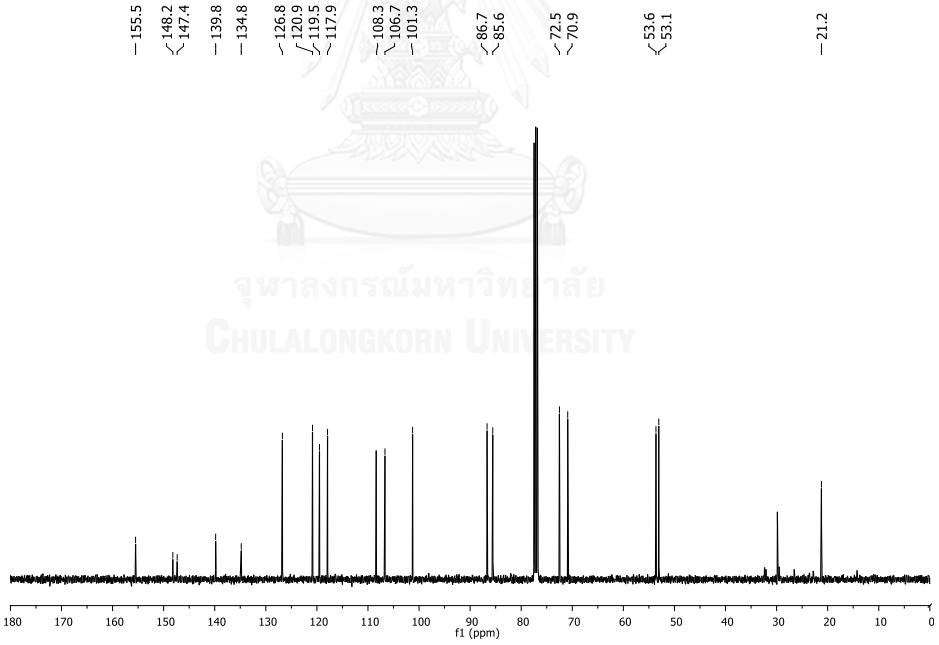

Figure 5. ^{13}C NMR spectrum of compound **3.1b** in $CDCl_3$

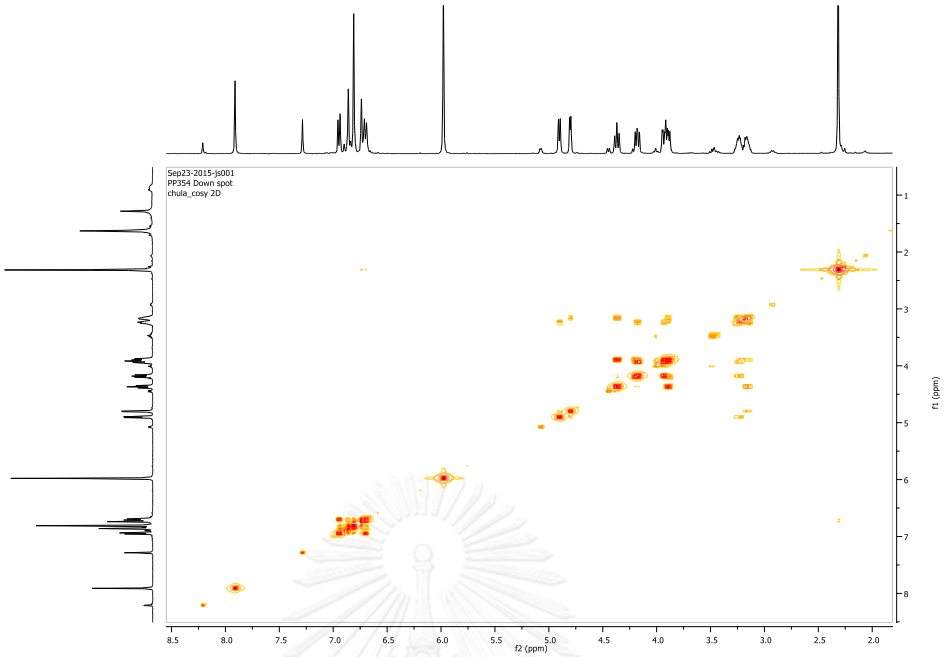

Figure 6. COSY experiment of **3.1b** in $CDCl_3$

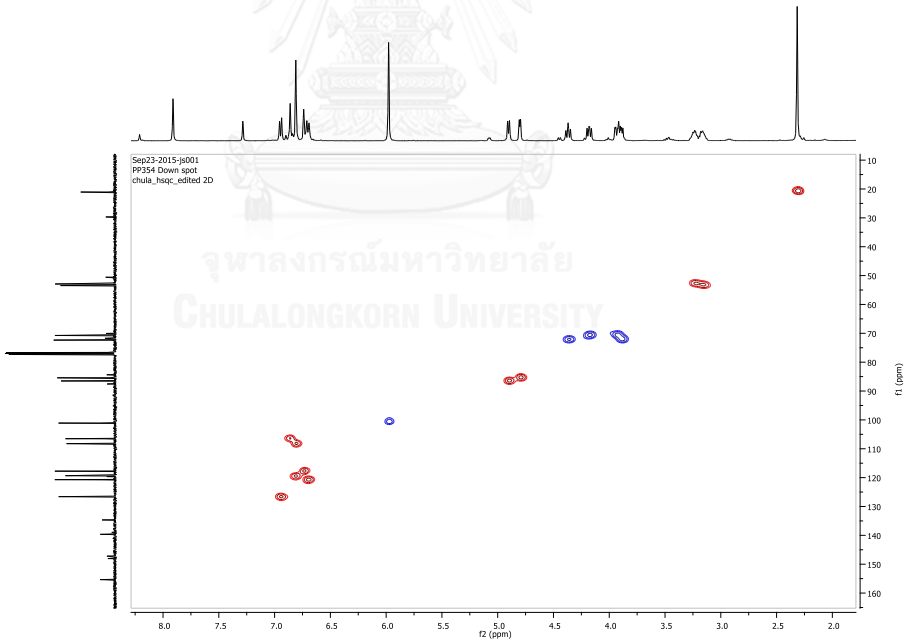

Figure 7. HSQC experiment of **3.1b** in $CDCl_3$

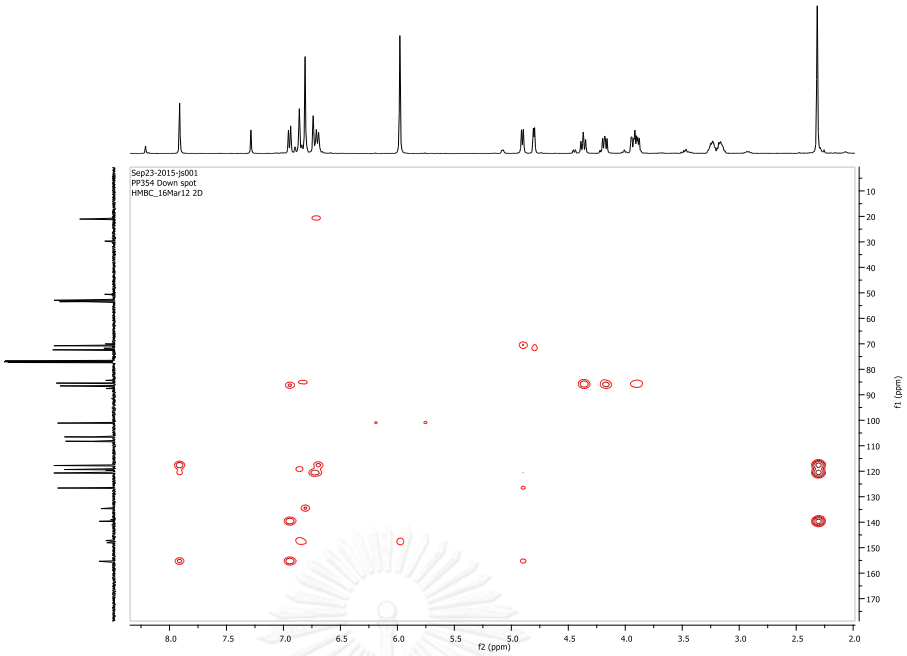

Figure 8. HMBC experiment of **3.1b** in $CDCl_3$

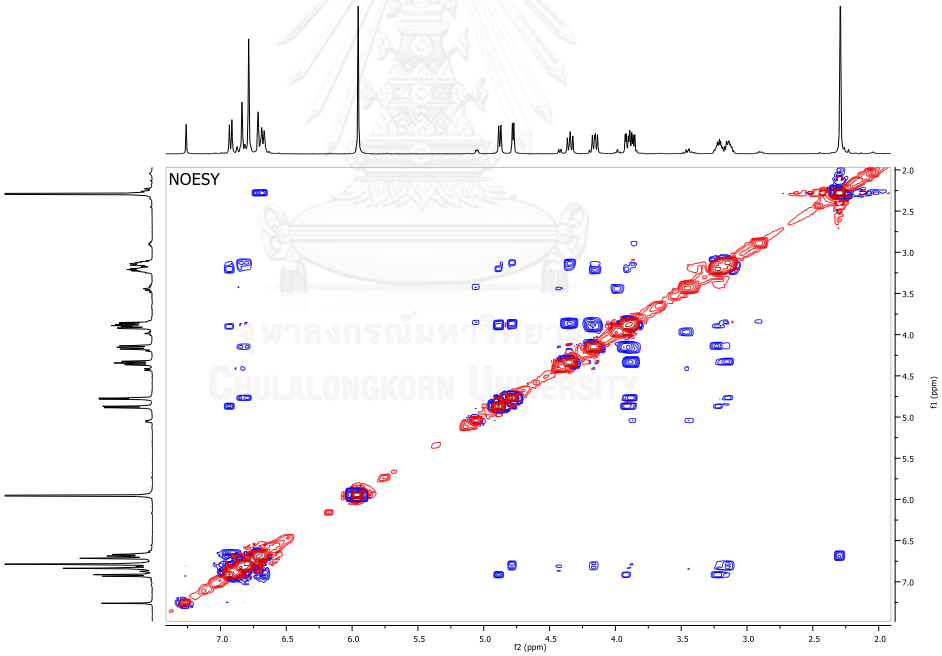

Figure 9. NOESY experiment of **3.1b** in $CDCl_3$

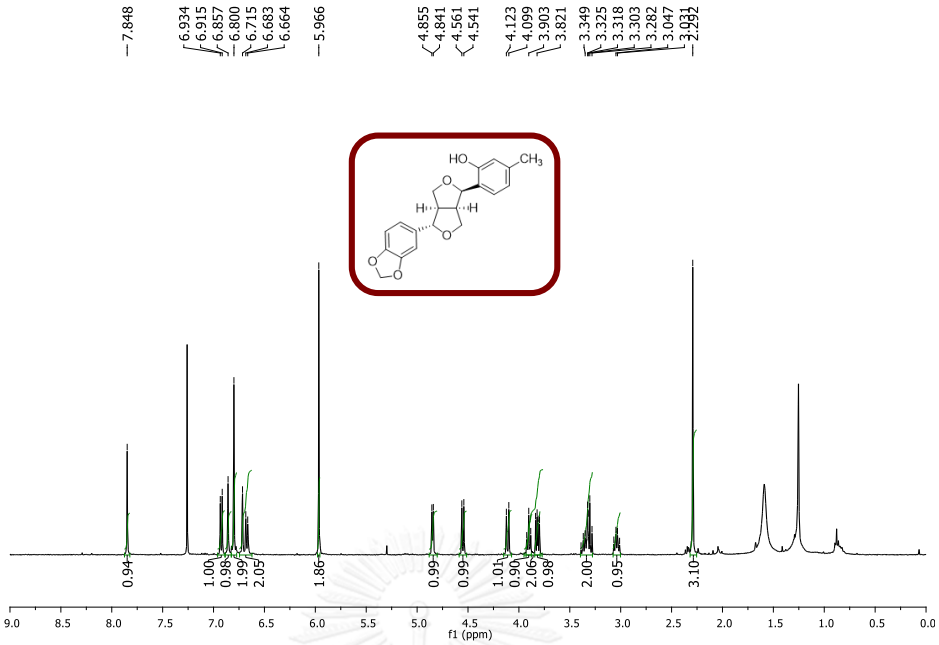

Figure 10. ^{1}H NMR spectrum of compound ***epi*-3.1b** in $CDCl_3$

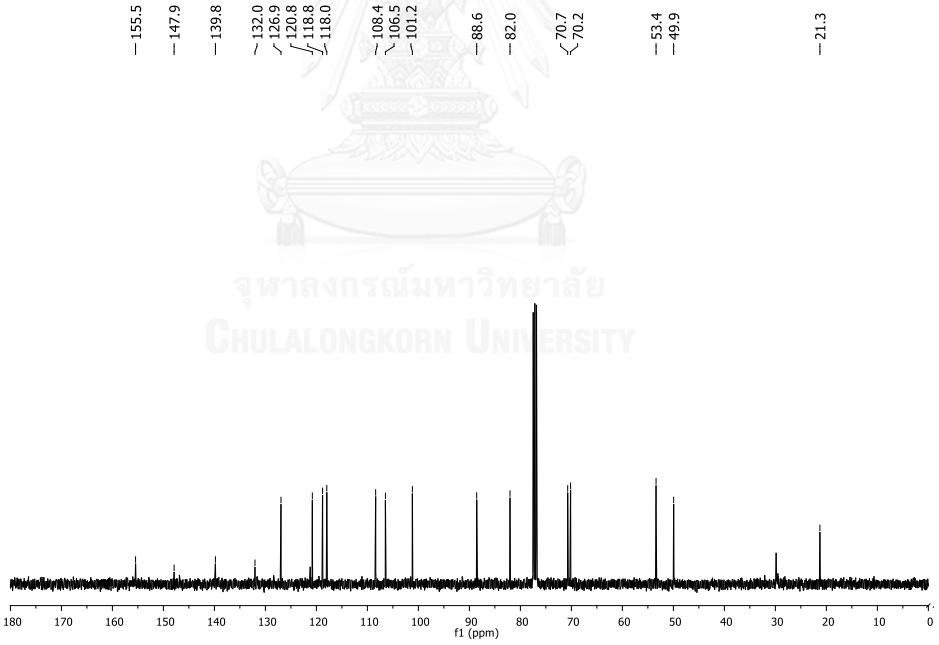

Figure 11. ^{13}C NMR spectrum of compound ***epi*-3.1b** in $CDCl_3$

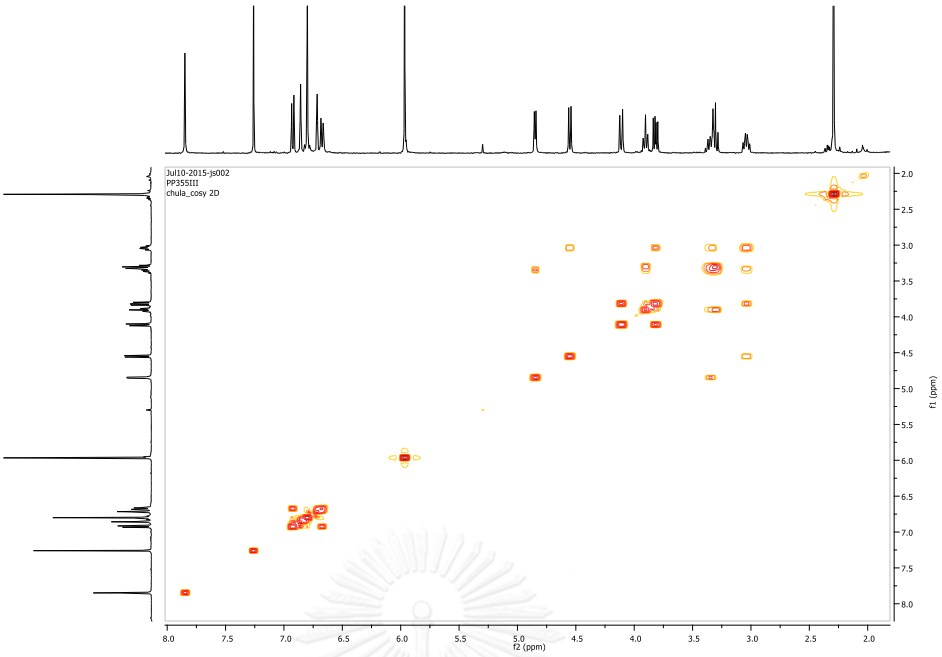

Figure 12. COSY experiment of ***epi*-3.1b** in $CDCl_3$

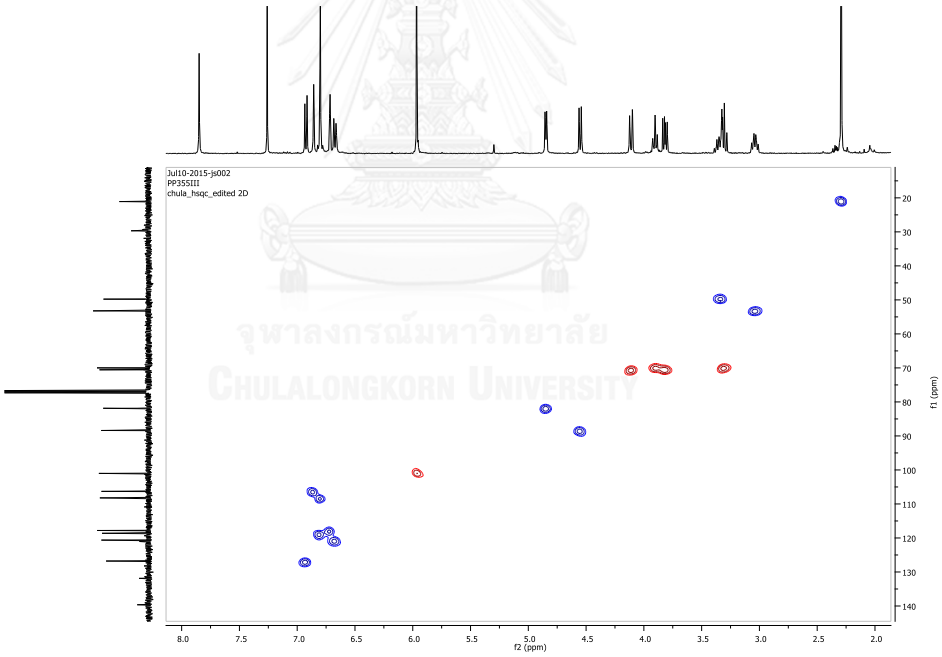

Figure 13. HSQC experiment of ***epi*-3.1b** in $CDCl_3$

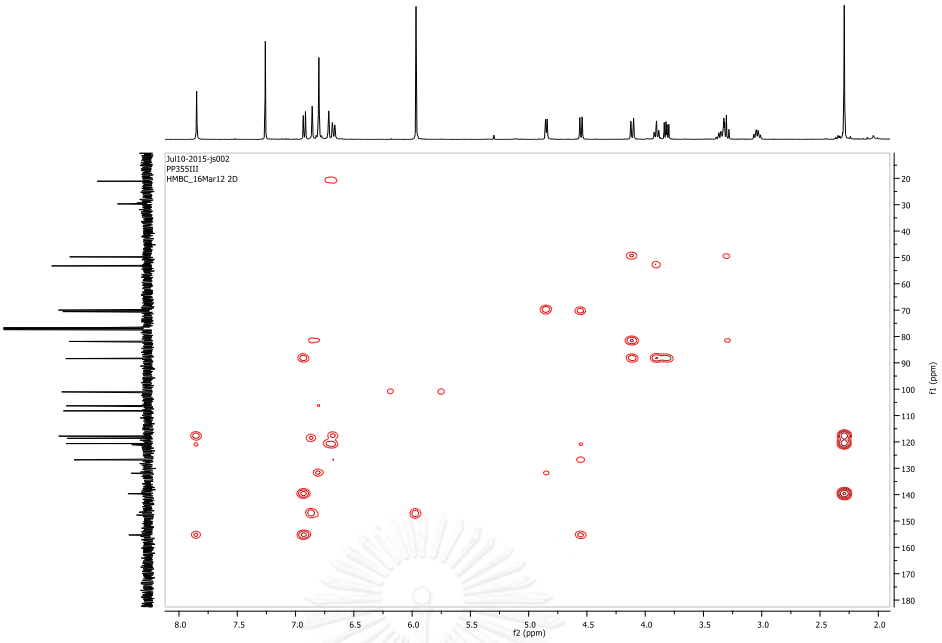

Figure 14. HMBC experiment of ***epi*-3.1b** in $CDCl_3$

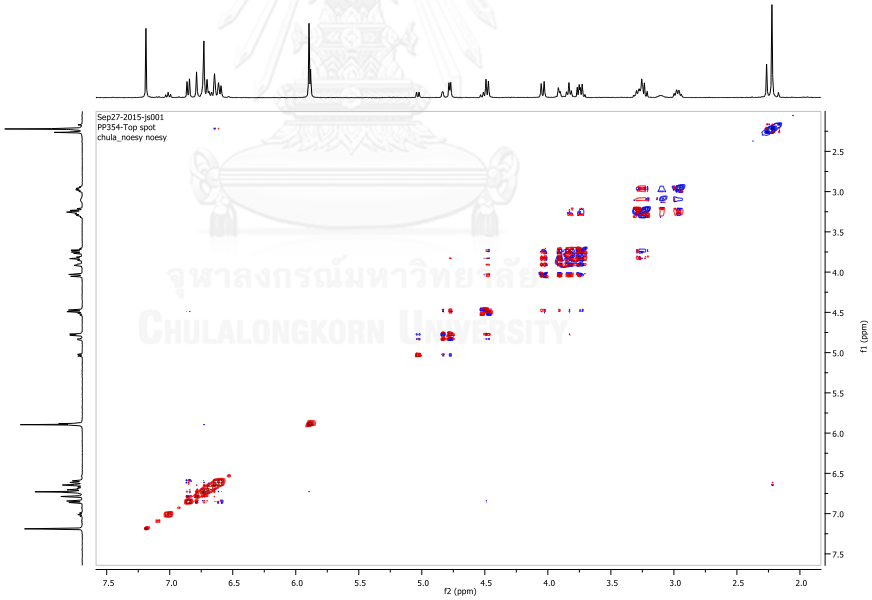

Figure 15. NOESY experiment of ***epi*-3.1b** in $CDCl_3$

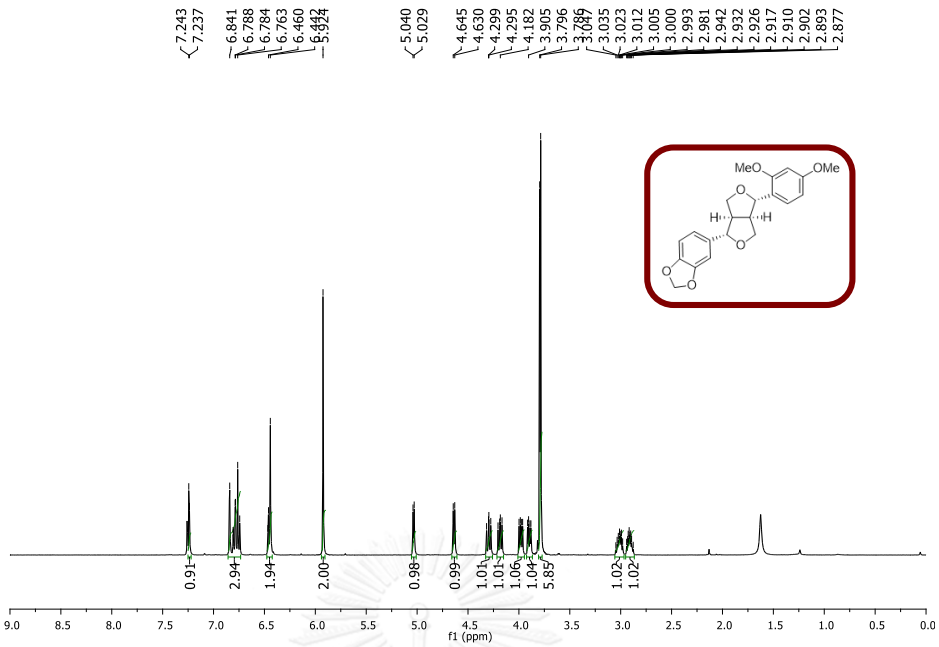

Figure 16. ^{1}H NMR spectrum of compound **3.1d** in $CDCl_3$

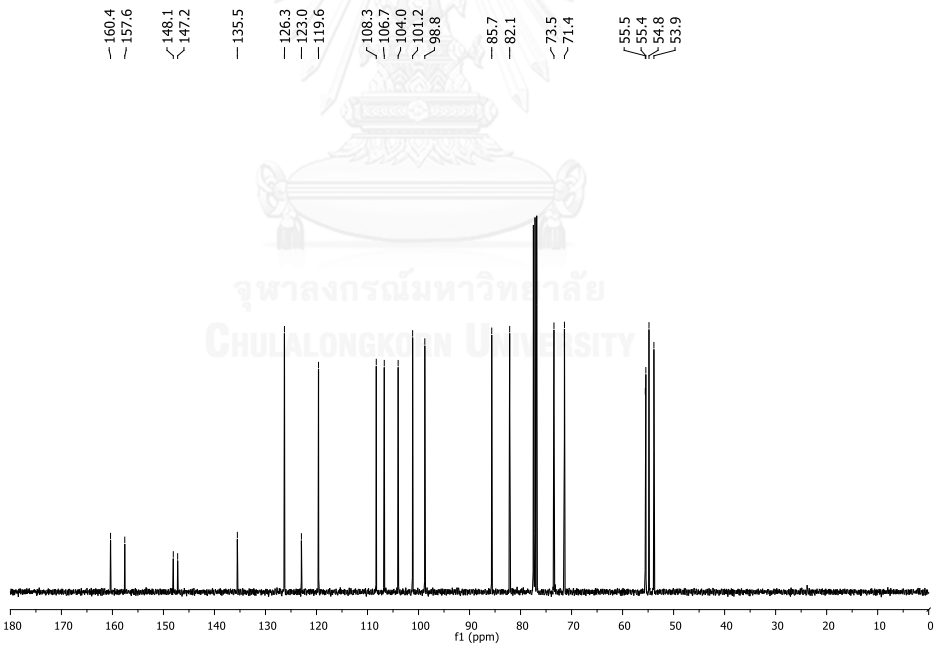

Figure 17. ^{13}C NMR spectrum of compound **3.1d** in $CDCl_3$

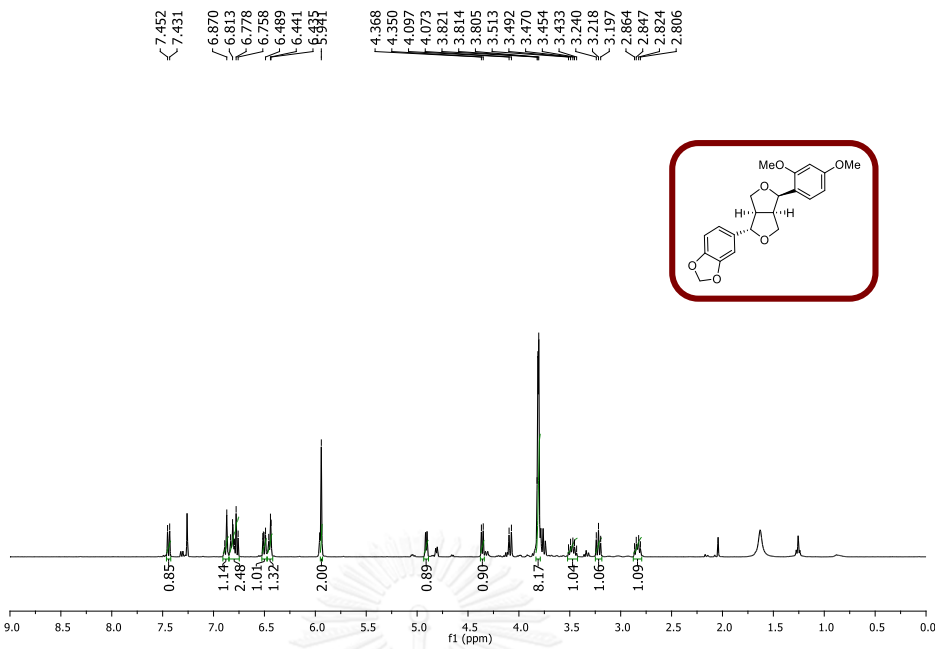

Figure 18. ^{1}H NMR spectrum of compound ***epi*-3.1d** in $CDCl_3$

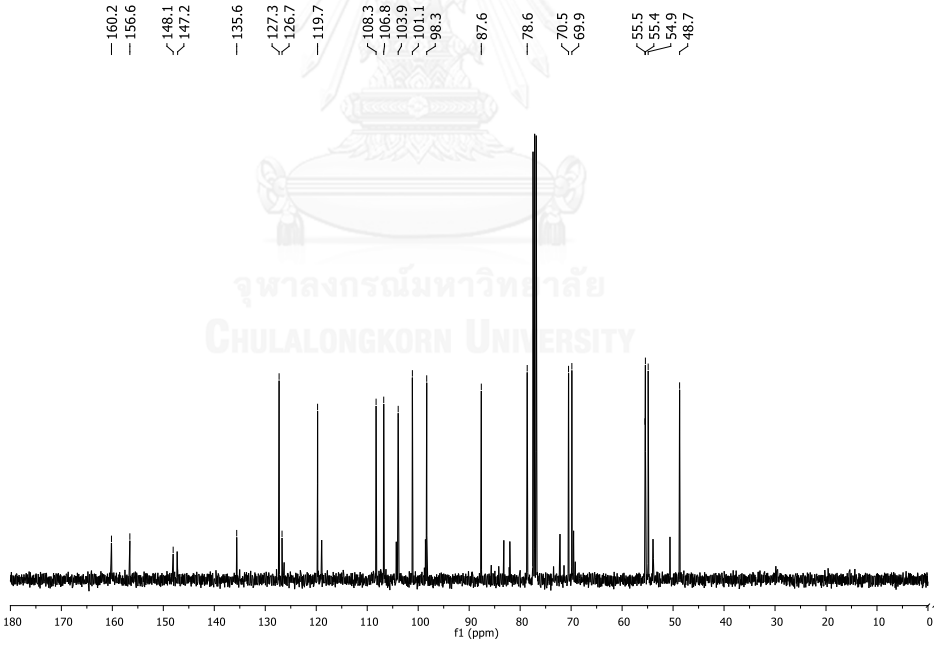

Figure 19. ^{13}C NMR spectrum of compound ***epi*-3.1d** in $CDCl_3$

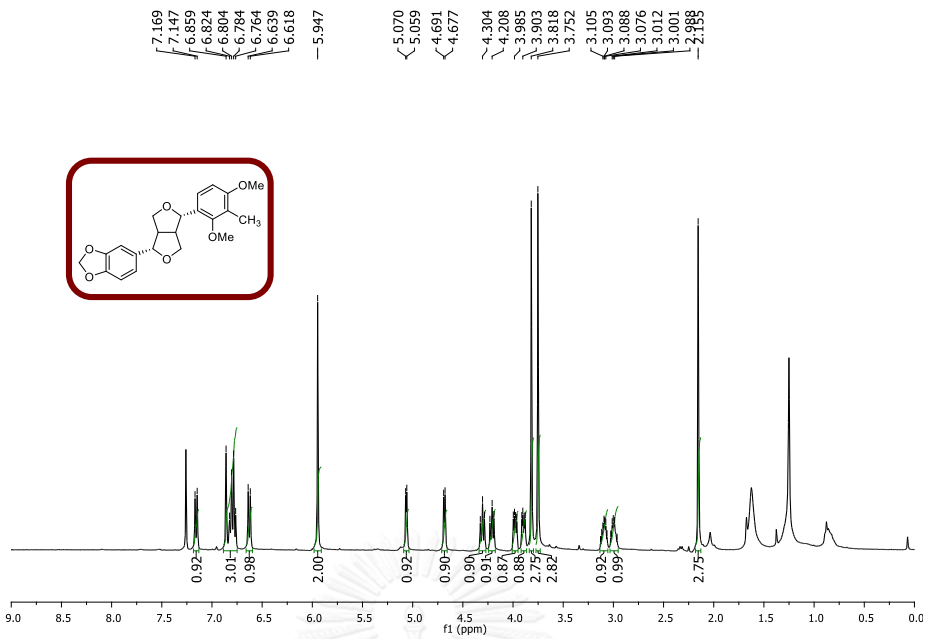

Figure 20. ^{1}H NMR spectrum of compound **3.1e** in $CDCl_3$

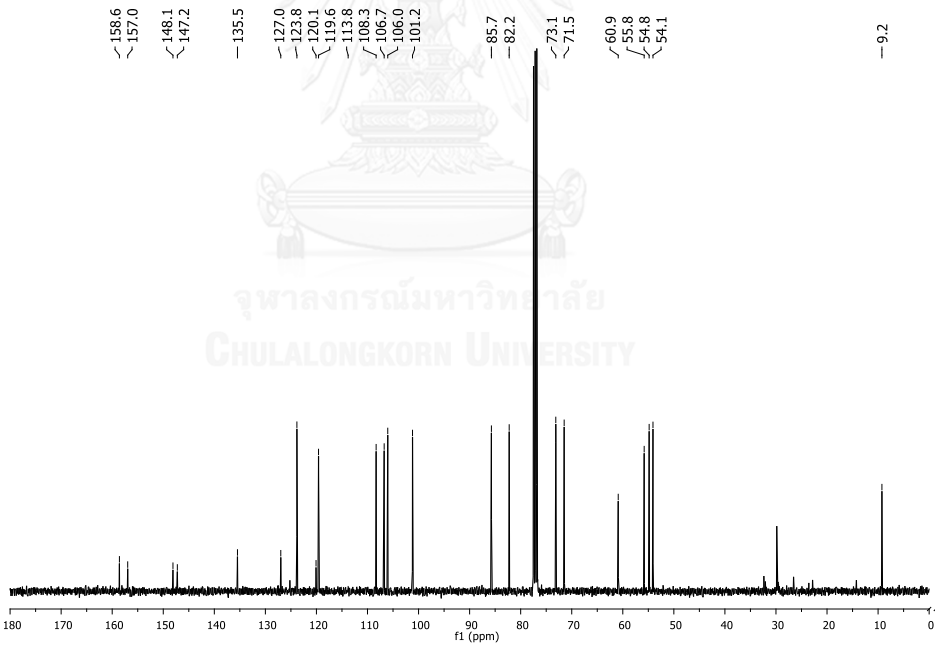

Figure 21. ^{13}C NMR spectrum of compound **3.1e** in $CDCl_3$

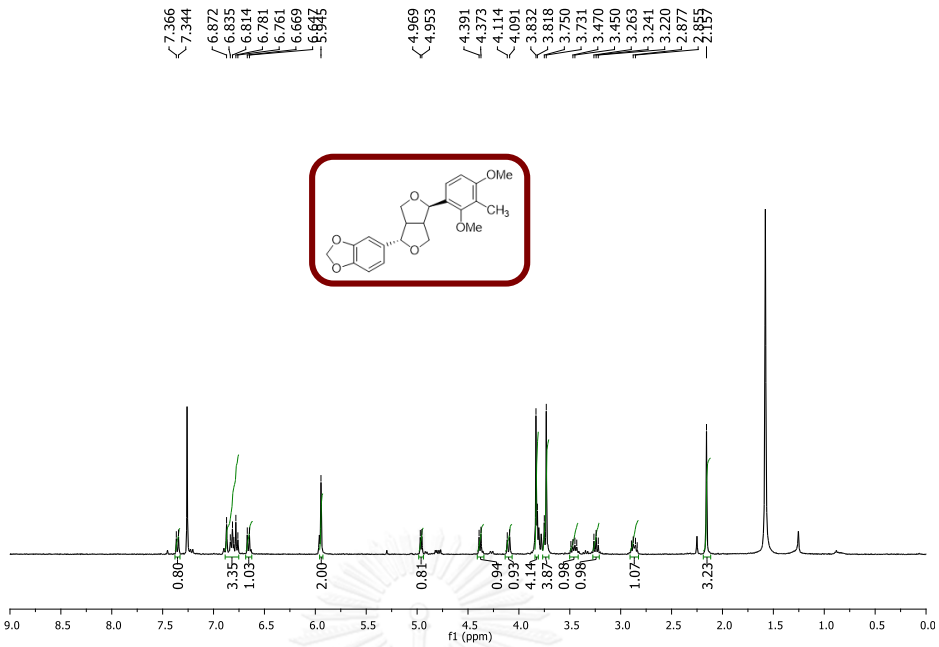

Figure 22. ^{1}H NMR spectrum of compound ***epi*-3.1e** in $CDCl_3$

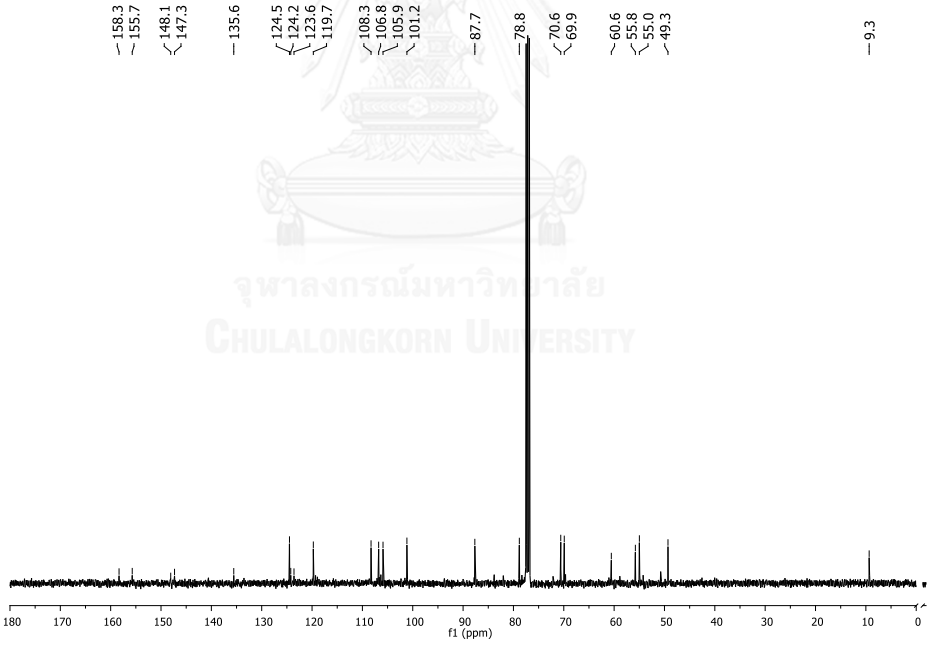

Figure 23. ^{13}C NMR spectrum of compound ***epi*-3.1e** in $CDCl_3$

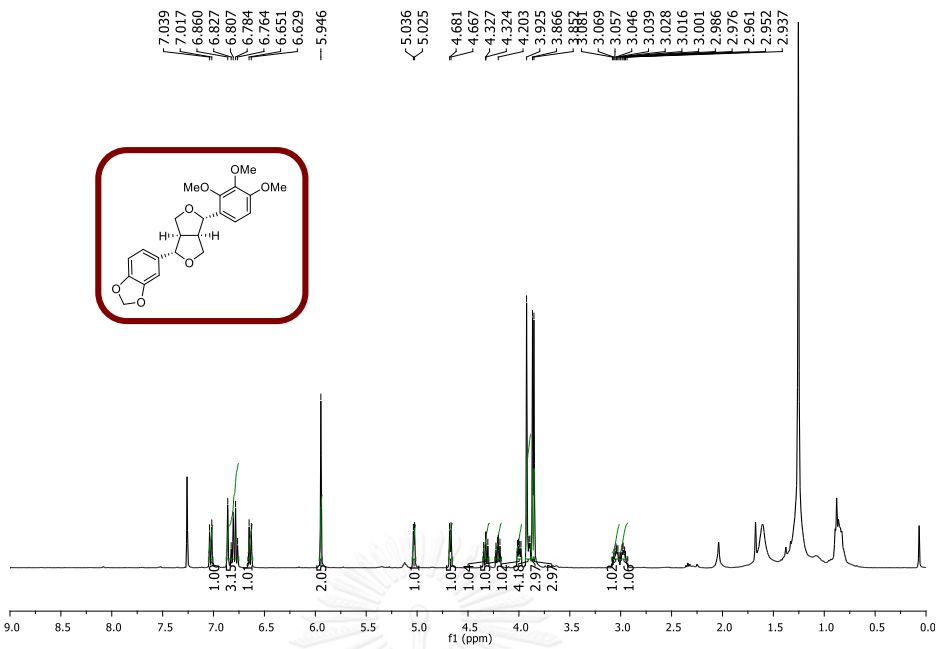

Figure 24. ^{1}H NMR spectrum of compound **3.1g** in $CDCl_3$

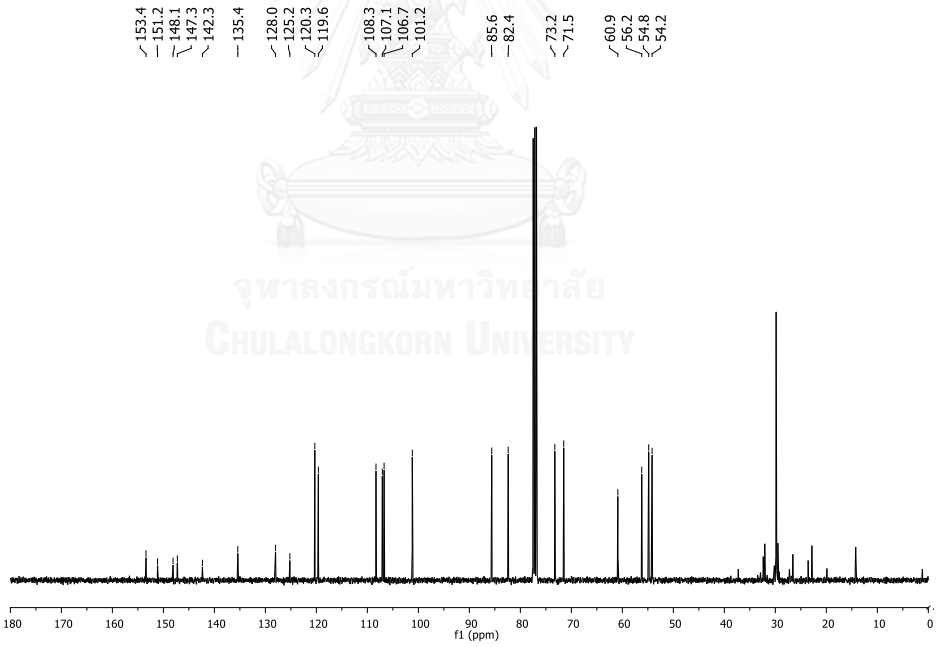

Figure 25. ^{13}C NMR spectrum of compound **3.1g** in $CDCl_3$

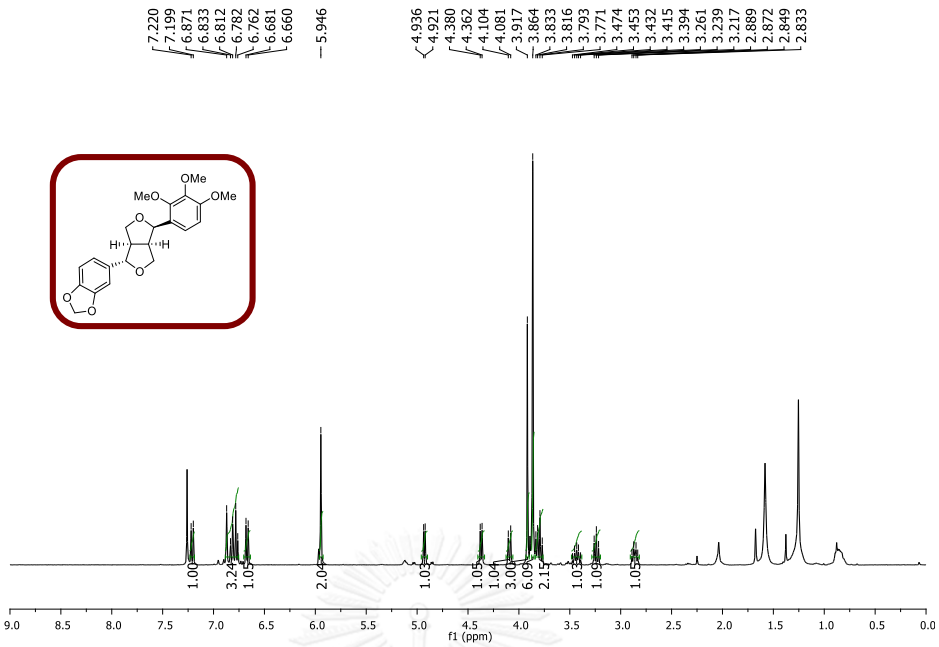

Figure 26. ^{1}H NMR spectrum of compound ***epi*-3.1g** in $CDCl_3$

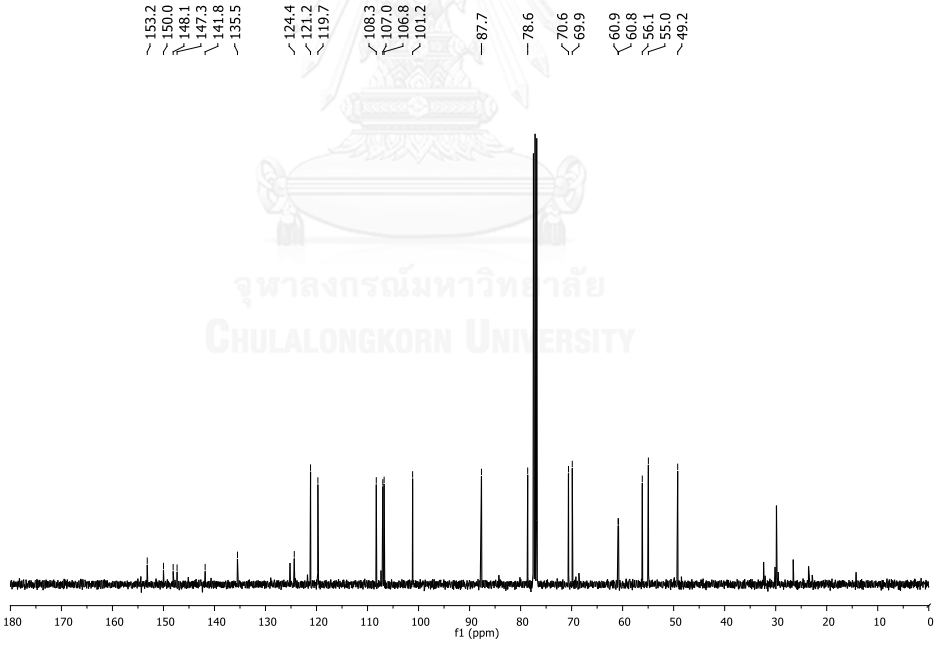

Figure 27. ^{13}C NMR spectrum of compound ***epi*-3.1g** in $CDCl_3$

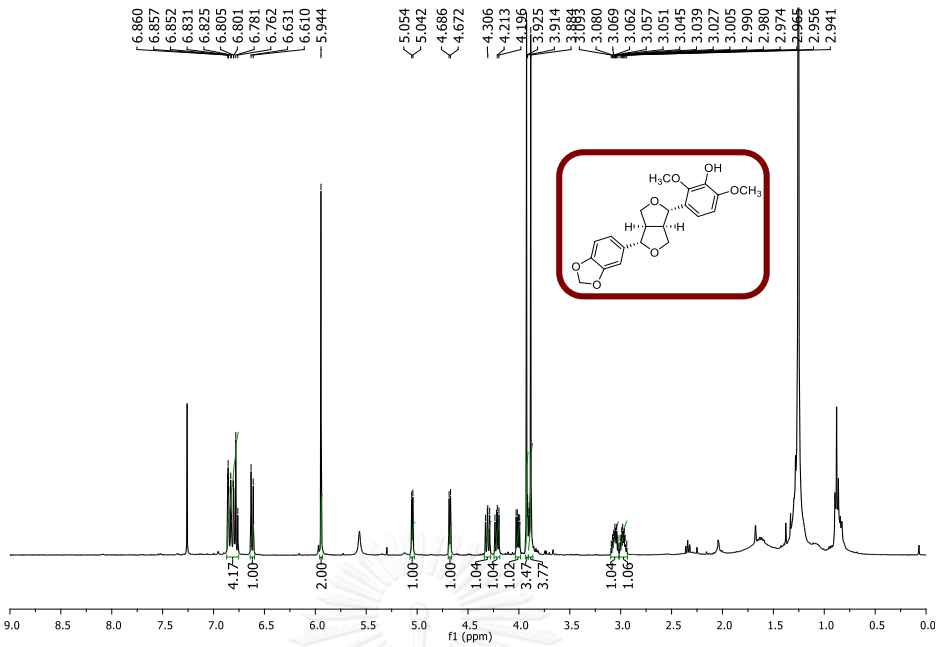

Figure 28. ^{1}H NMR spectrum of compound **3.1h** in $CDCl_3$

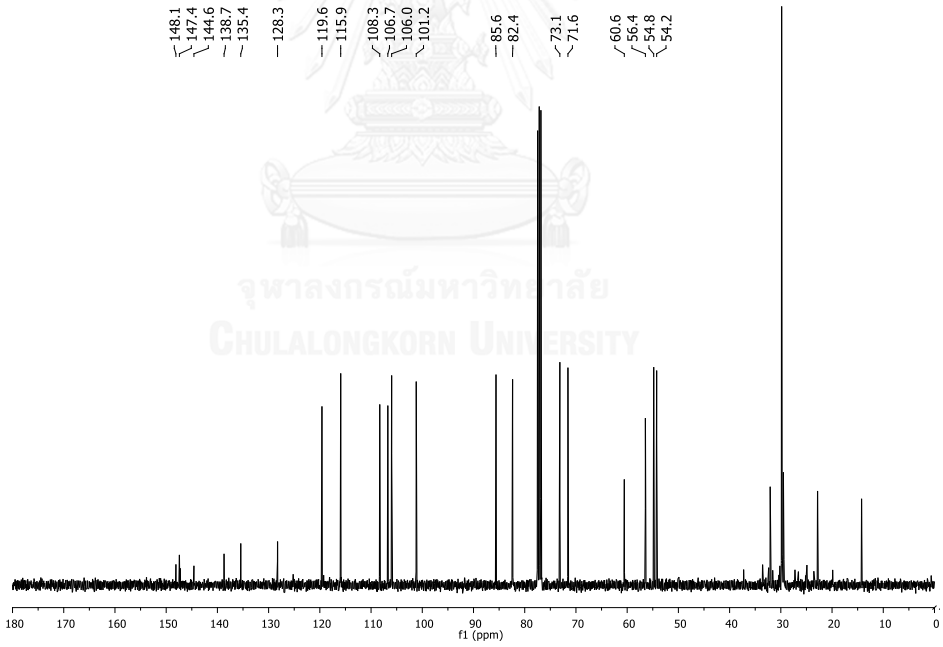

Figure 29. ^{13}C NMR spectrum of compound **3.1h** in $CDCl_3$

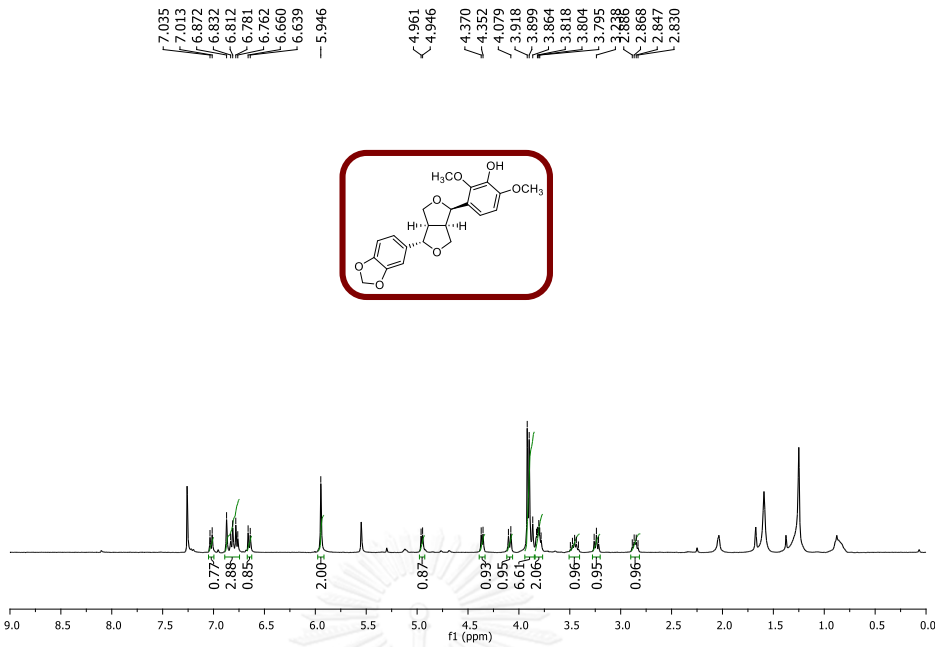

Figure 30. ^{1}H NMR spectrum of compound ***epi*-3.1h** in $CDCl_3$

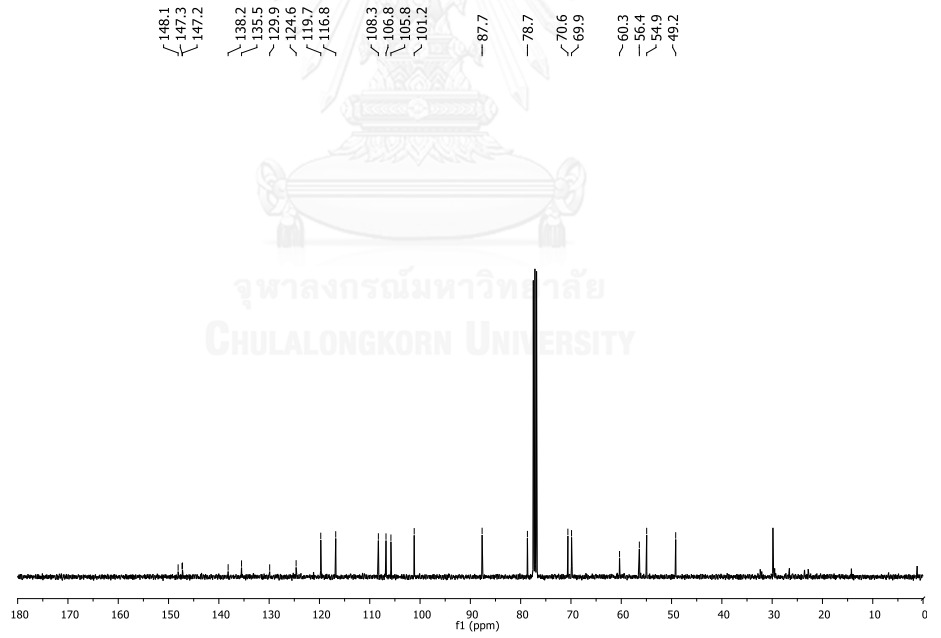

Figure 31. ^{13}C NMR spectrum of compound ***epi*-3.1h** in $CDCl_3$

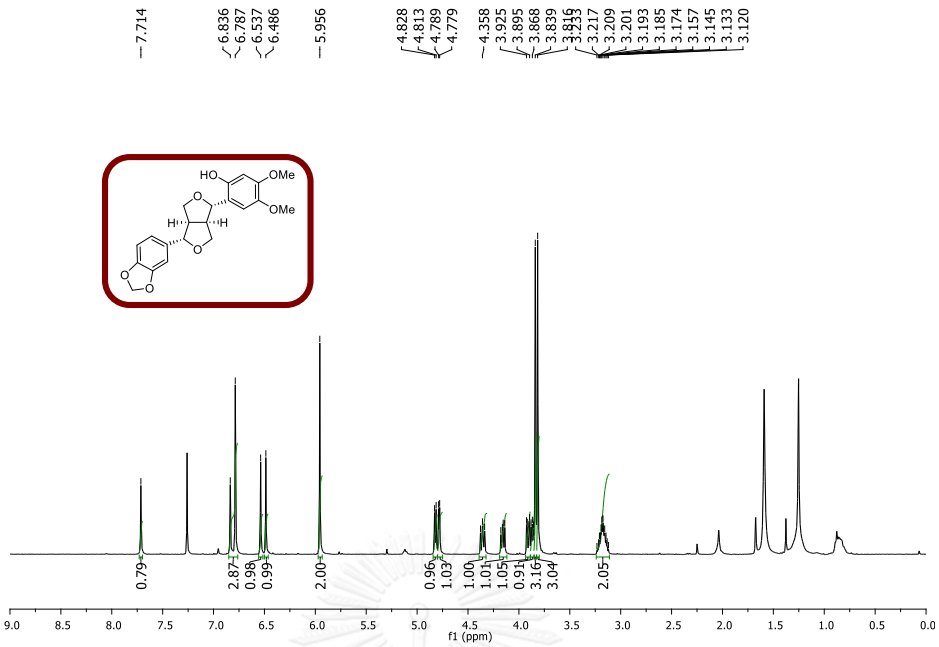

Figure 32. ^{1}H NMR spectrum of compound **3.1i** in $CDCl_3$

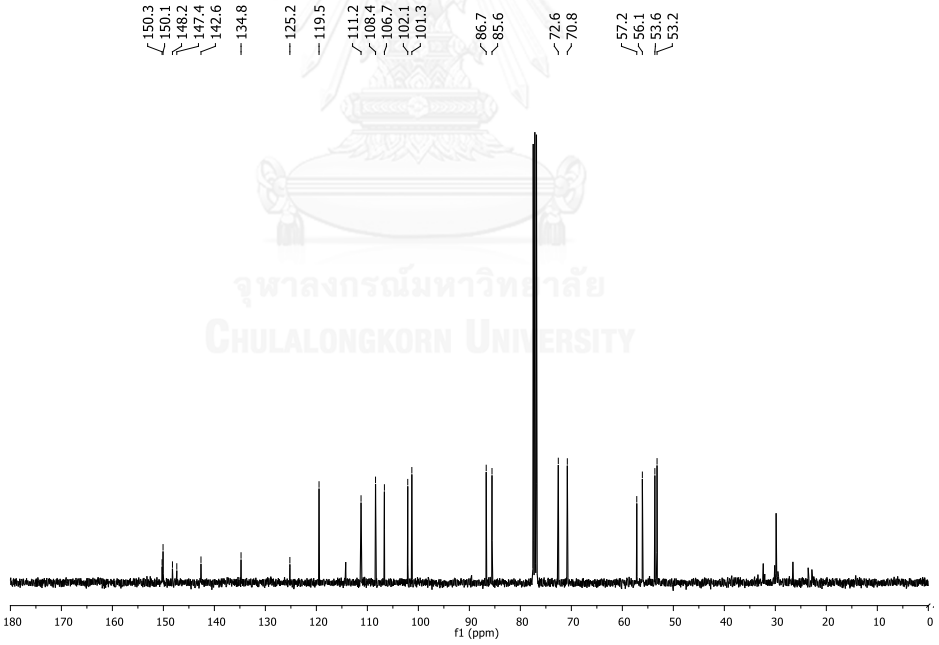

Figure 33. ^{13}C NMR spectrum of compound **3.1i** in $CDCl_3$

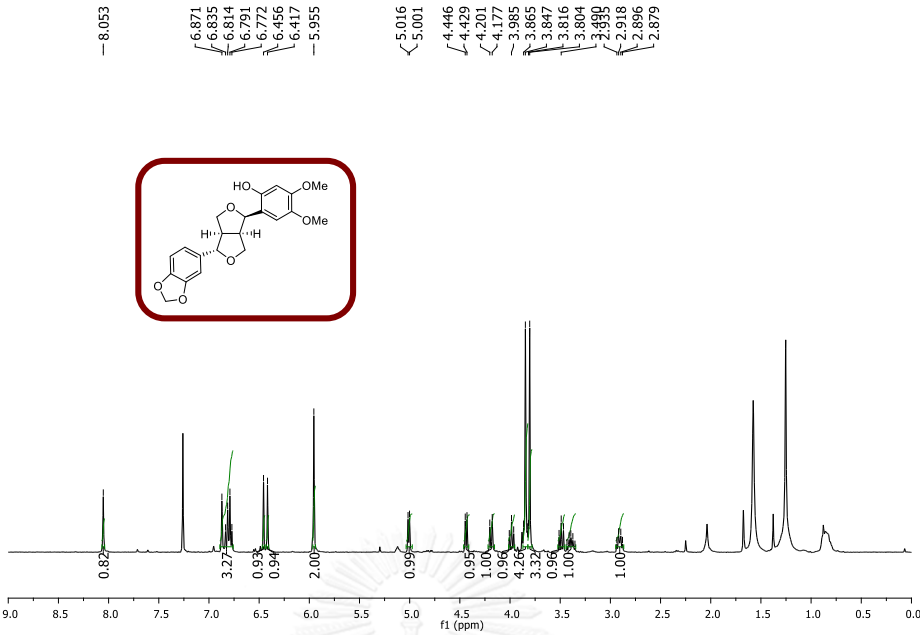

Figure 34. ^{1}H NMR spectrum of compound ***epi*-3.1i** in $CDCl_3$

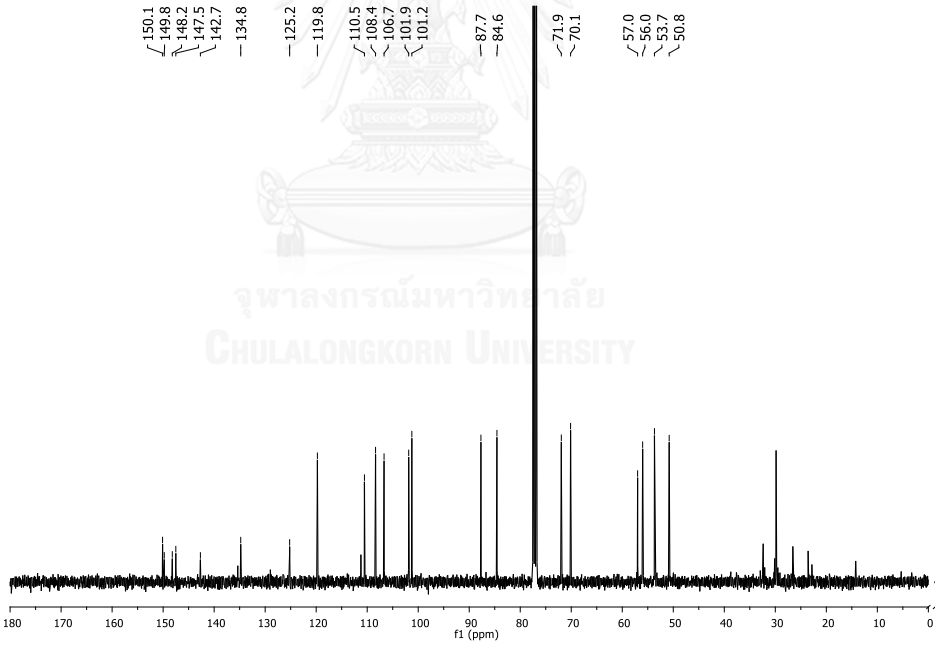

Figure 35. ^{13}C NMR spectrum of compound ***epi*-3.1i** in $CDCl_3$

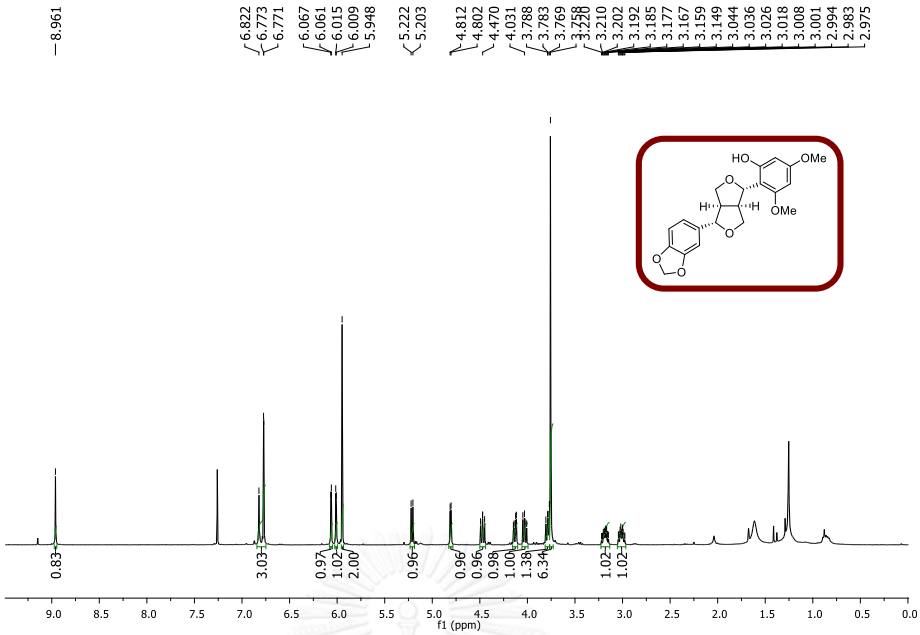

Figure 36. ^{1}H NMR spectrum of compound **3.1j** in $CDCl_3$

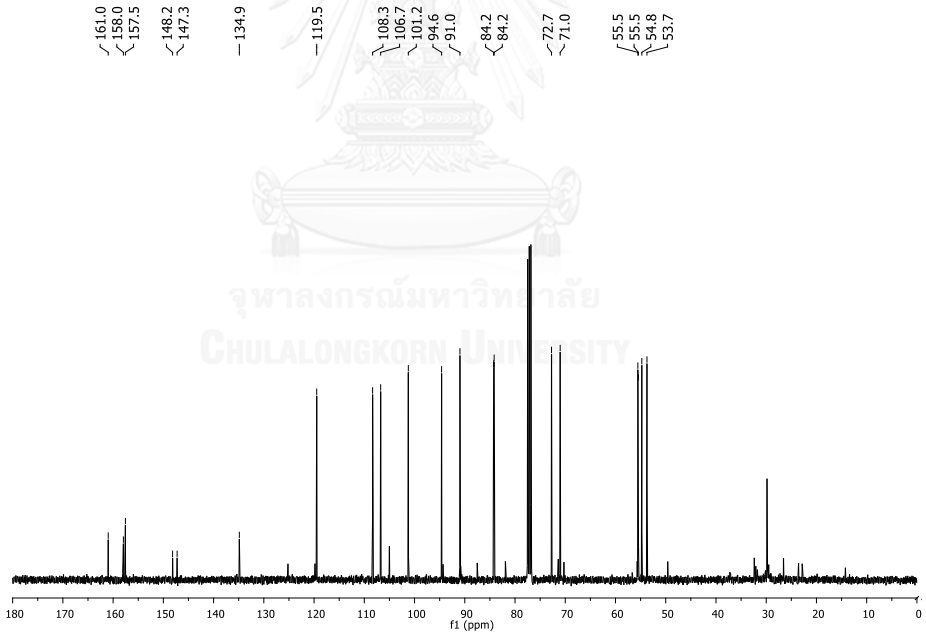

Figure 37. ^{13}C NMR spectrum of compound **3.1j** in $CDCl_3$

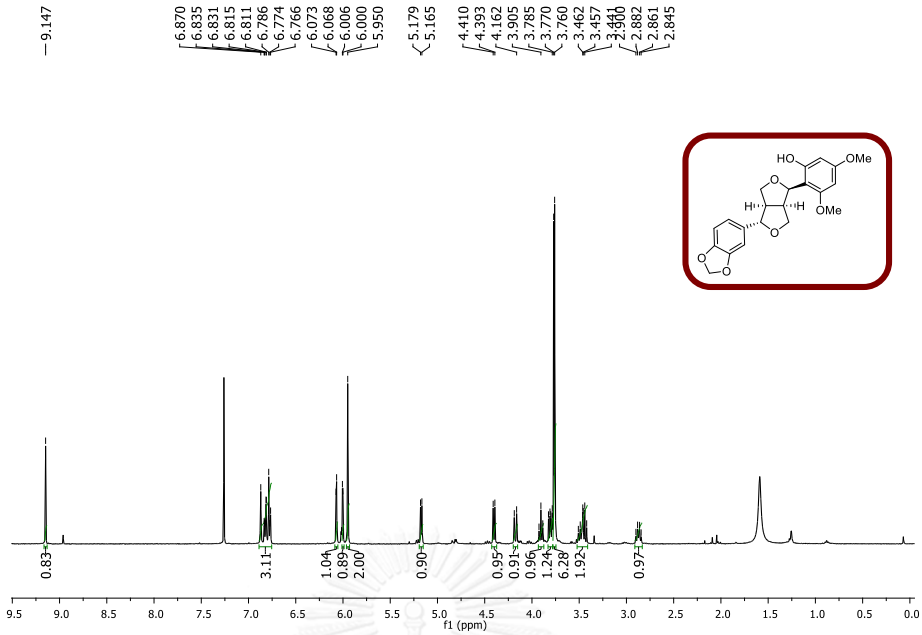

Figure 38. ^{1}H NMR spectrum of compound ***epi*-3.1j** in $CDCl_3$

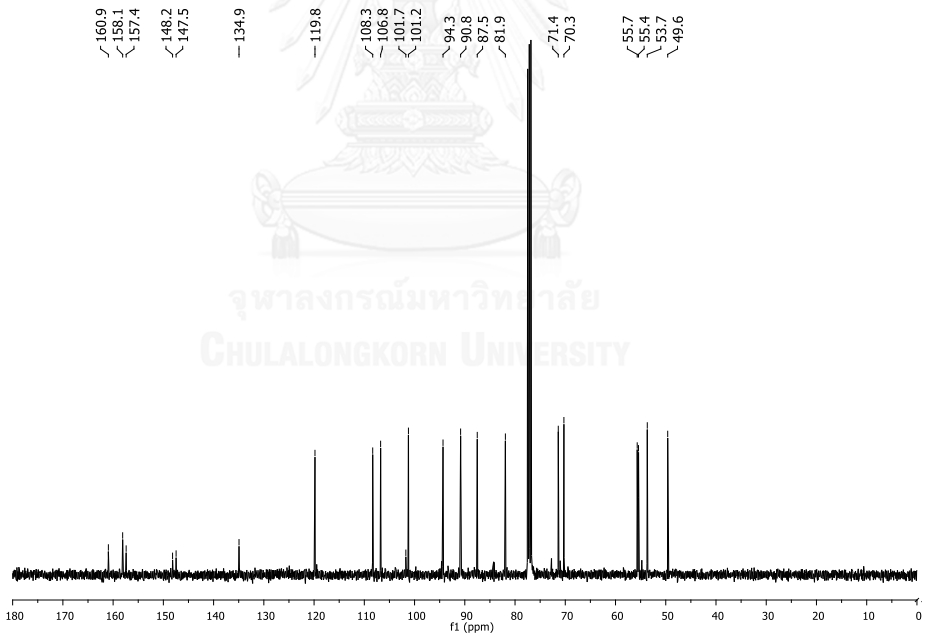

Figure 39. ^{13}C NMR spectrum of compound ***epi*-3.1j** in $CDCl_3$

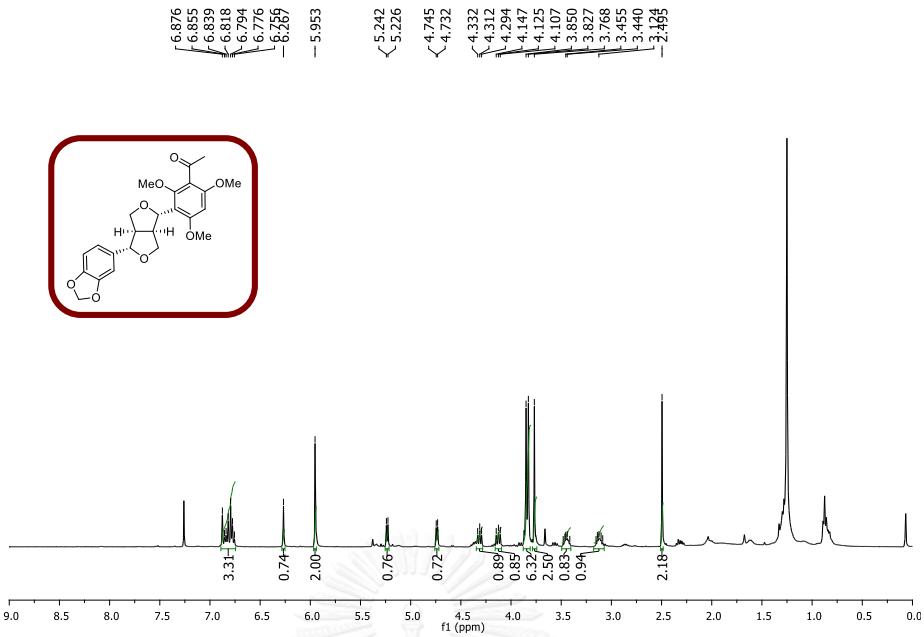

Figure 40. ^{1}H NMR spectrum of compound **3.1k** in $CDCl_3$

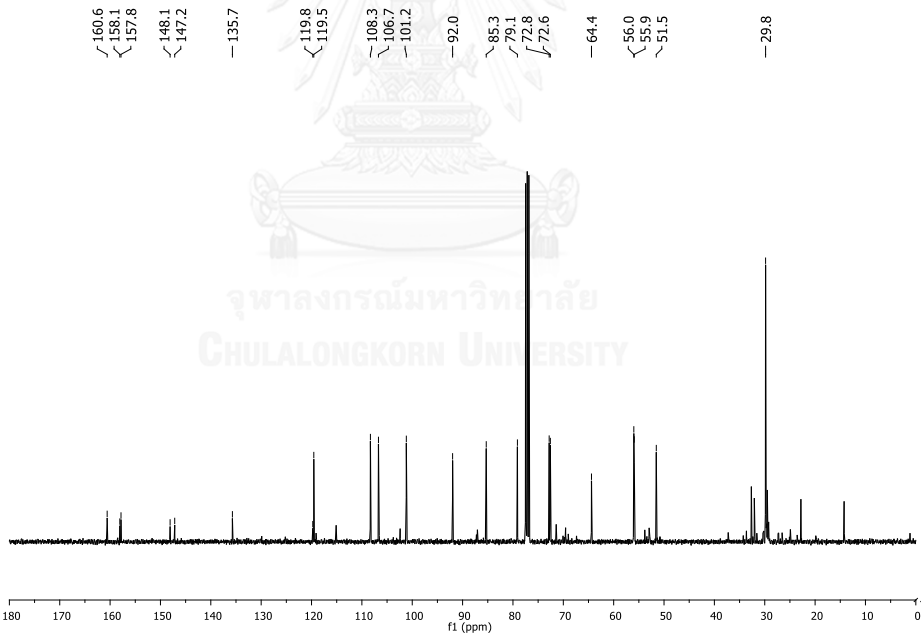

Figure 41. ^{13}C NMR spectrum of compound **3.1k** in $CDCl_3$

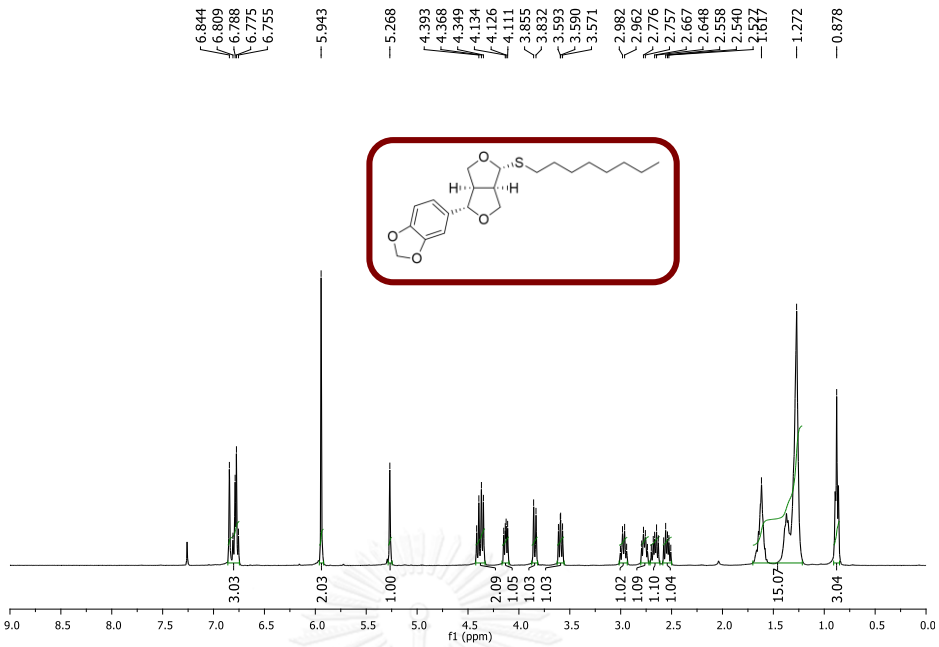

Figure 42. ^{1}H NMR spectrum of compound **3.2l** in $CDCl_3$

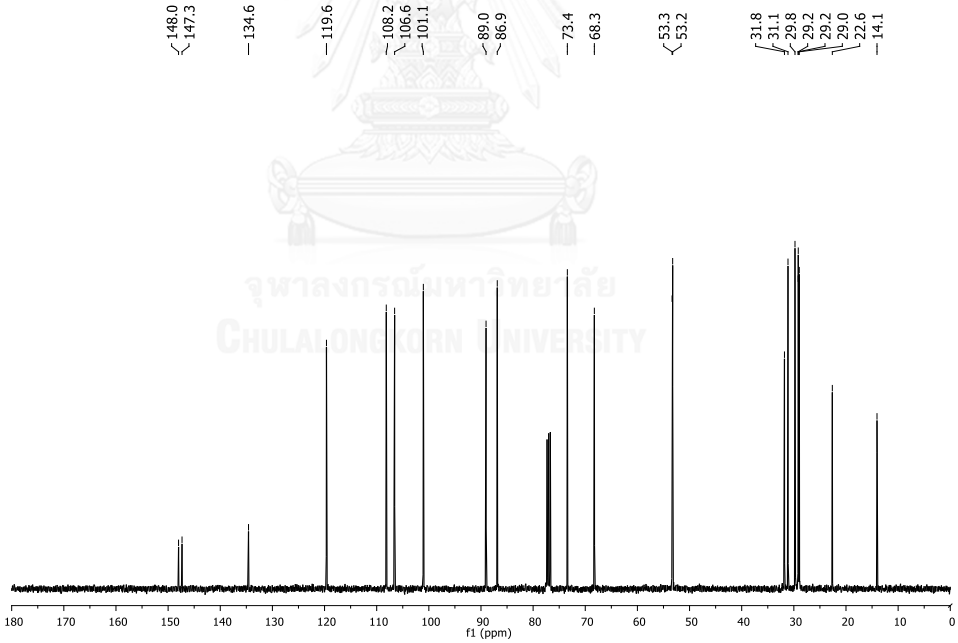

Figure 43. ^{13}C NMR spectrum of compound **3.2l** in $CDCl_3$

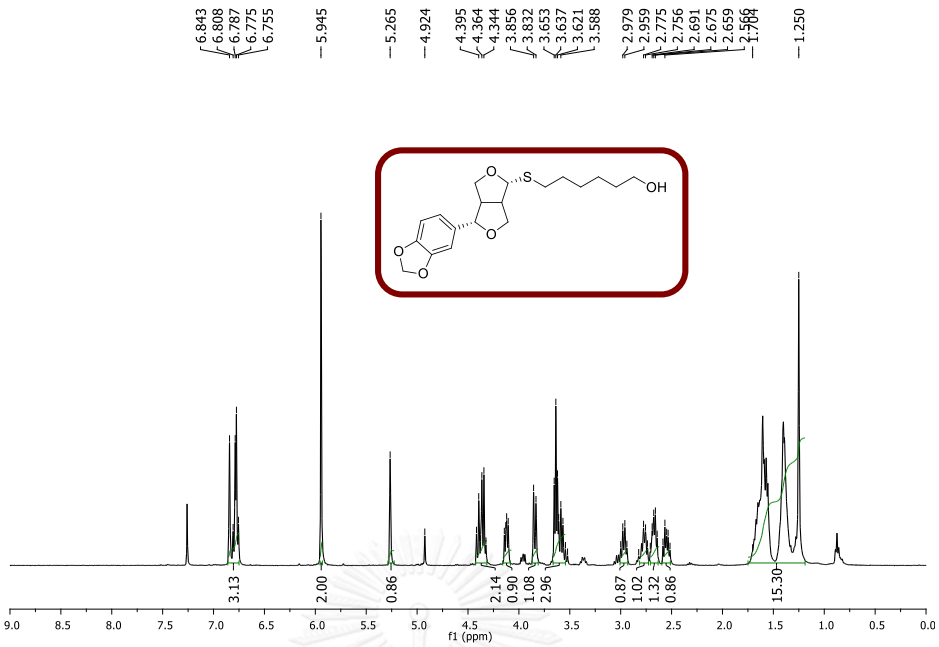

Figure 44. ^{1}H NMR spectrum of compound **3.2m** in $CDCl_3$

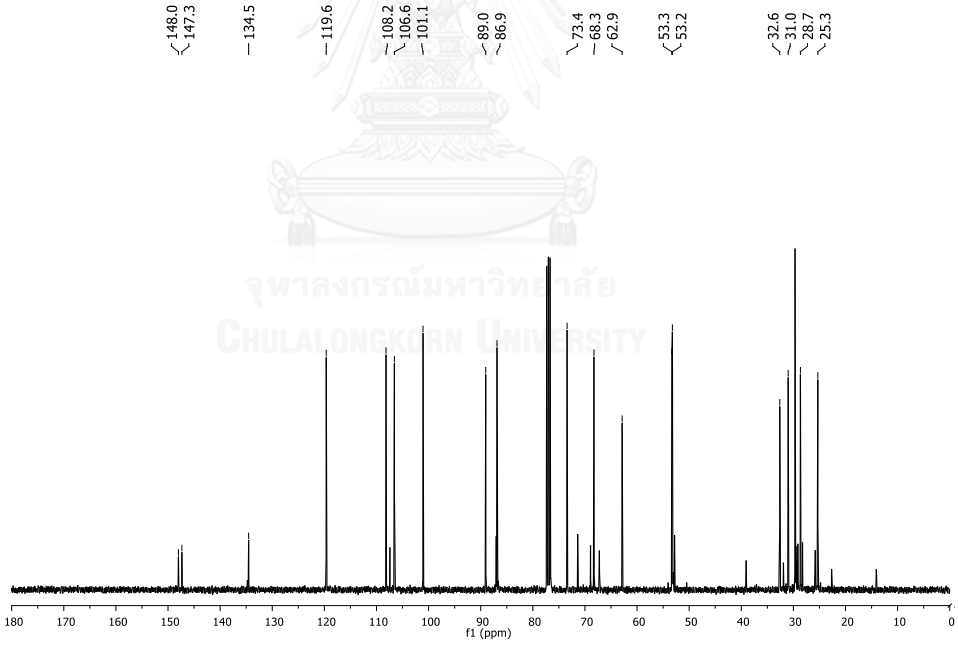

Figure 45. ^{13}C NMR spectrum of compound **3.2m** in $CDCl_3$

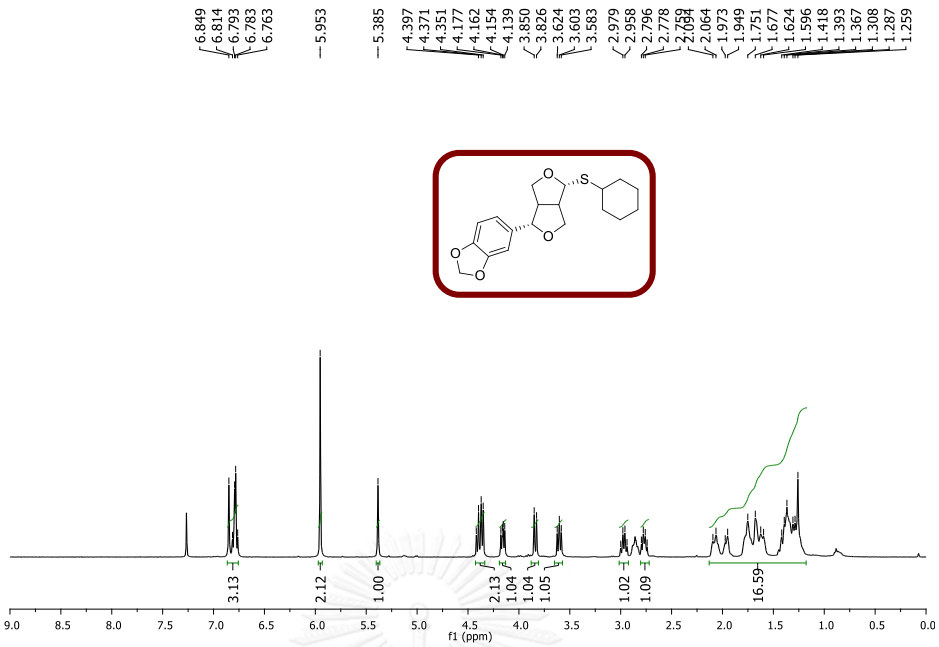

Figure 46. ^{1}H NMR spectrum of compound **3.2n** in $CDCl_3$

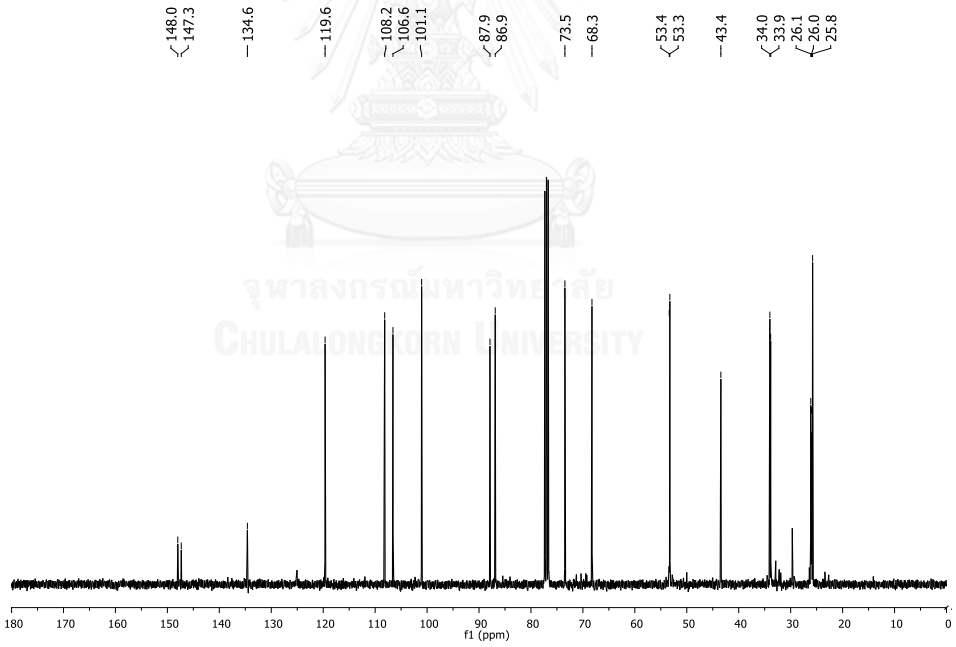

Figure 47. ^{13}C NMR spectrum of compound **3.2n** in $CDCl_3$

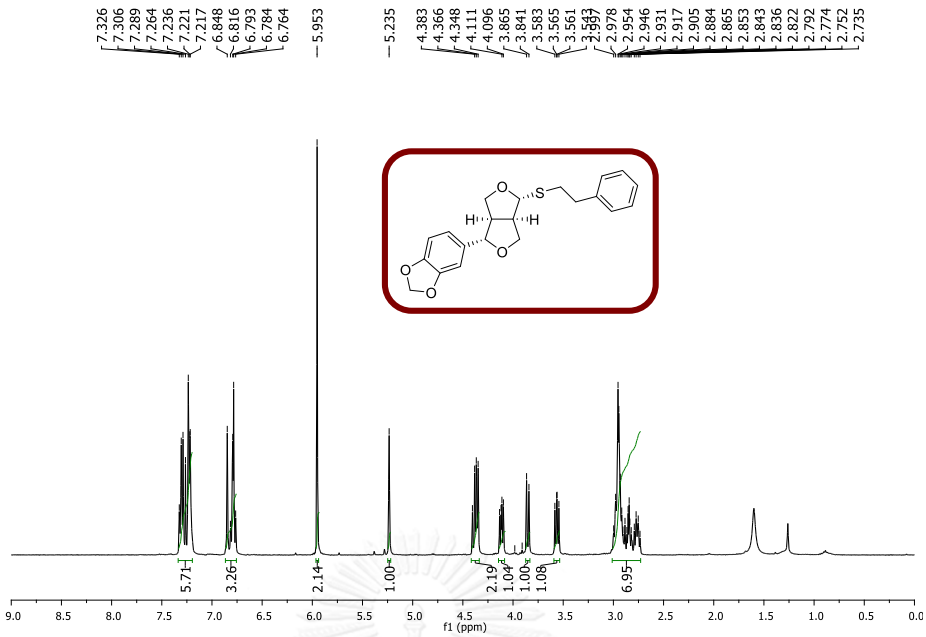

Figure 48. ^{1}H NMR spectrum of compound **3.2o** in $CDCl_3$

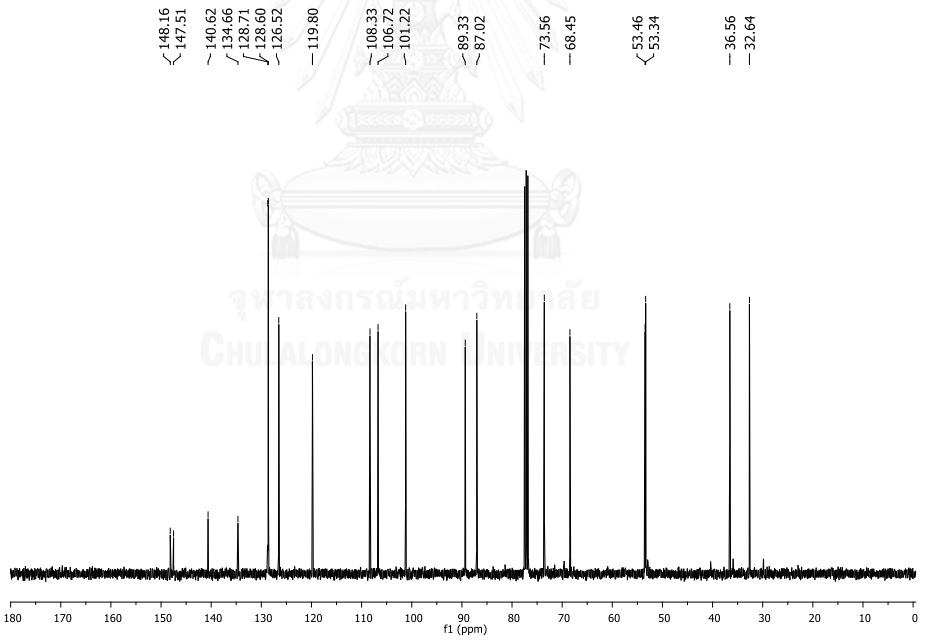

Figure 49. ^{13}C NMR spectrum of compound **3.2o** in $CDCl_3$

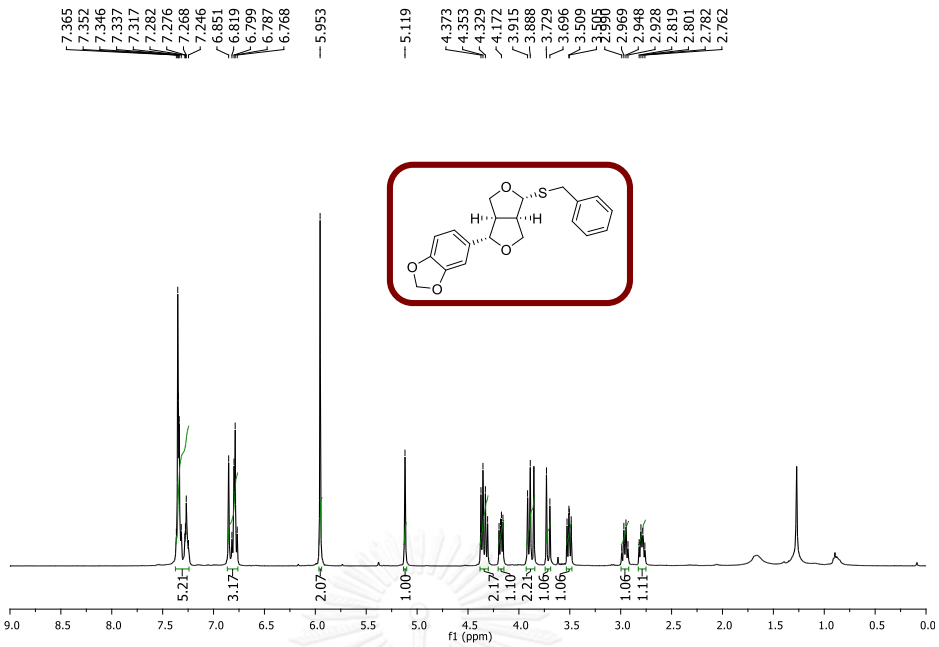

Figure 50. ^{1}H NMR spectrum of compound **3.2p** in $CDCl_3$

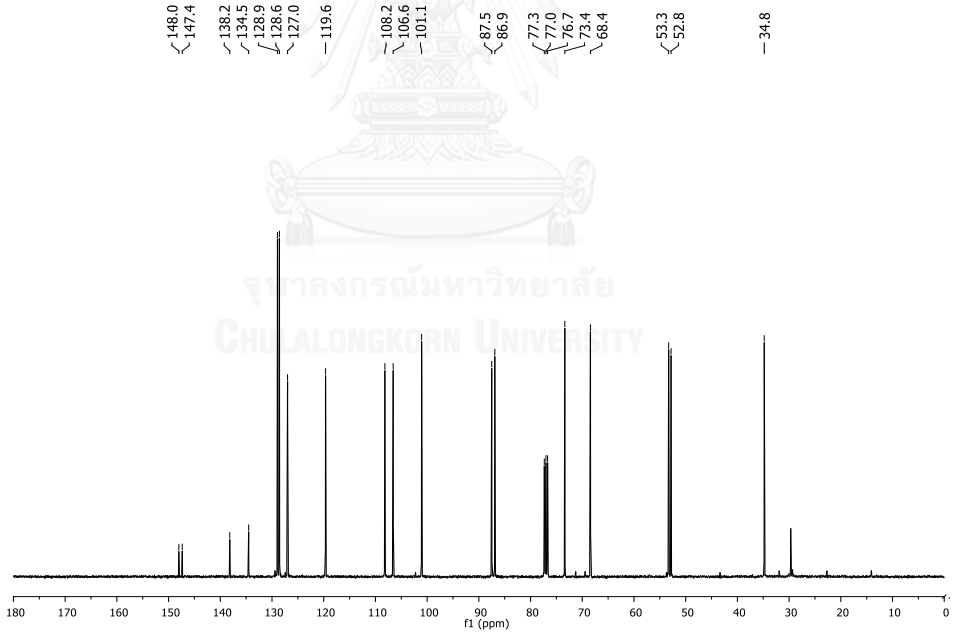

Figure 51. ^{13}C NMR spectrum of compound **3.2p** in $CDCl_3$

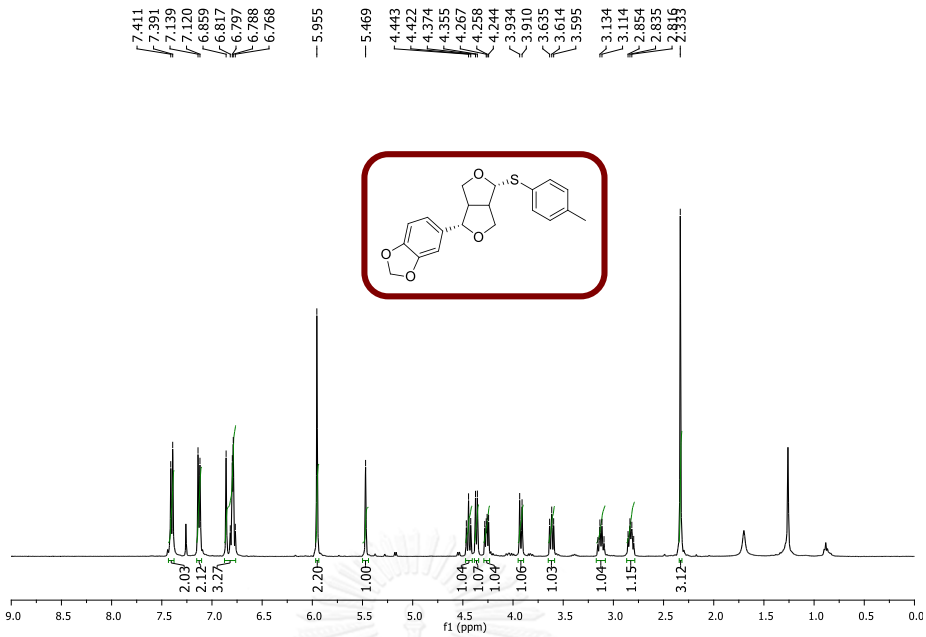

Figure 52. ^{1}H NMR spectrum of compound **3.2q** in $CDCl_3$

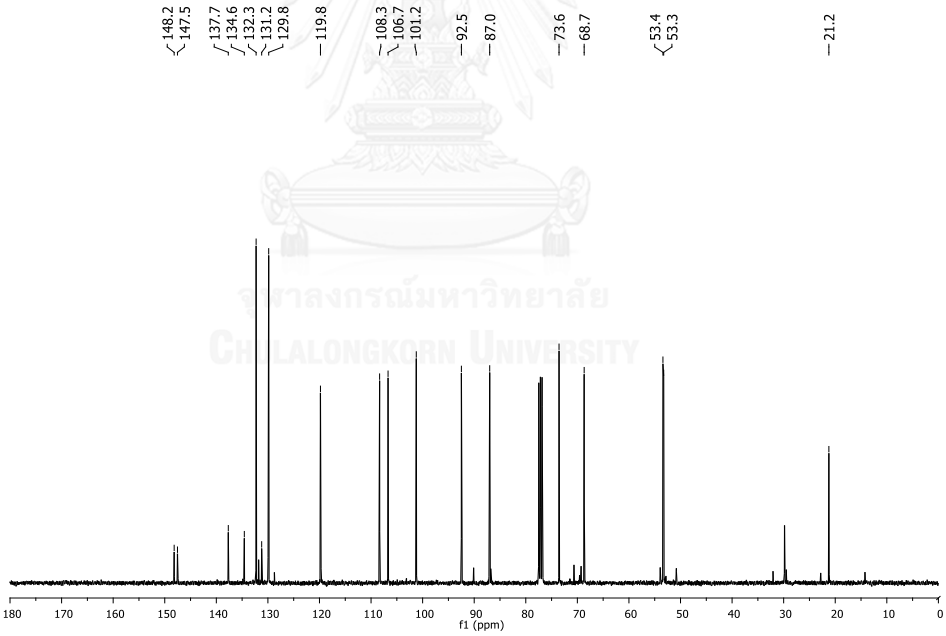

Figure 53. ^{13}C NMR spectrum of compound **3.2q** in $CDCl_3$

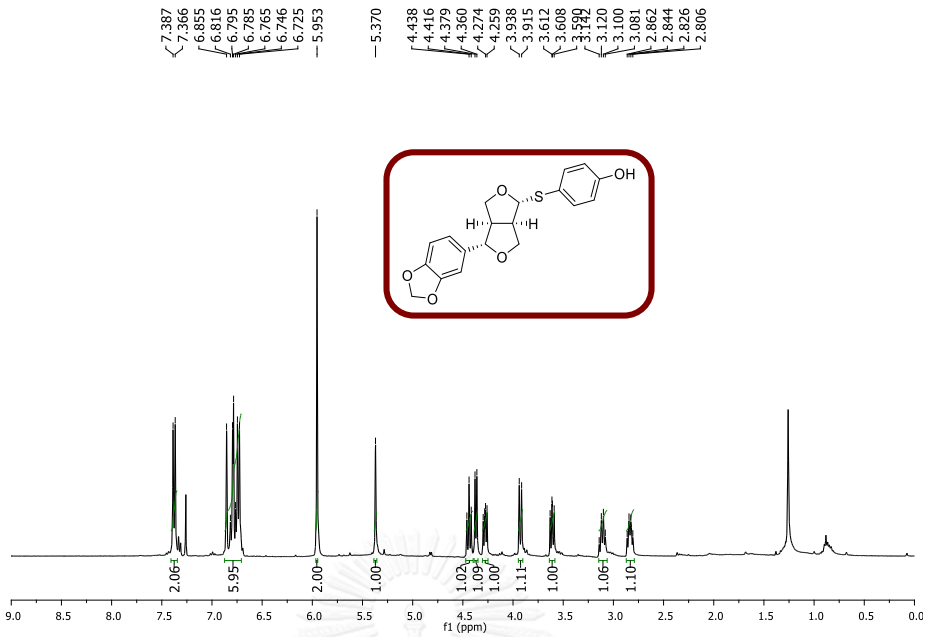

Figure 54. ^{1}H NMR spectrum of compound **3.2r** in $CDCl_3$

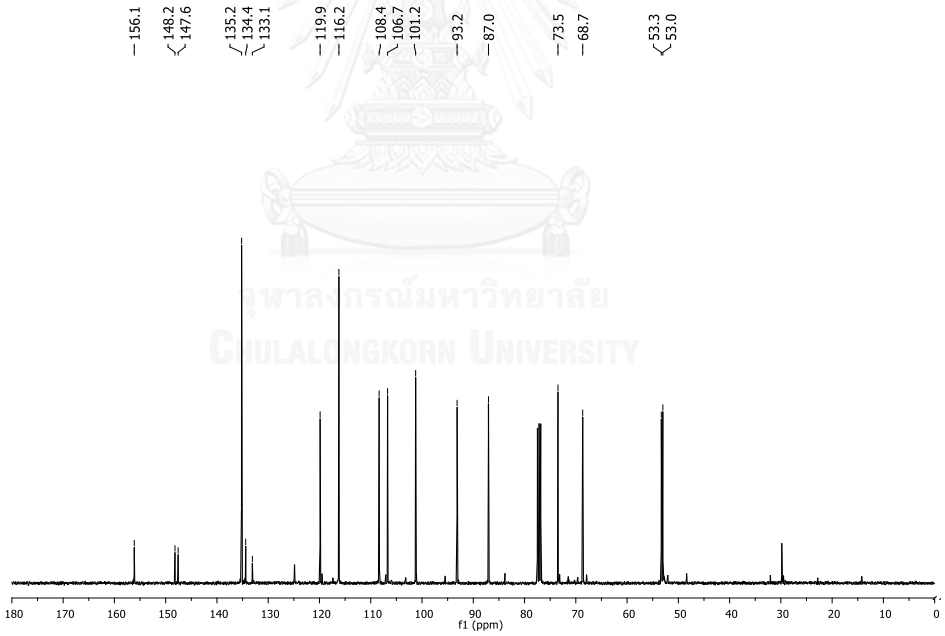

Figure 55. ^{13}C NMR spectrum of compound **3.2r** in $CDCl_3$

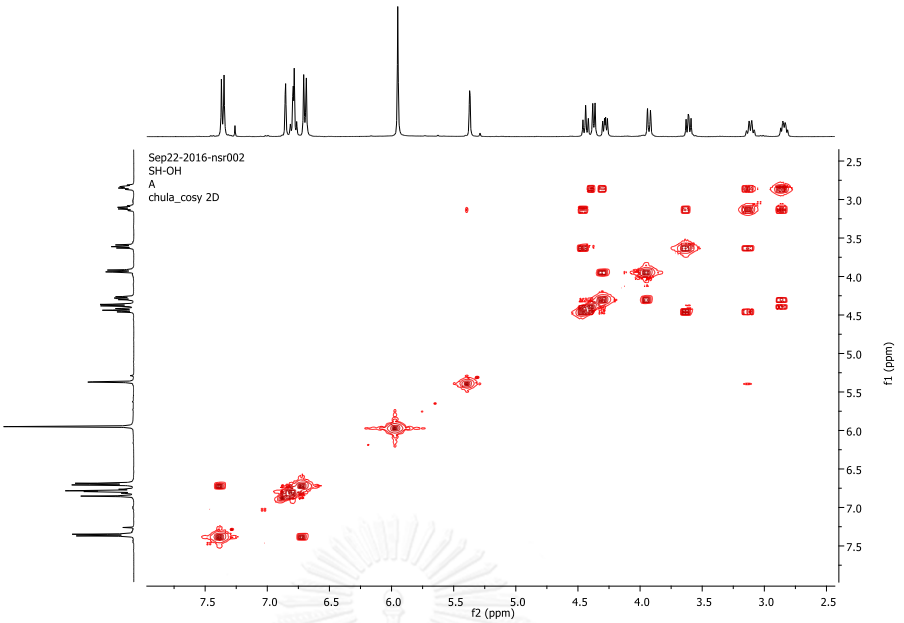

Figure 56. NOESY experiment of **3.2r** in $CDCl_3$

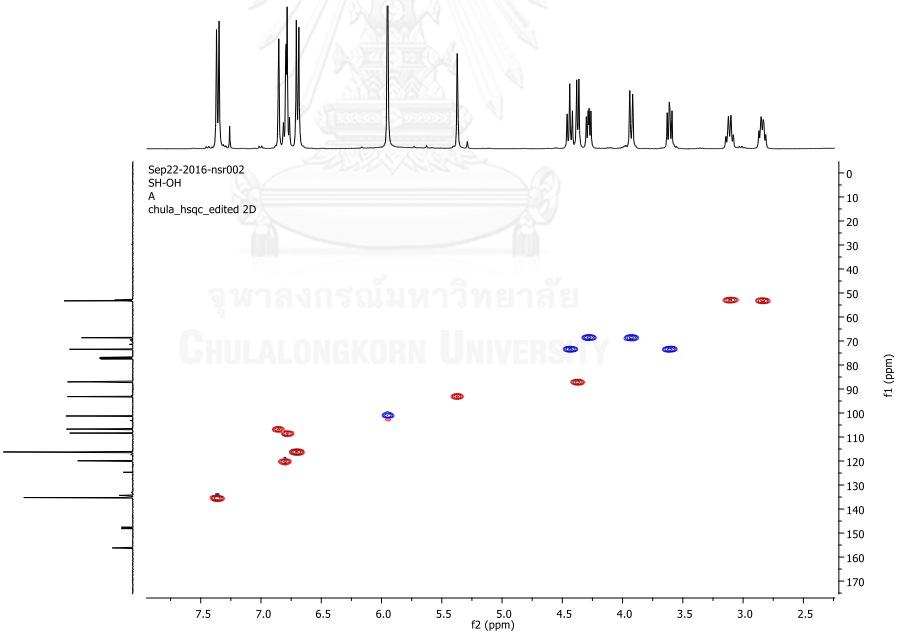

Figure 57. HSQC experiment of **3.2r** in $CDCl_3$

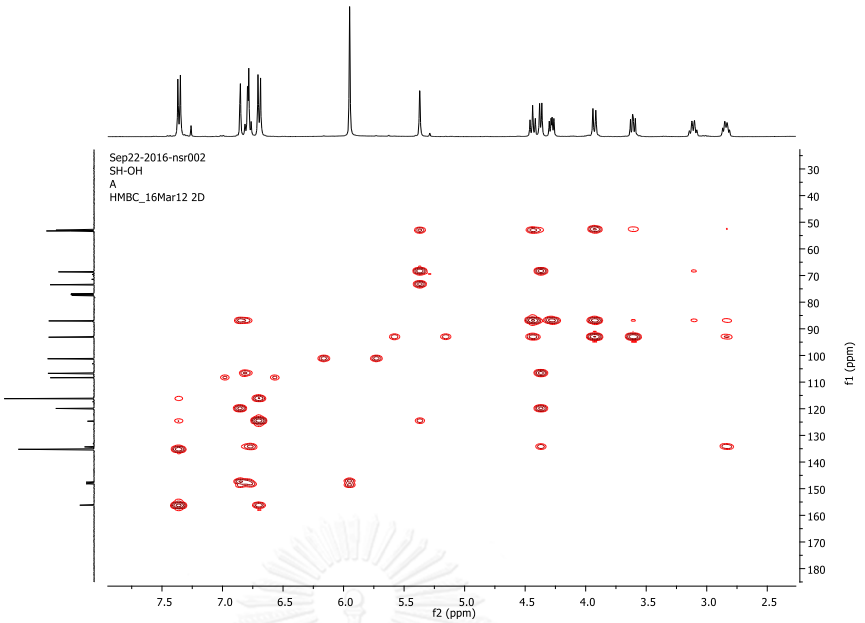

Figure 58. HMBC experiment of **3.2r** in $CDCl_3$

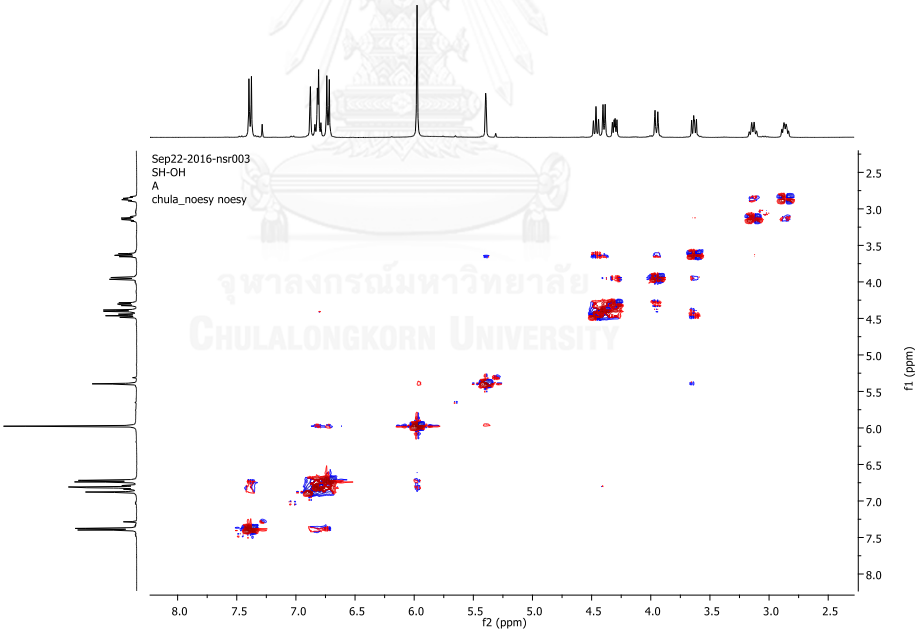

Figure 59. NOESY experiment of **3.2r** in $CDCl_3$

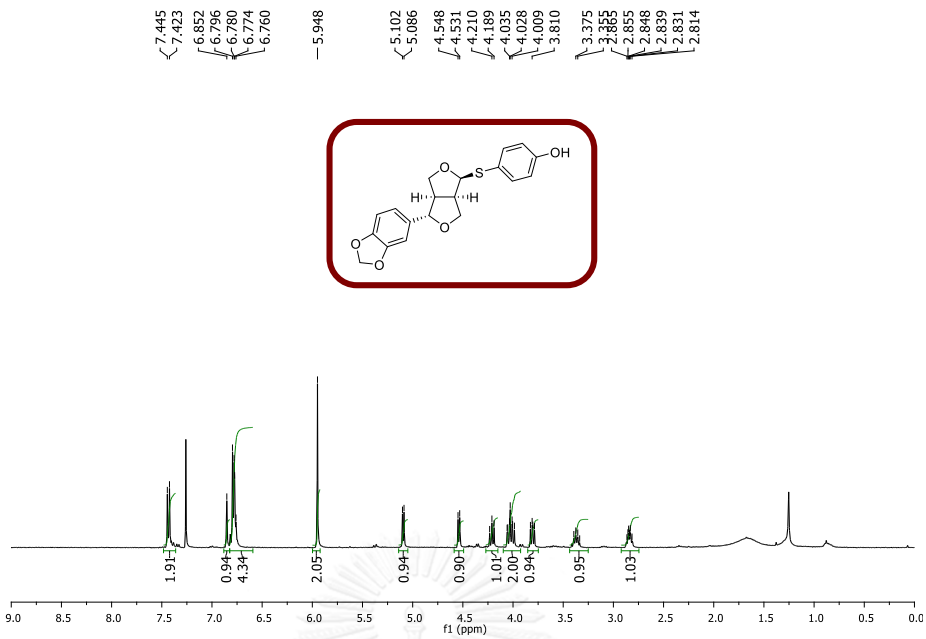

Figure 60. ^{13}C NMR spectrum of compound ***epi*-3.2r** in $CDCl_3$

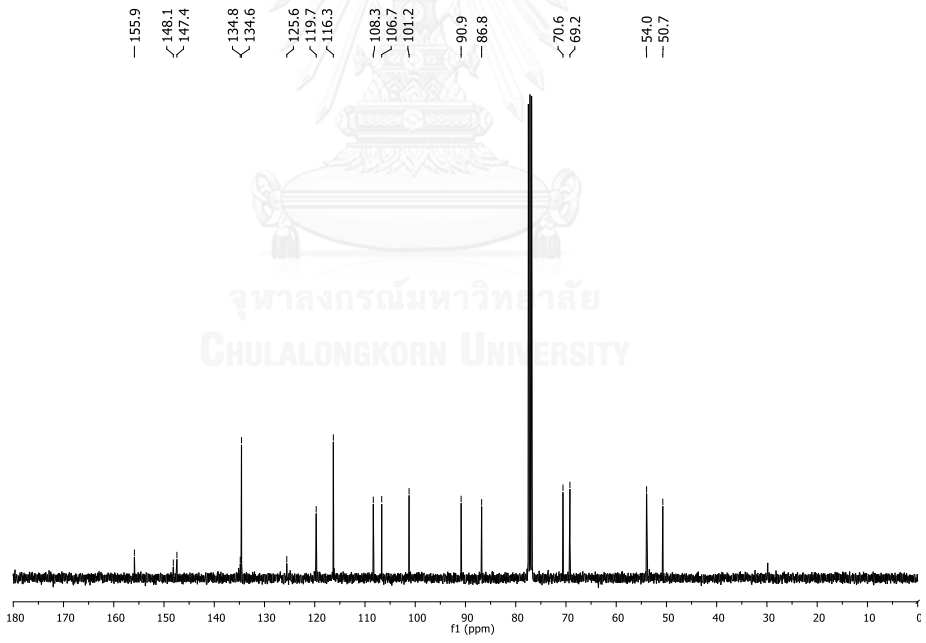

Figure 61. ^{13}C NMR spectrum of compound ***epi*-3.2r** in $CDCl_3$

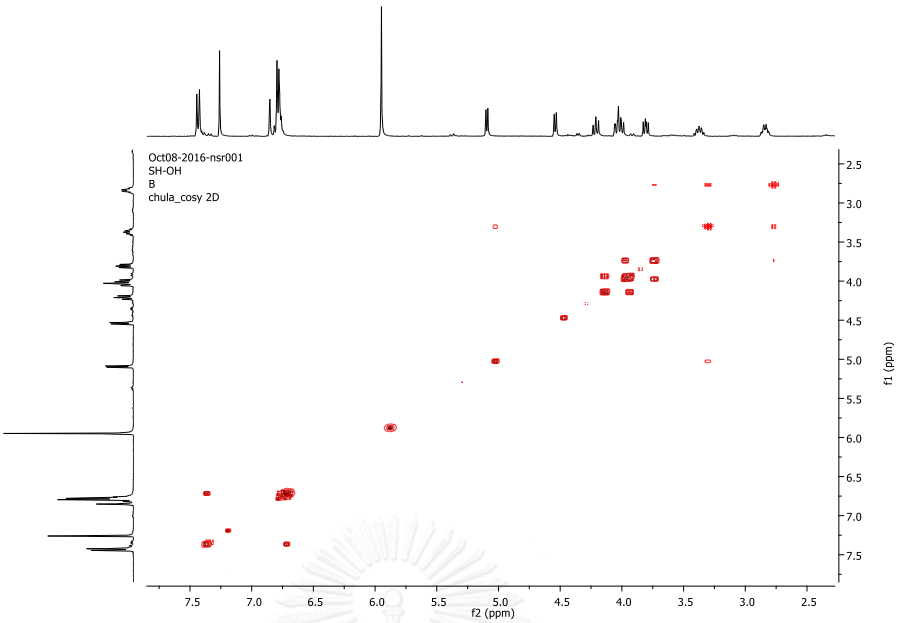

Figure 62. COSY experiment of ***epi*-3.2r** in $CDCl_3$

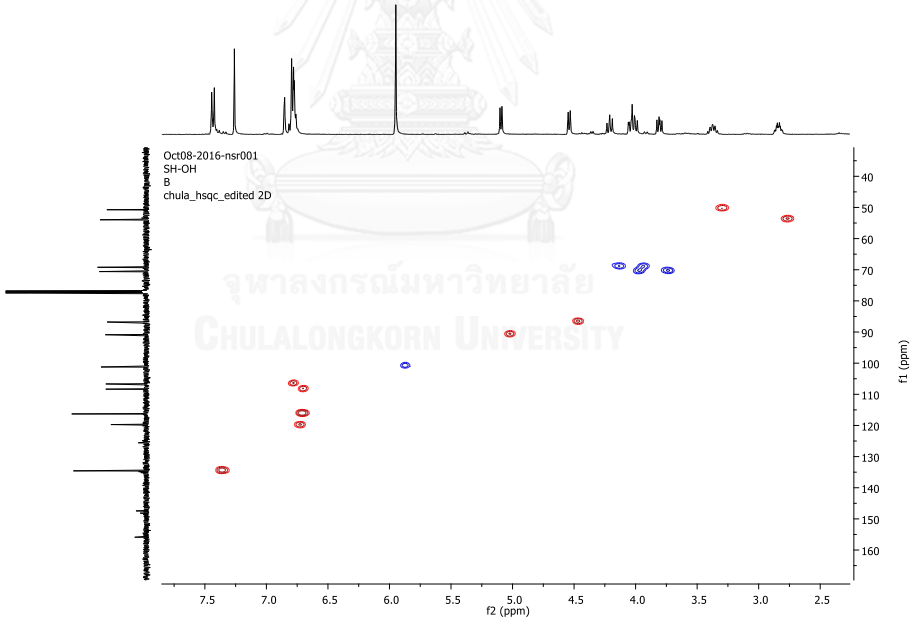

Figure 63. HSQC experiment of ***epi*-3.2r** in $CDCl_3$

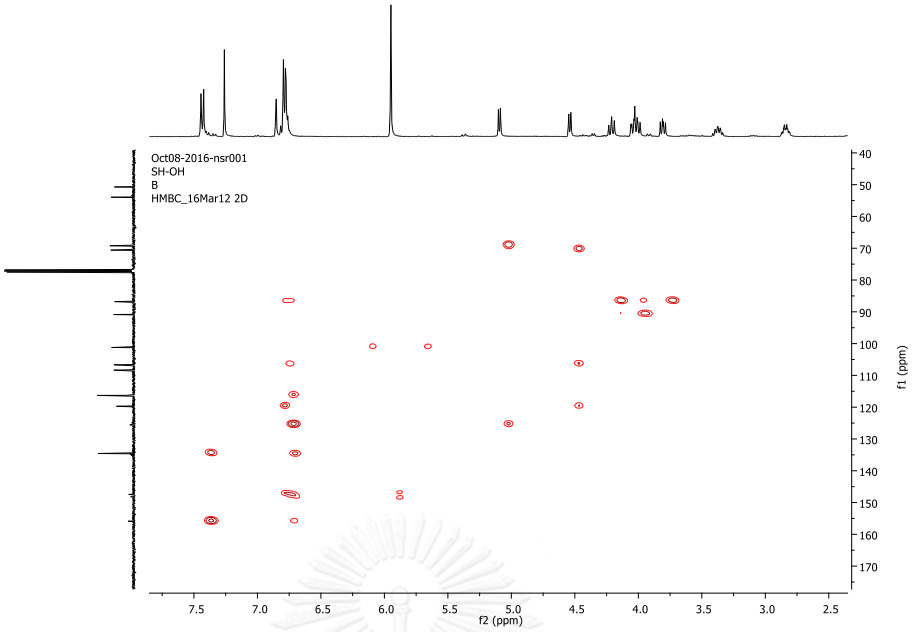

Figure 64. HMBC experiment of ***epi*-3.2r** in $CDCl_3$

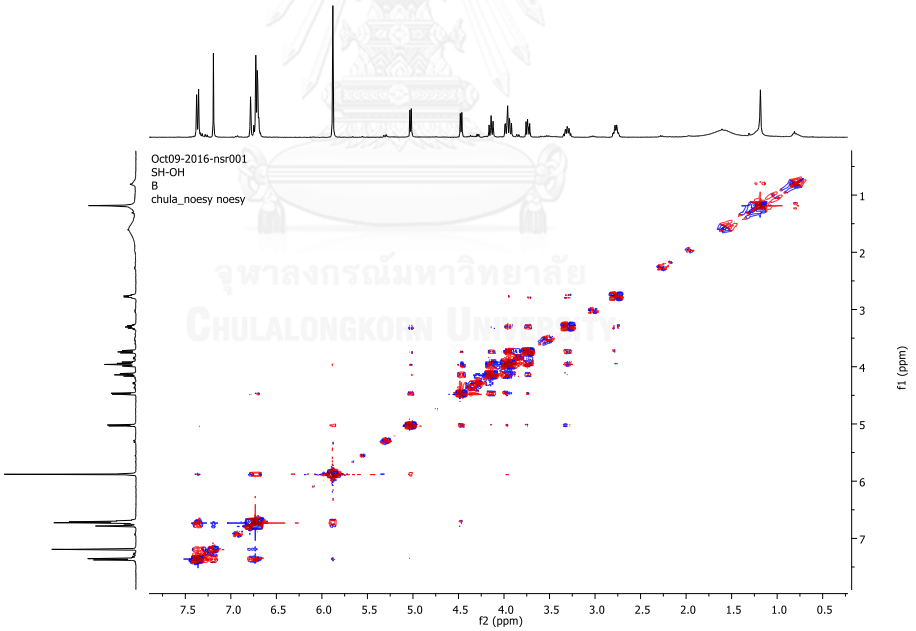

Figure 65. NOESY experiment of ***epi*-3.2r** in $CDCl_3$

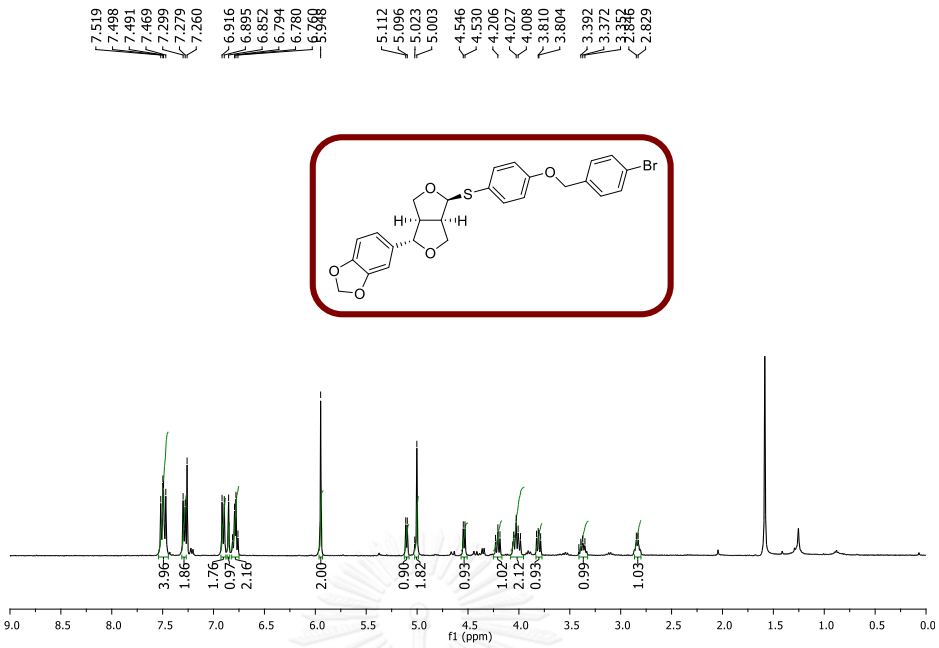

Figure 66. ^{13}C NMR spectrum of compound ***epi*-3.2r-*p*BBE** in $CDCl_3$

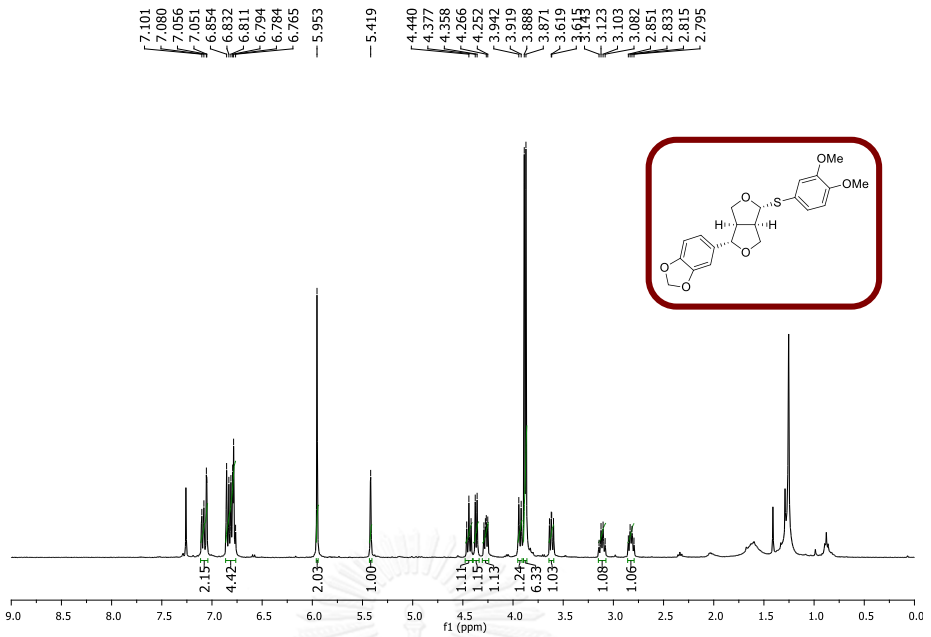

Figure 67. ^{1}H NMR spectrum of compound **3.2s** in $CDCl_3$

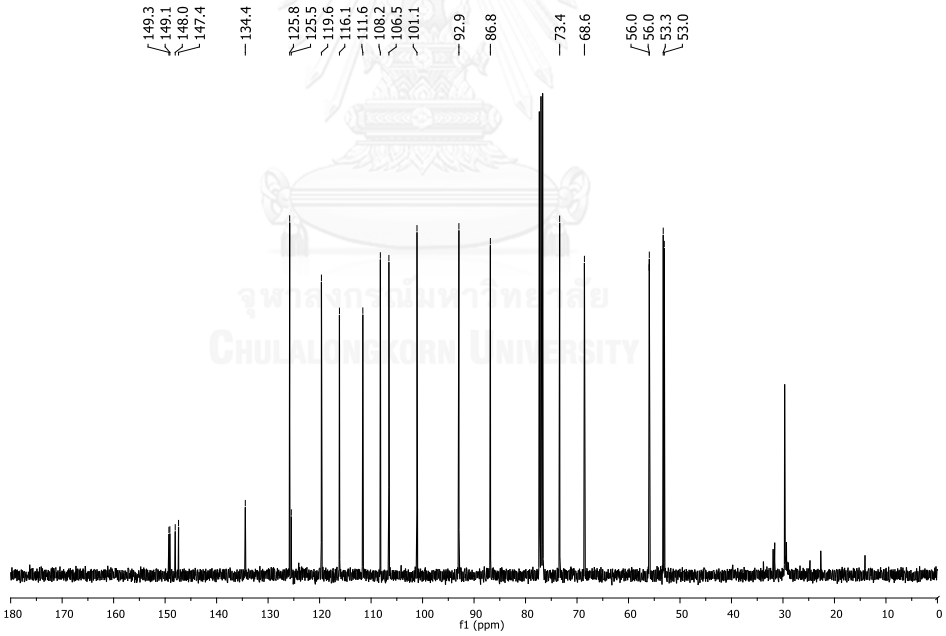

Figure 68. ^{13}C NMR spectrum of compound **3.2s** in $CDCl_3$

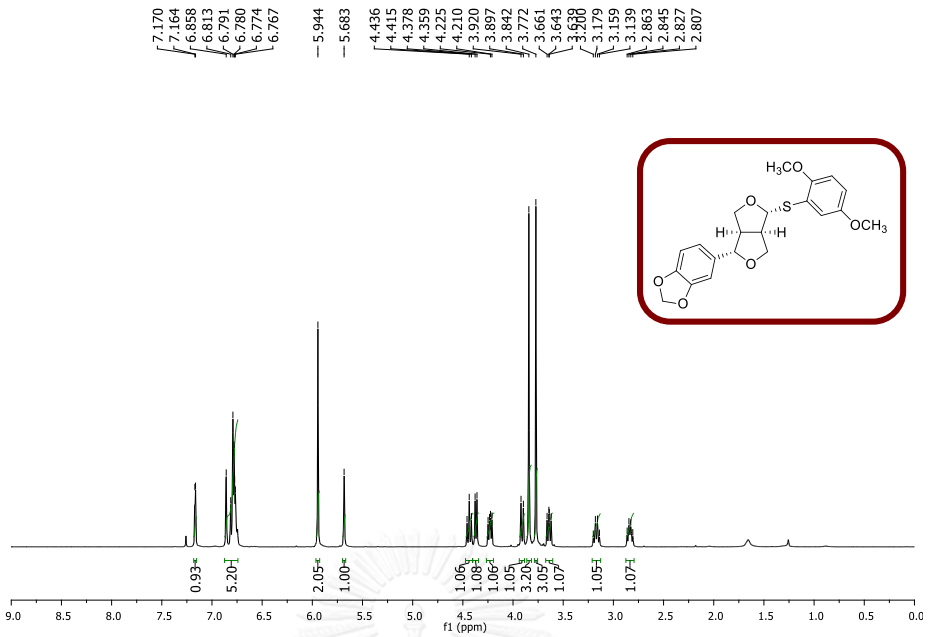

Figure 69. ^{1}H NMR spectrum of compound **3.2t** in $CDCl_3$

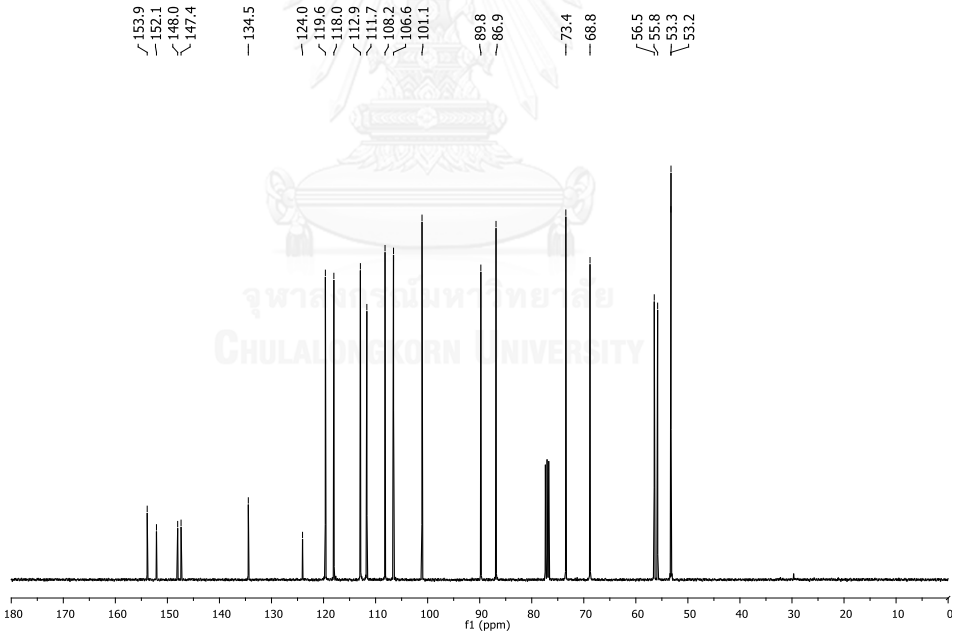

Figure 70. ^{13}C NMR spectrum of compound **3.2t** in $CDCl_3$

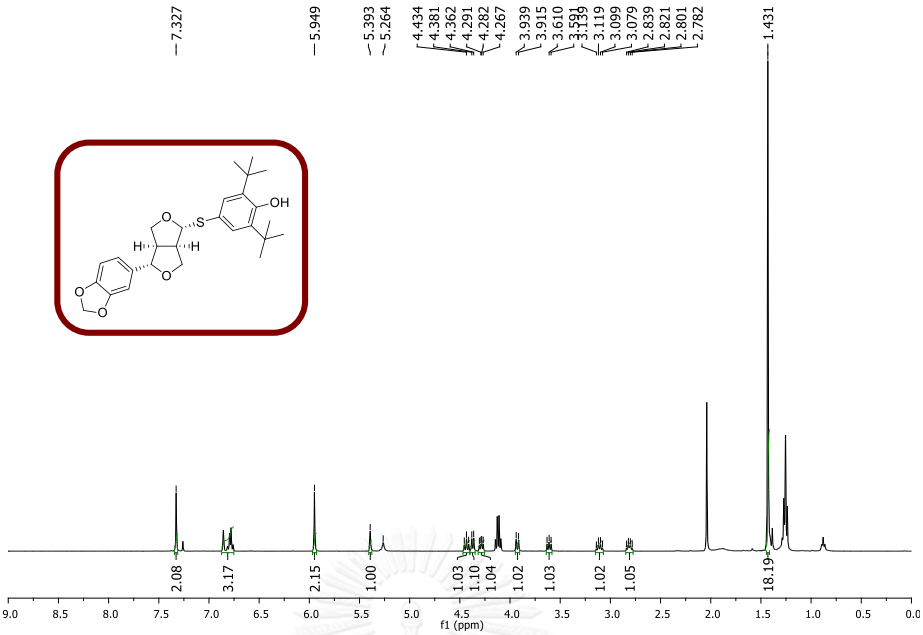

Figure 71. ^{1}H NMR spectrum of compound **3.2u** in $CDCl_3$

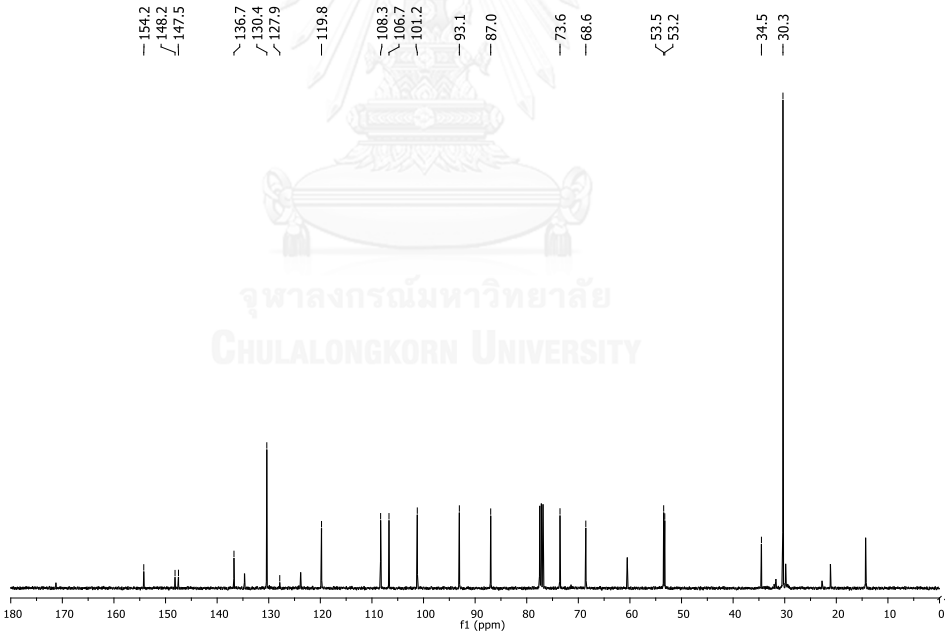

Figure 72. ^{13}C NMR spectrum of compound **3.2u** in $CDCl_3$

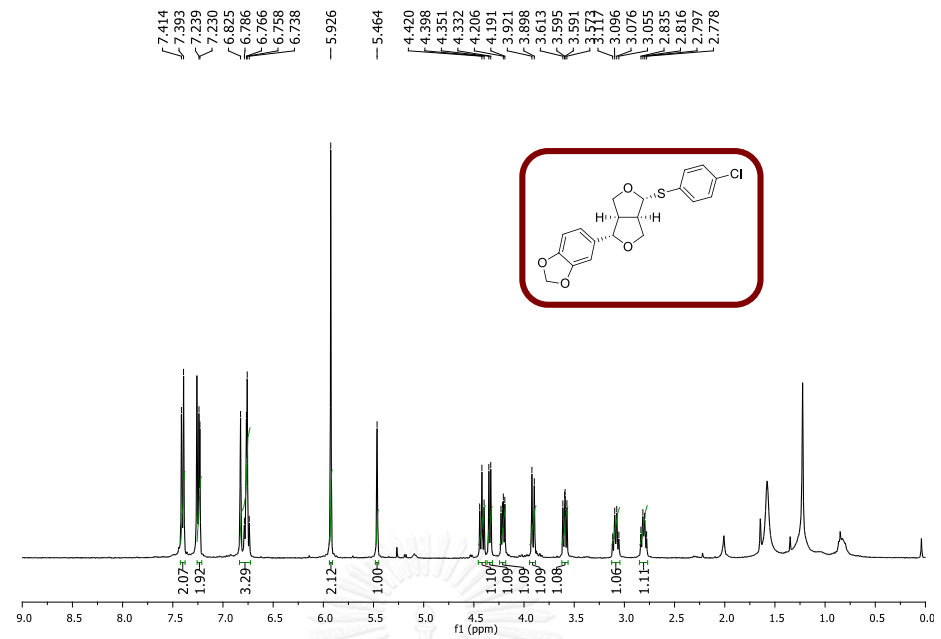

Figure 73. ^{1}H NMR spectrum of compound **3.2v** in $CDCl_3$

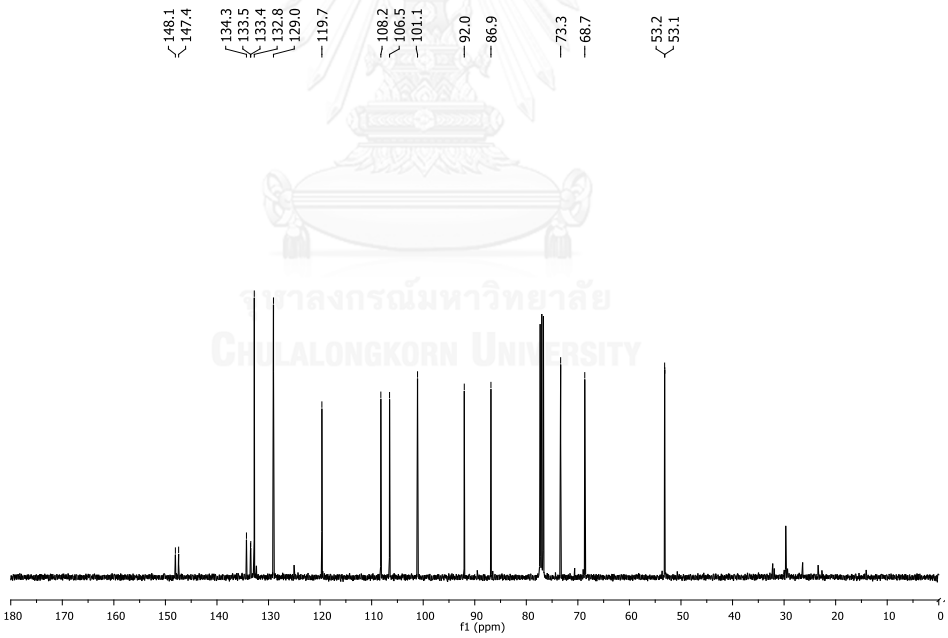

Figure 74. ^{13}C NMR spectrum of compound **3.2v** in $CDCl_3$

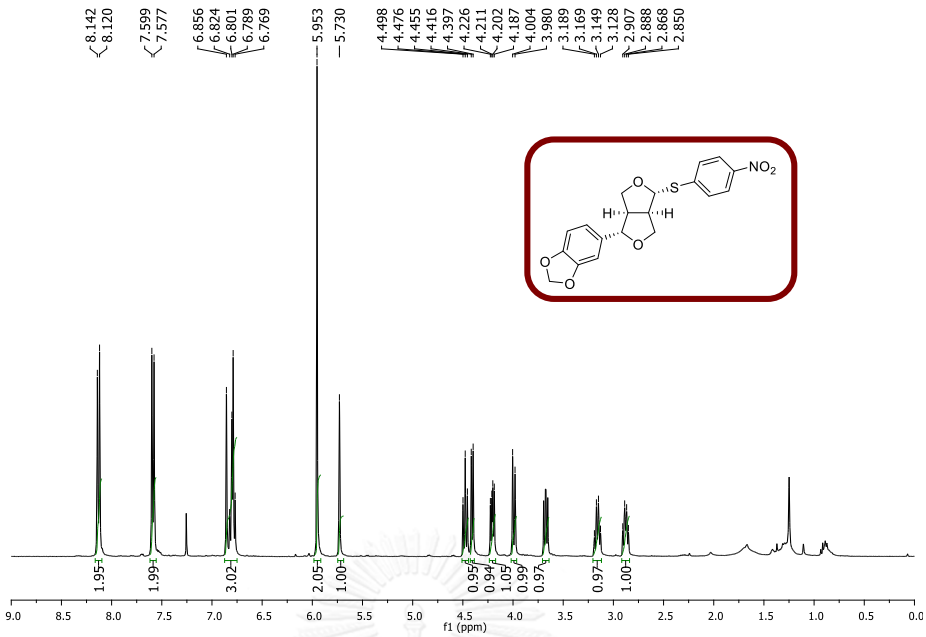

Figure 75. ^{1}H NMR spectrum of compound **3.2w** in $CDCl_3$

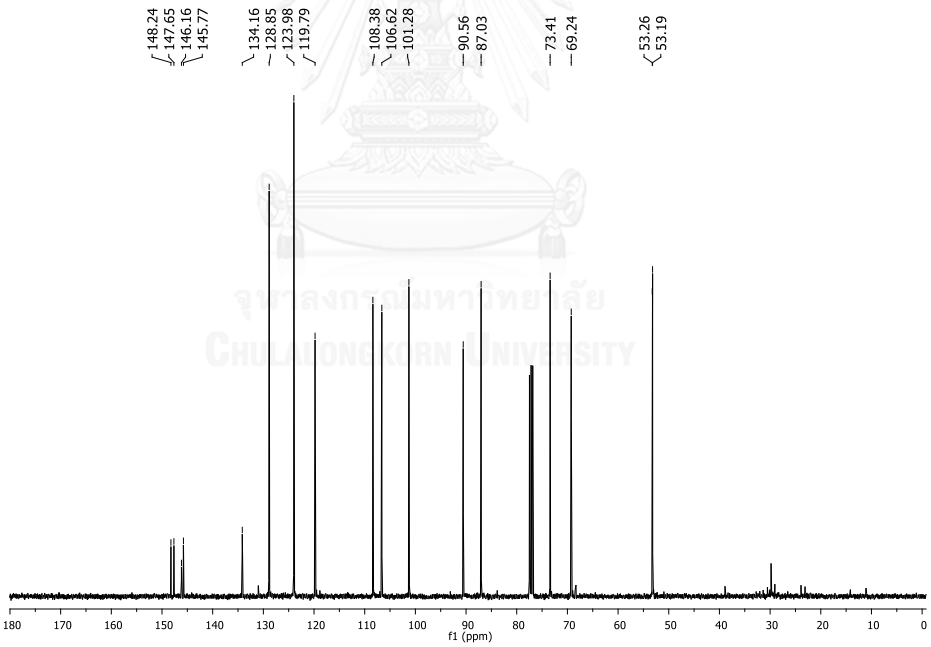

Figure 76. ^{13}C NMR spectrum of compound **3.2w** in $CDCl_3$

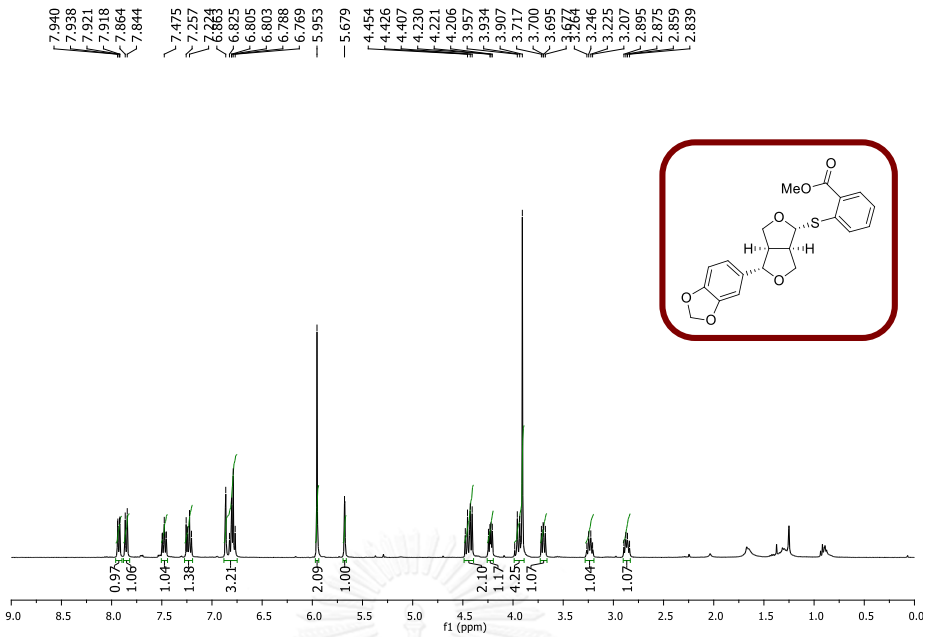

Figure 77. ^{1}H NMR spectrum of compound **3.2x** in $CDCl_3$

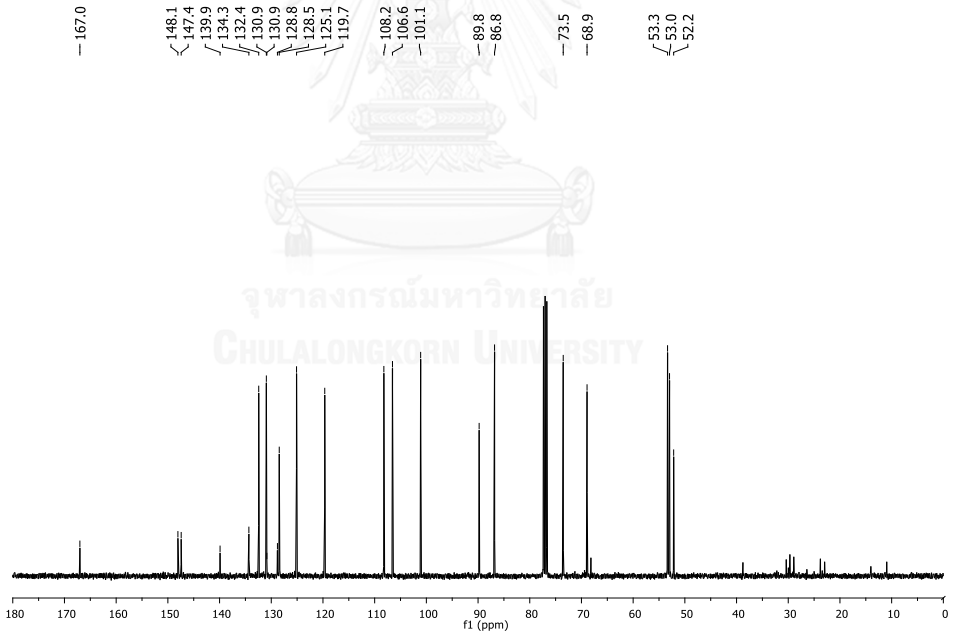

Figure 78. ^{13}C NMR spectrum of compound **3.2x** in $CDCl_3$

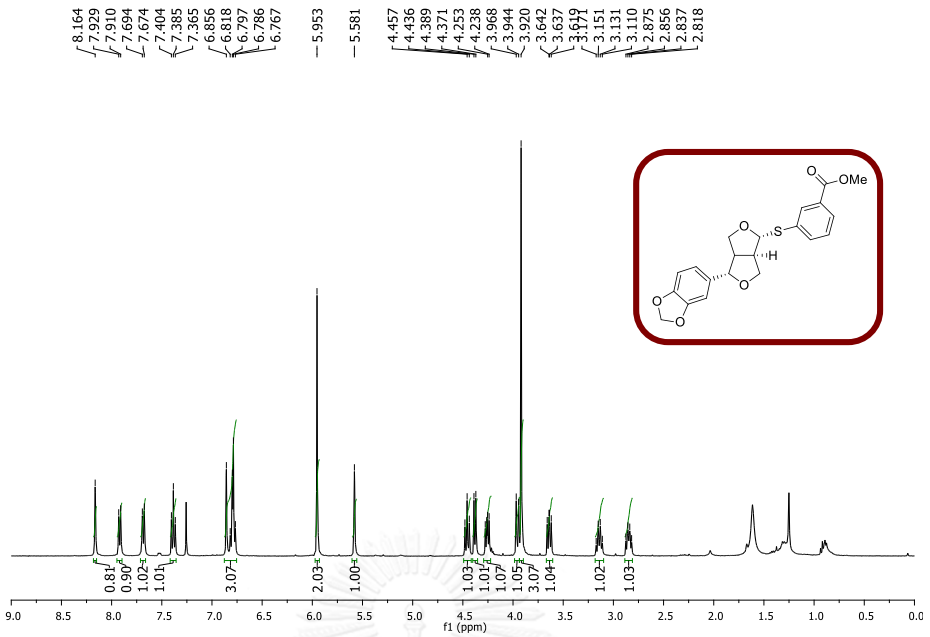

Figure 79. ^{1}H NMR spectrum of compound **3.2y** in $CDCl_3$

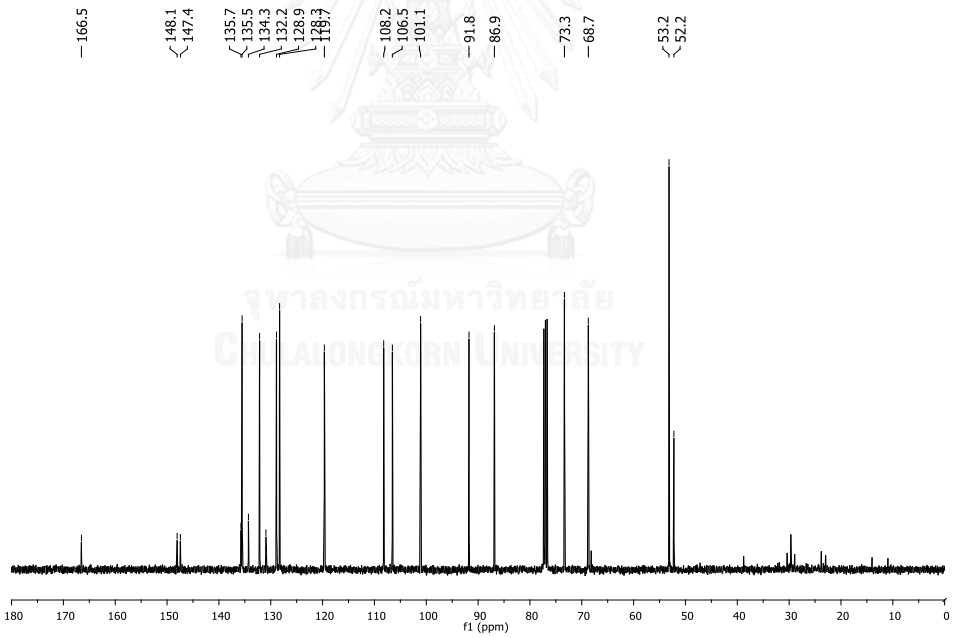

Figure 80. ^{13}C NMR spectrum of compound **3.2y** in $CDCl_3$

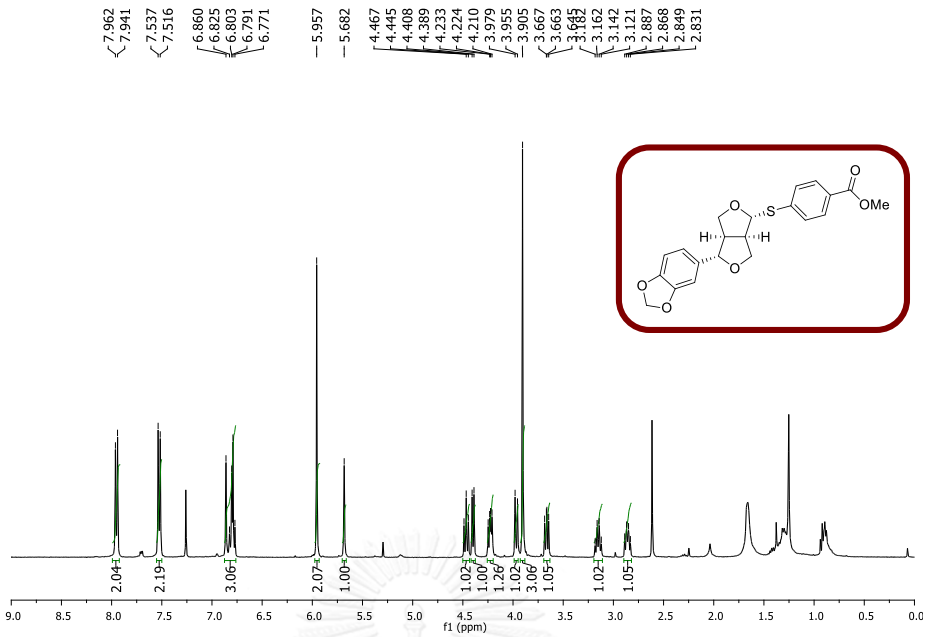

Figure 81. ^{1}H NMR spectrum of compound **3.2z** in $CDCl_3$

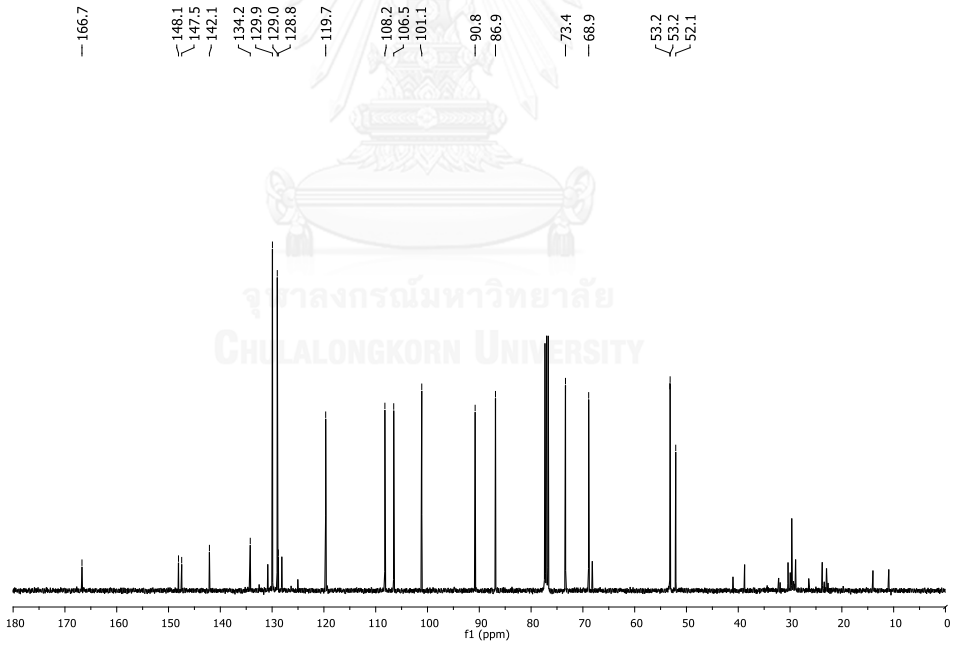

Figure 82. ^{13}C NMR spectrum of compound **3.2z** in $CDCl_3$

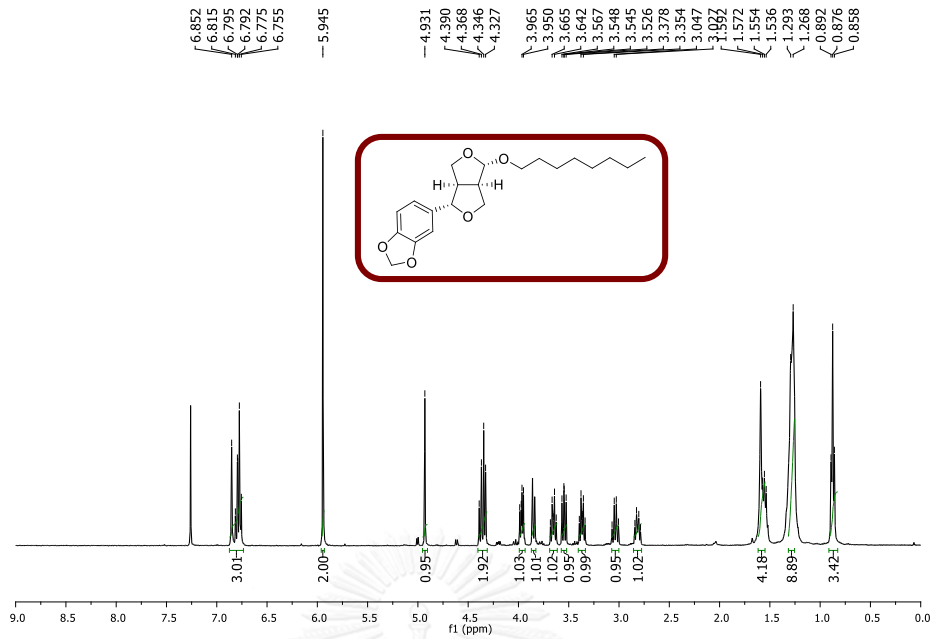

Figure 83. ^{1}H NMR spectrum of compound **3.3A** in $CDCl_3$

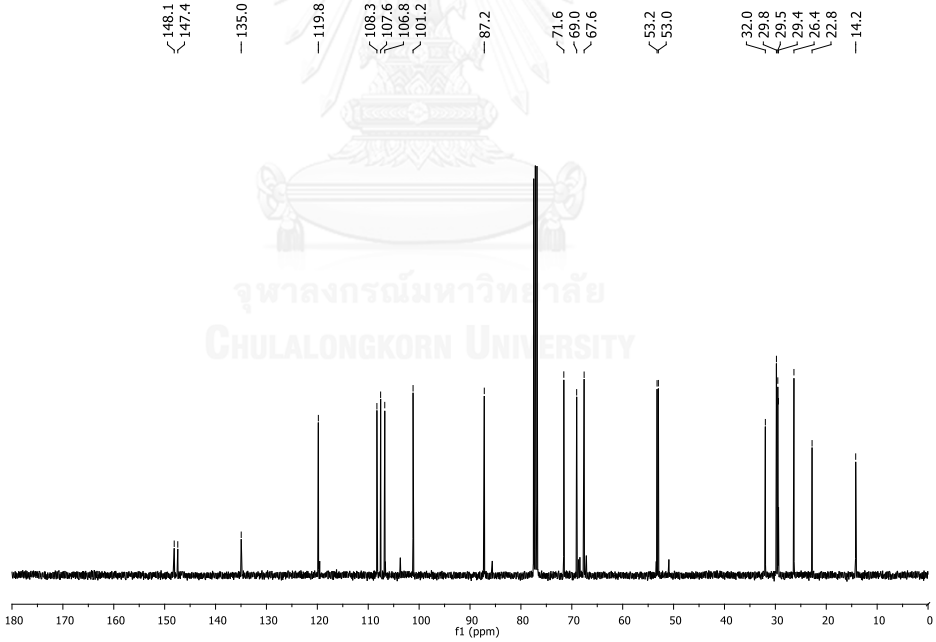

Figure 84. ^{13}C NMR spectrum of compound **3.3A** in $CDCl_3$

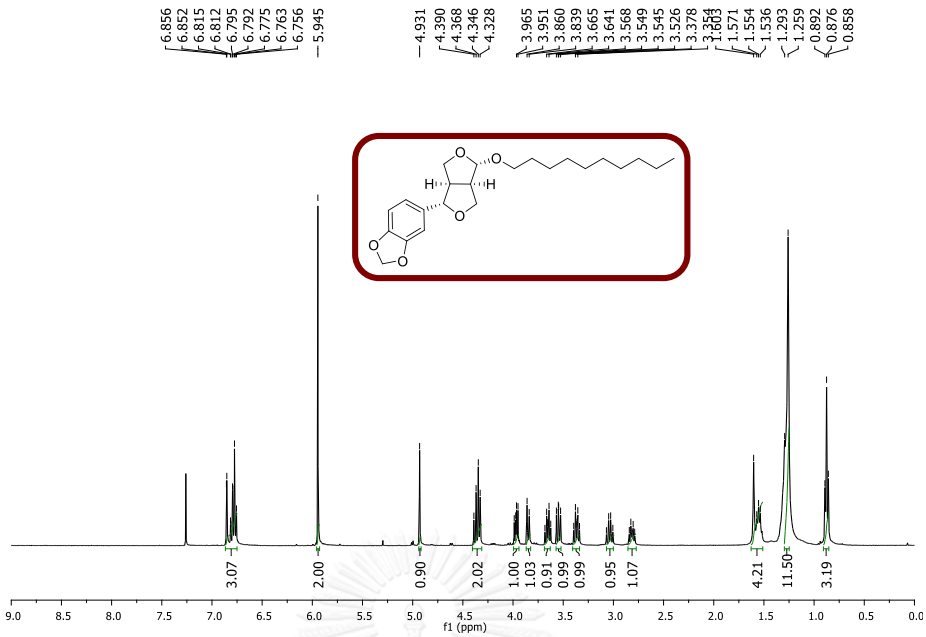

Figure 85. ^{1}H NMR spectrum of compound **3.3B** in $CDCl_3$

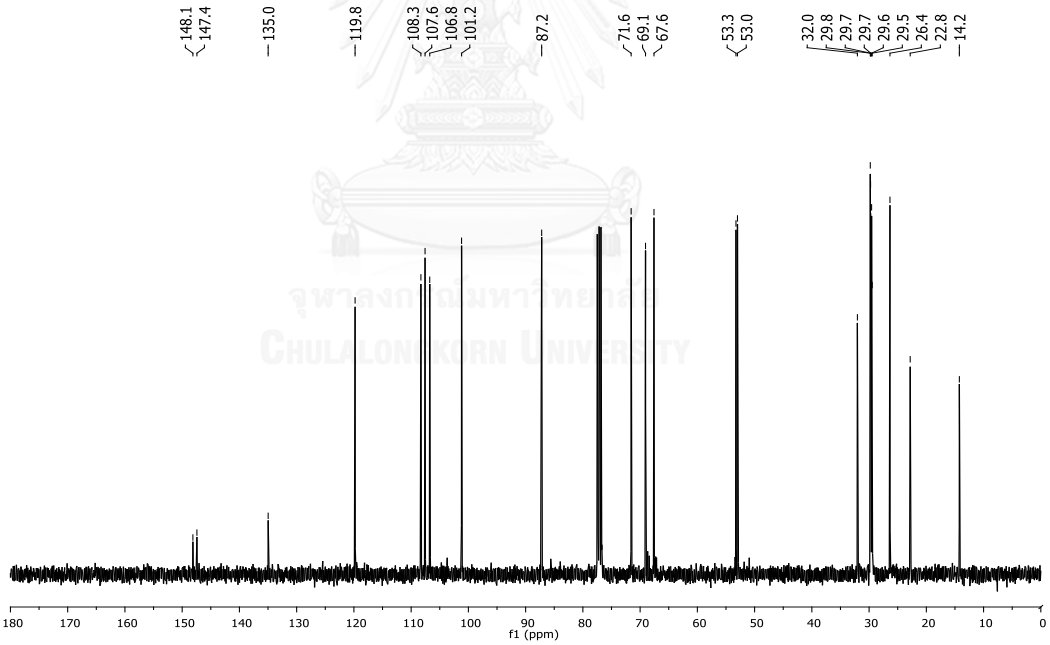

Figure 86. ^{13}C NMR spectrum of compound **3.3B** in $CDCl_3$

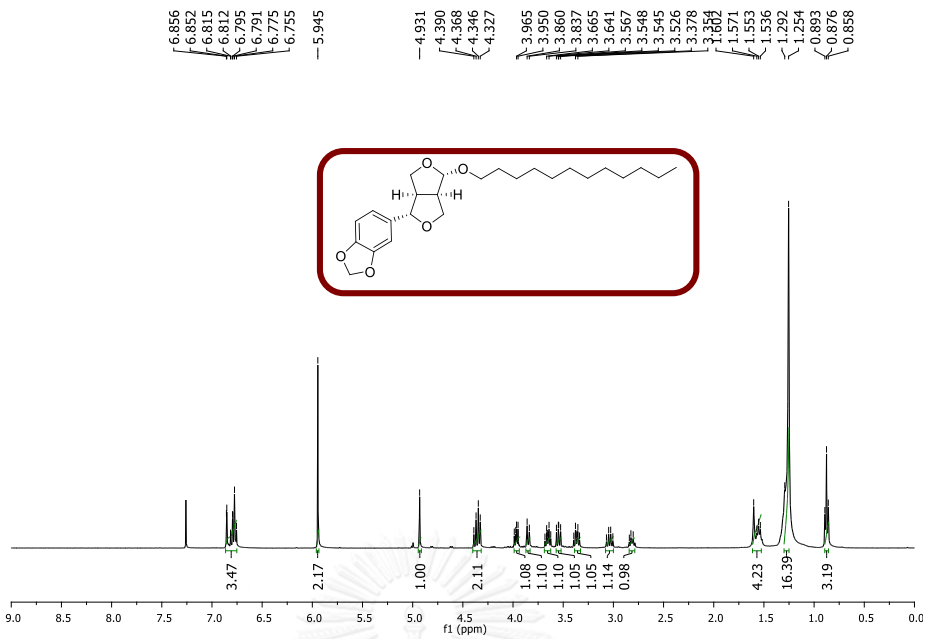

Figure 87. ^{1}H NMR spectrum of compound **3.3C** in $CDCl_3$

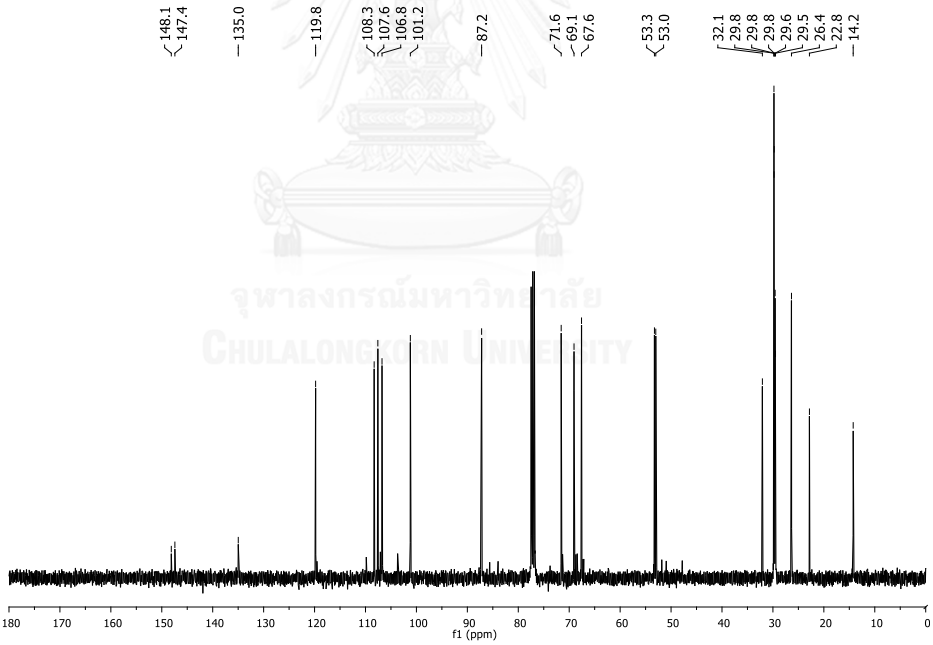

Figure 88. ^{13}C NMR spectrum of compound **3.3C** in $CDCl_3$

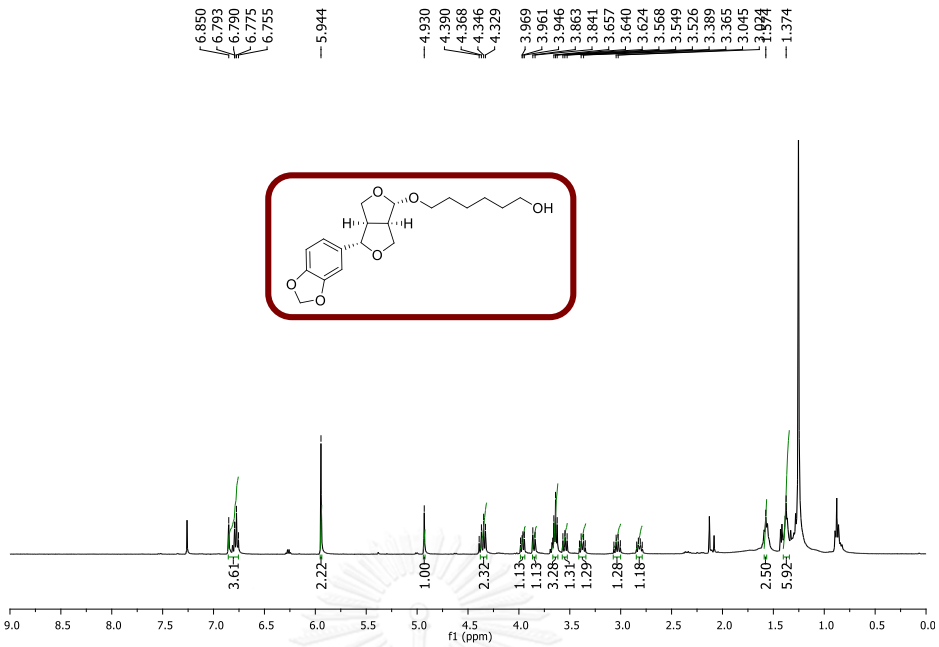

Figure 89. ^{1}H NMR spectrum of compound **3.3D** in $CDCl_3$

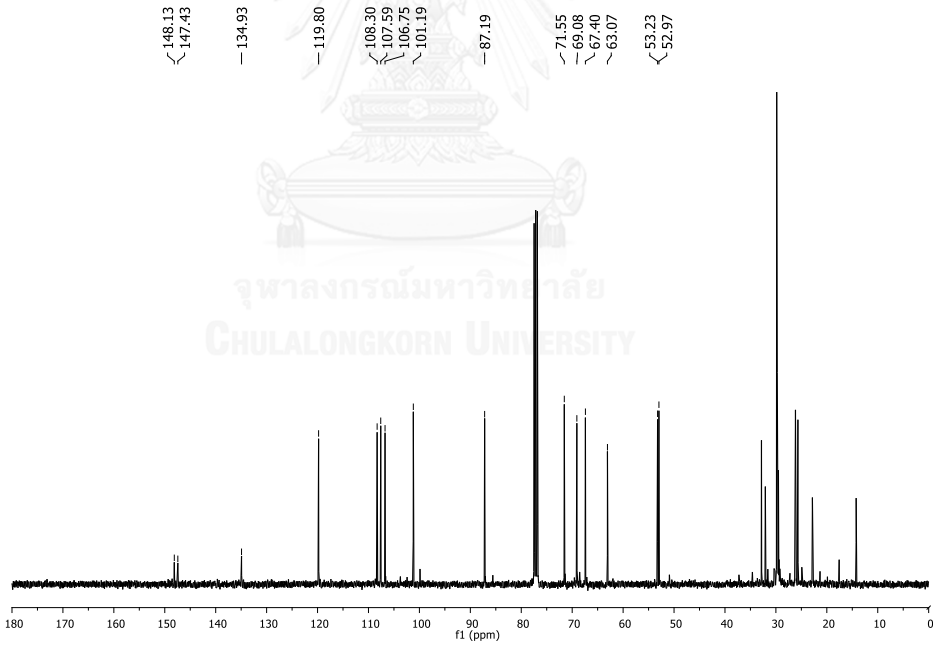

Figure 90. ^{13}C NMR spectrum of compound **3.3D** in $CDCl_3$

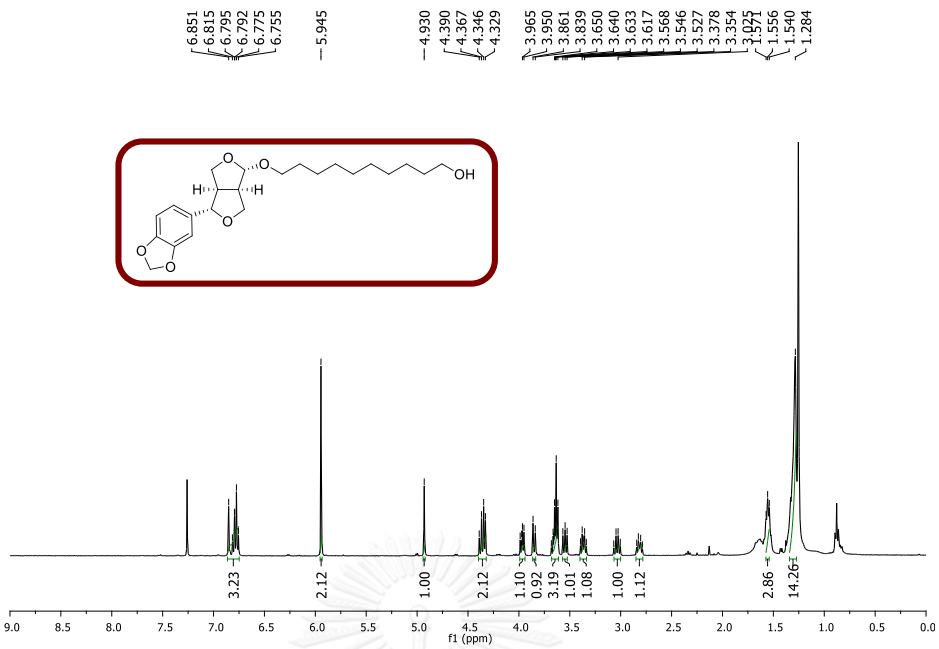

Figure 91. ^{1}H NMR spectrum of compound **3.3E** in $CDCl_3$

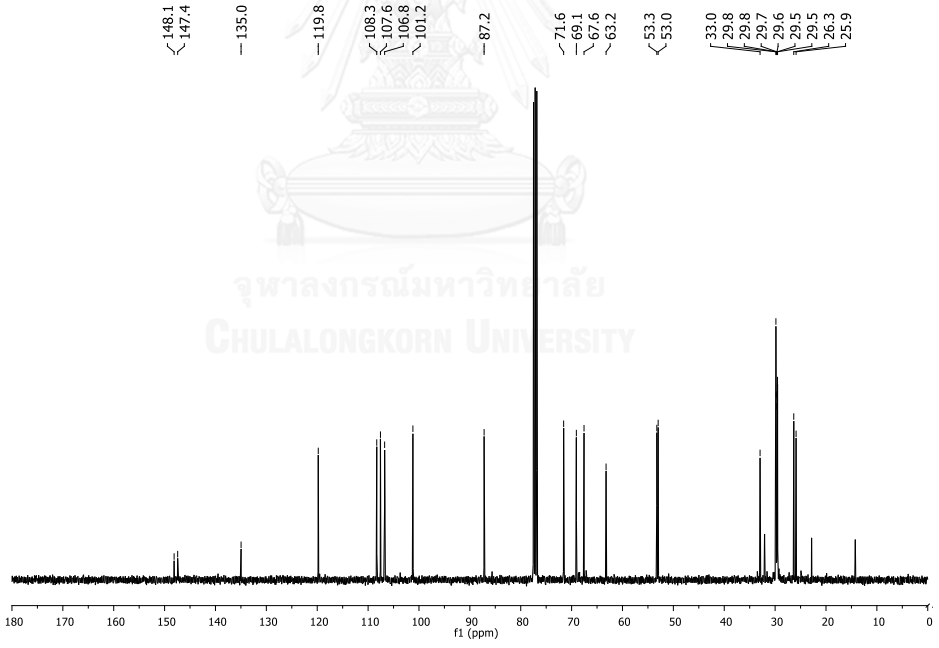

Figure 92. ^{13}C NMR spectrum of compound **3.3**E in $CDCl_3$

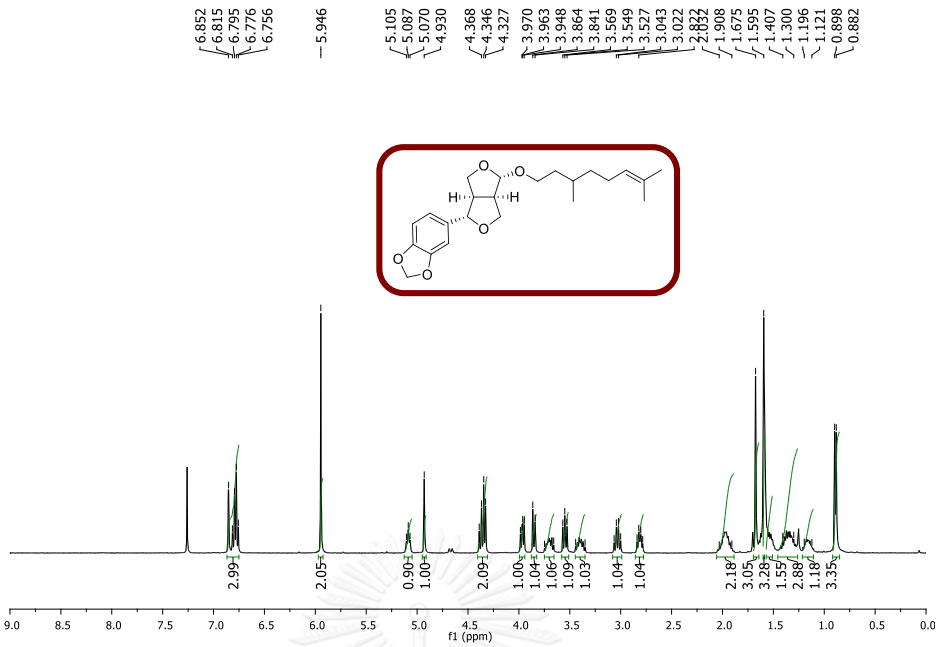

Figure 93. ^{1}H NMR spectrum of compound **3.3F** in $CDCl_3$

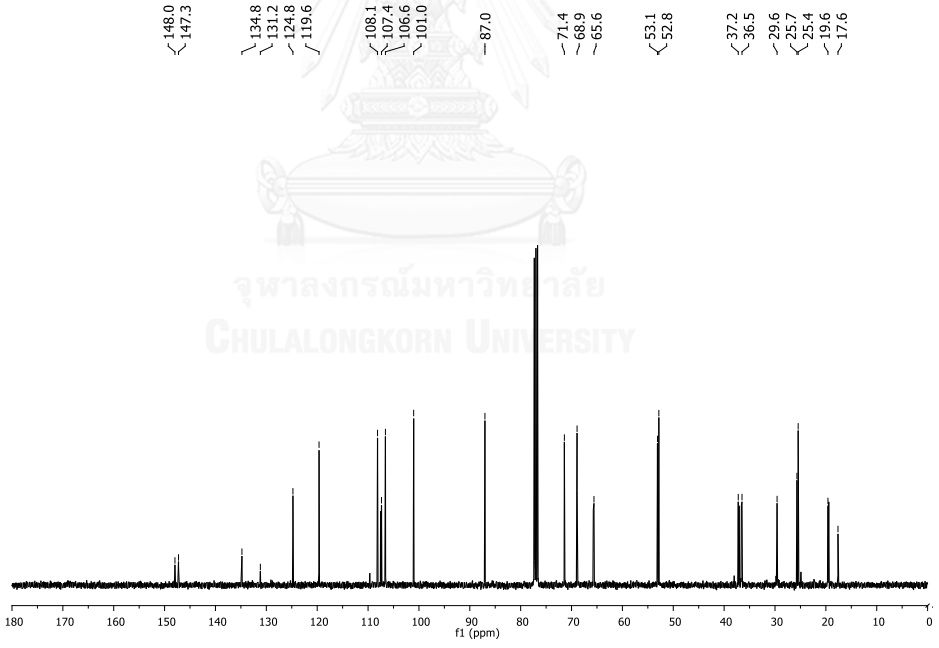

Figure 94. ^{13}C NMR spectrum of compound **3.3**F in $CDCl_3$

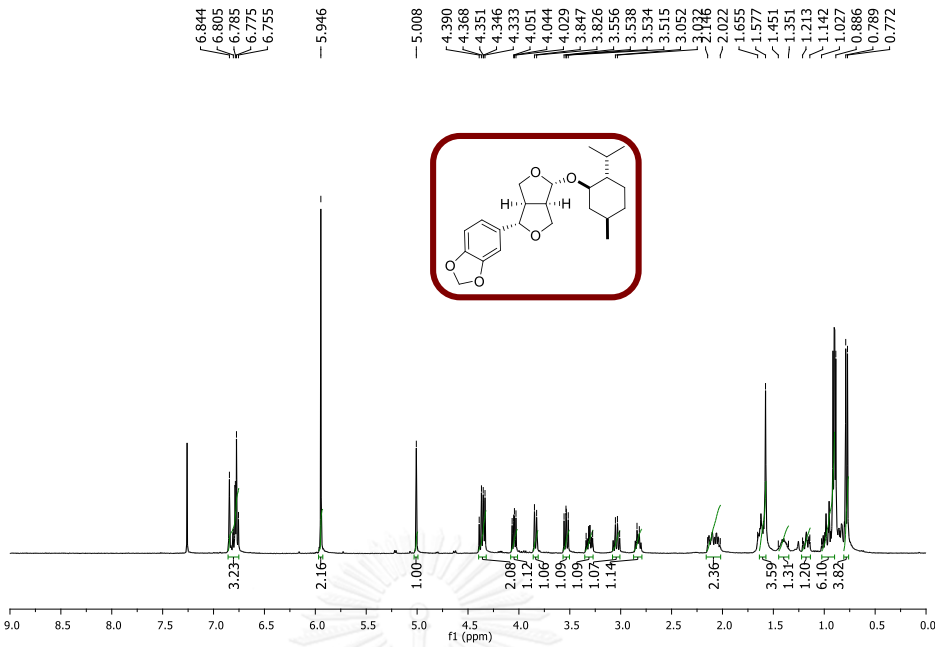

Figure 95. ^{1}H NMR spectrum of compound **3.3G** in $CDCl_3$

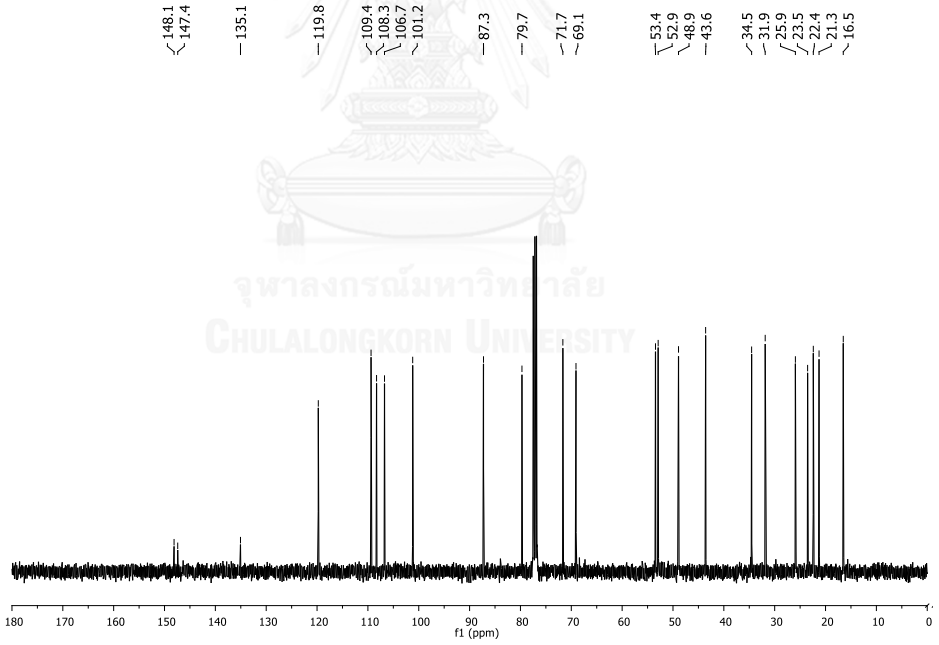

Figure 96. ^{13}C NMR spectrum of compound **3.3G** in $CDCl_3$

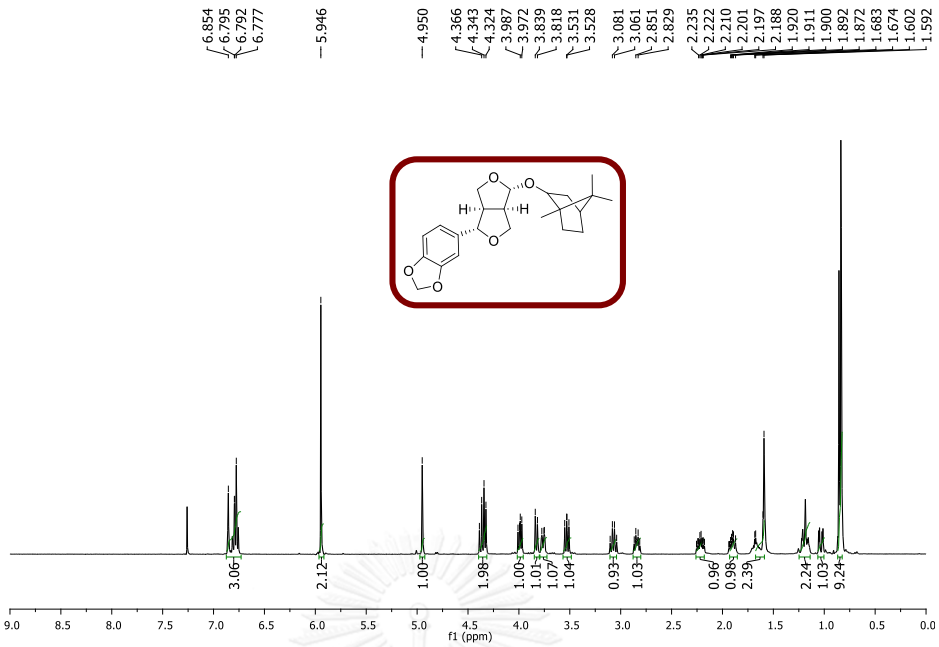

Figure 97. ^{1}H NMR spectrum of compound **3.3H** in $CDCl_3$

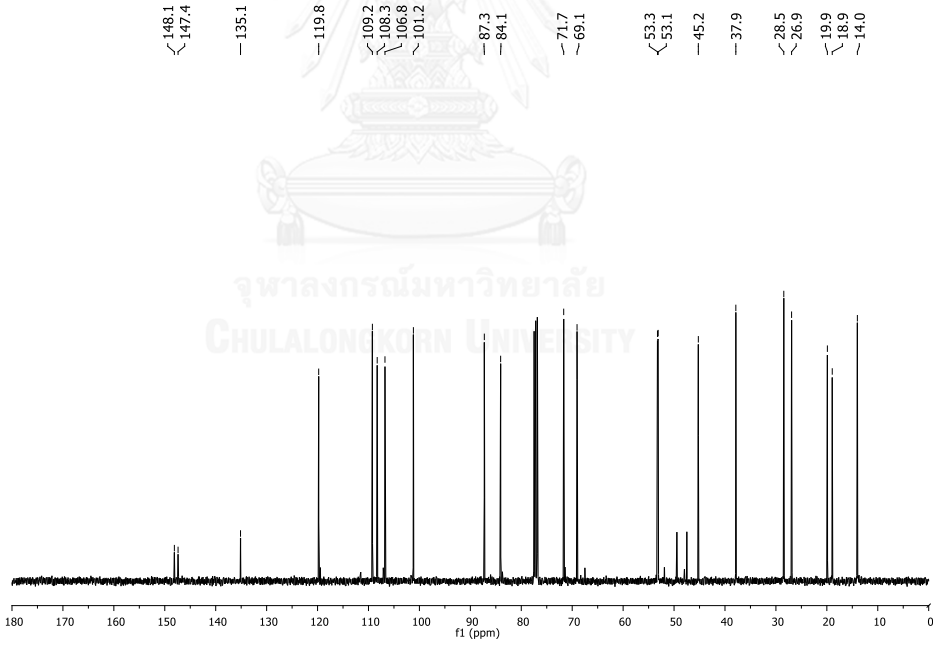

Figure 98. ^{13}C NMR spectrum of compound **3.3H** in $CDCl_3$

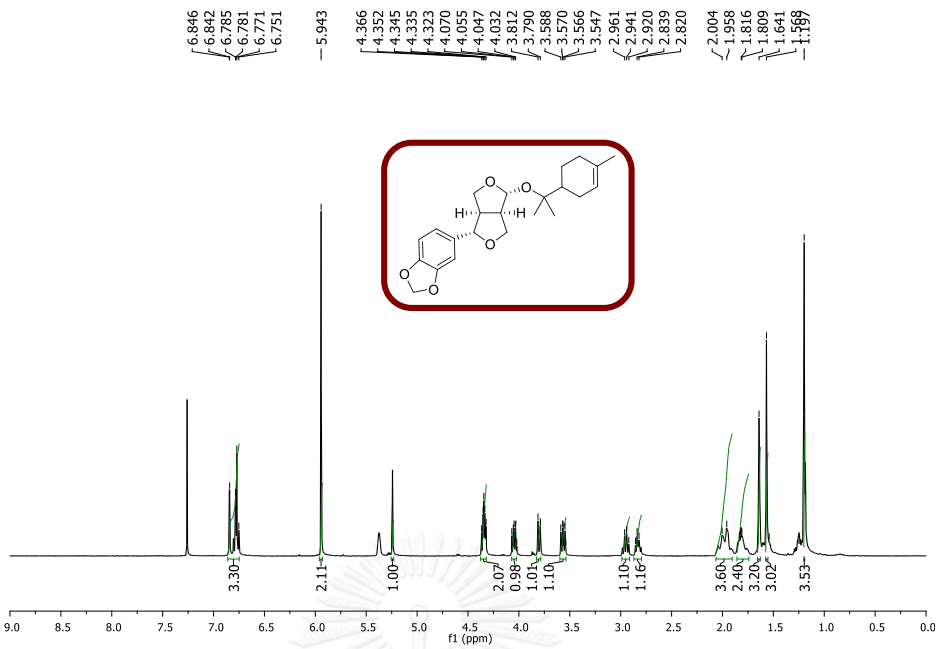

Figure 99. ^{1}H NMR spectrum of compound **3.3l** in $CDCl_3$

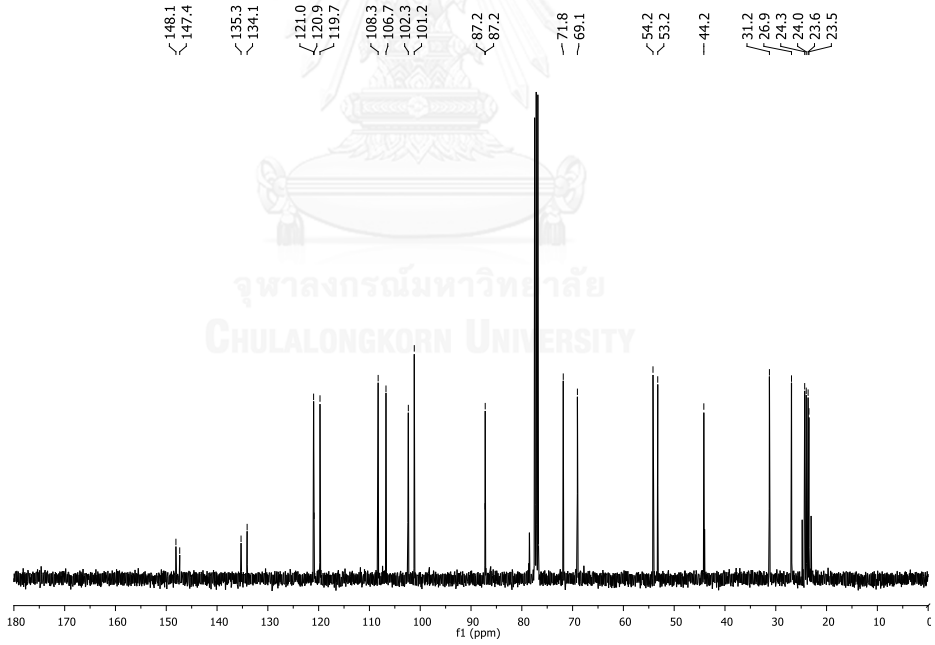

Figure 100. ^{13}C NMR spectrum of compound **3.3l** in $CDCl_3$

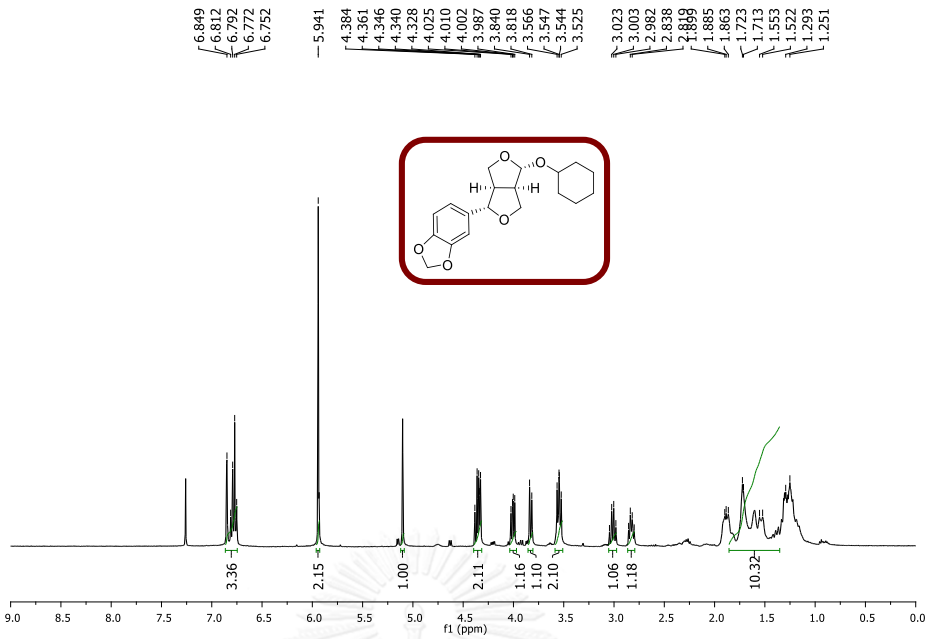

Figure 101. ^{1}H NMR spectrum of compound **3.3J** in $CDCl_3$

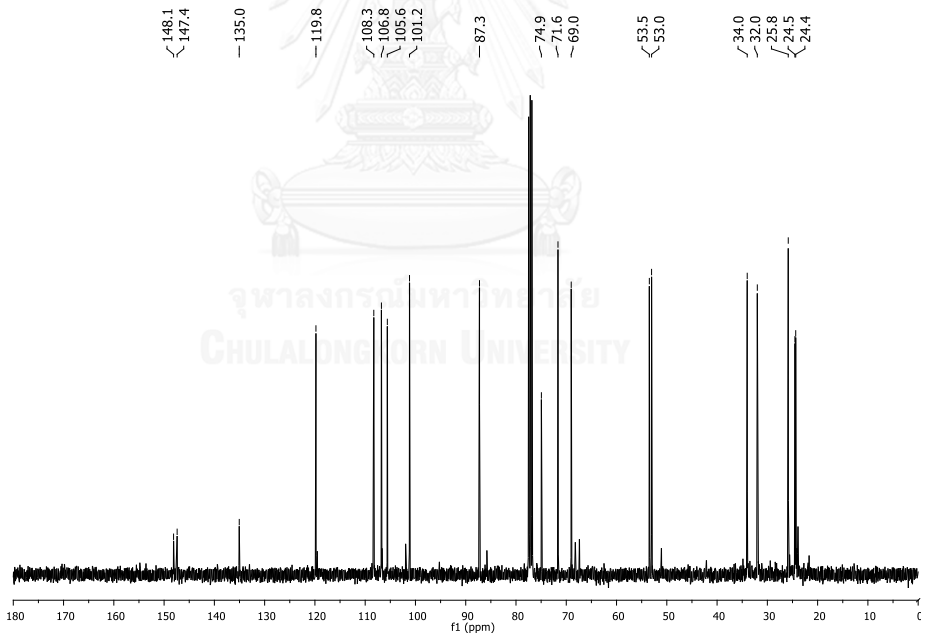

Figure 102. ^{13}C NMR spectrum of compound **3.3J** in $CDCl_3$

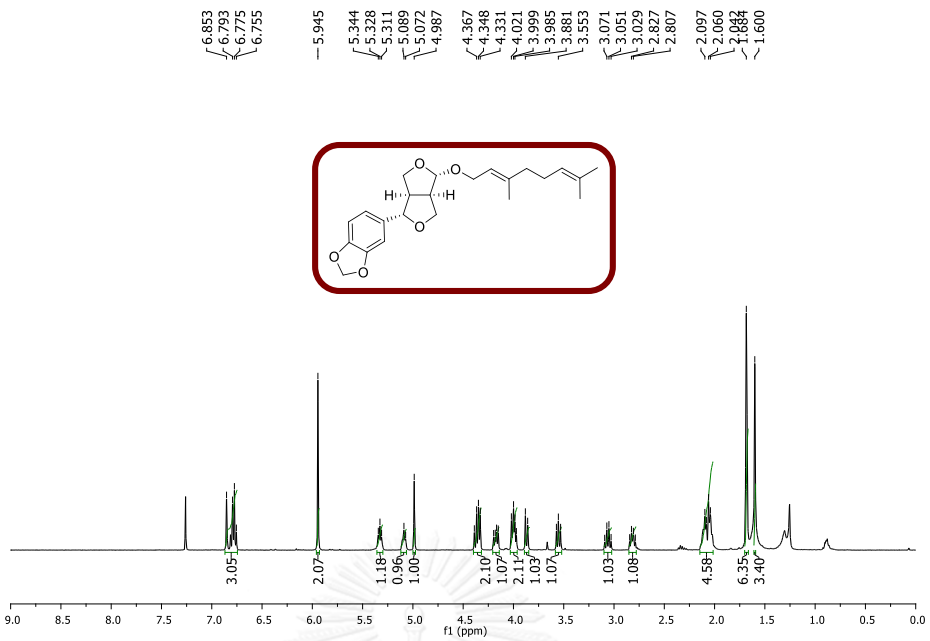

Figure 103. ^{1}H NMR spectrum of compound **3.3K** in $CDCl_3$

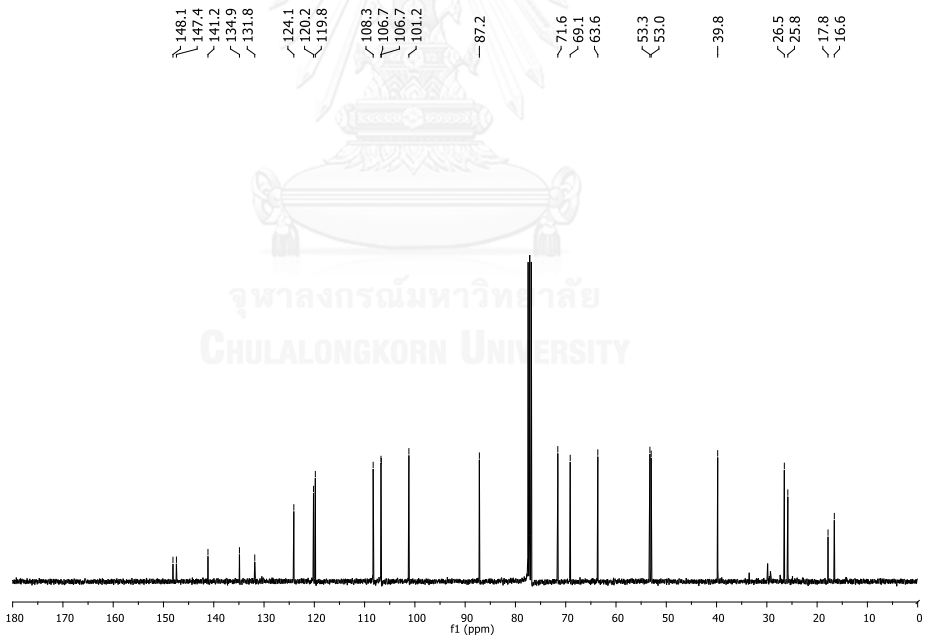

Figure 104. ^{13}C NMR spectrum of compound **3.3K** in $CDCl_3$

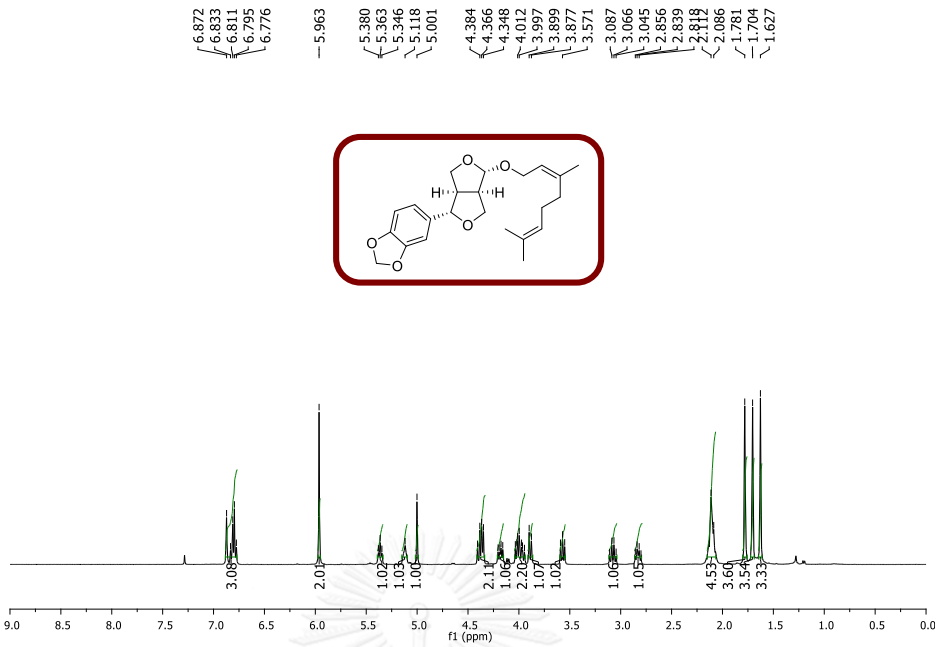

Figure 105. ^{1}H NMR spectrum of compound **3.3L** in $CDCl_3$

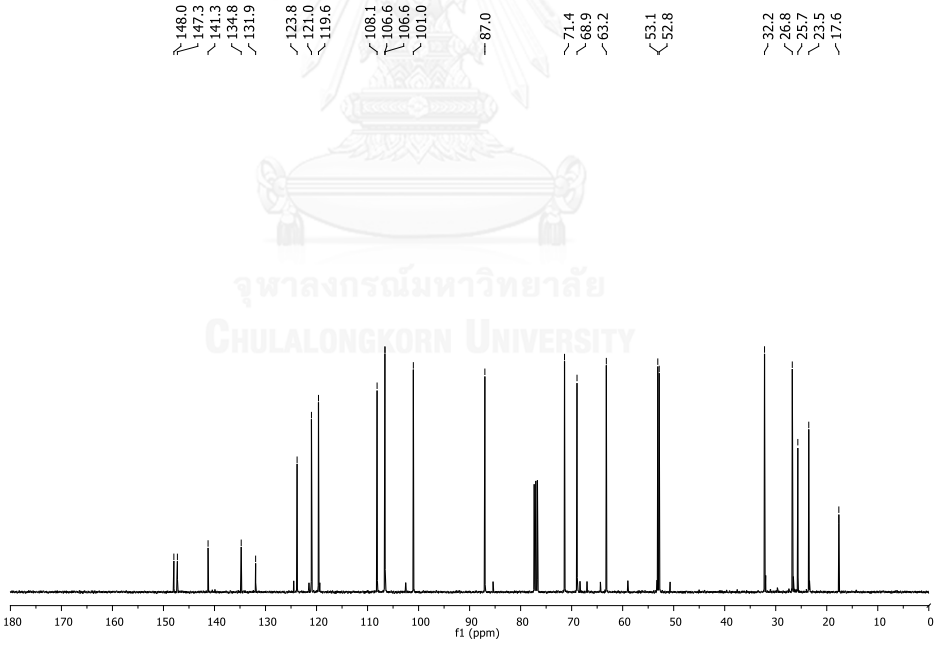

Figure 106. ^{13}C NMR spectrum of compound **3.3L** in $CDCl_3$

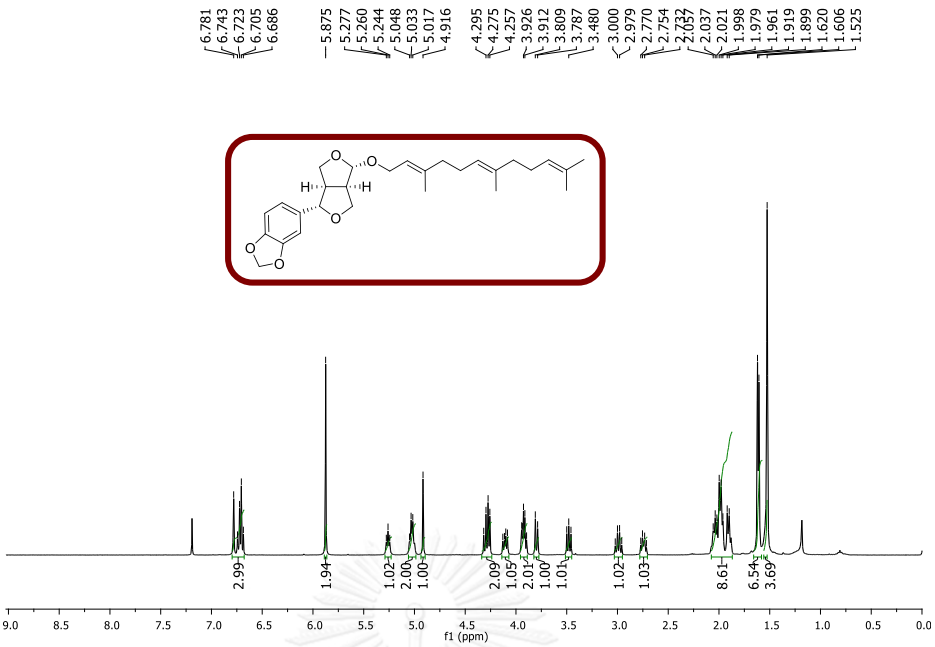

Figure 107. ^{1}H NMR spectrum of compound **3.3M** in $CDCl_3$

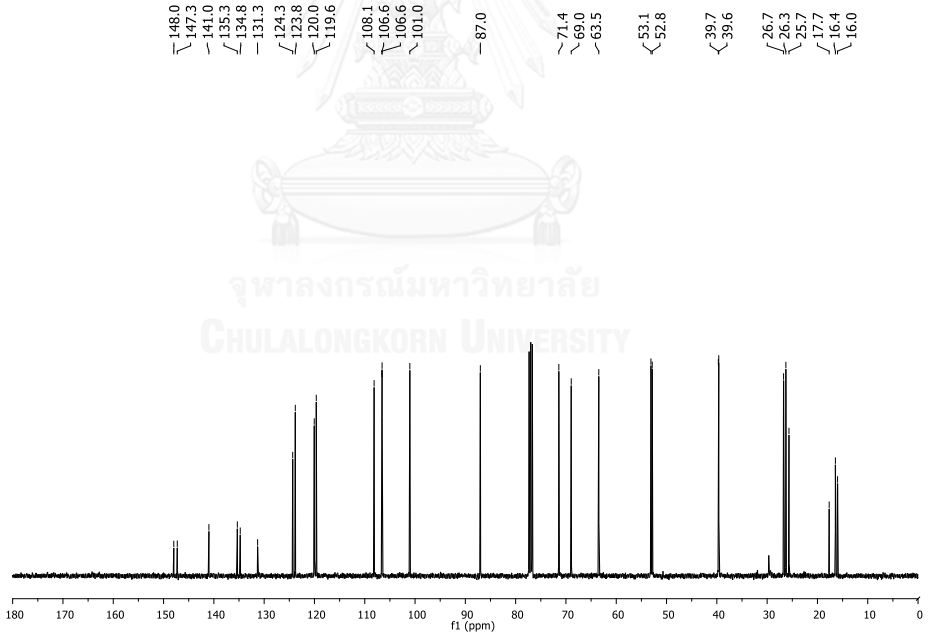

Figure 108. ^{13}C NMR spectrum of compound **3.3M** in $CDCl_3$

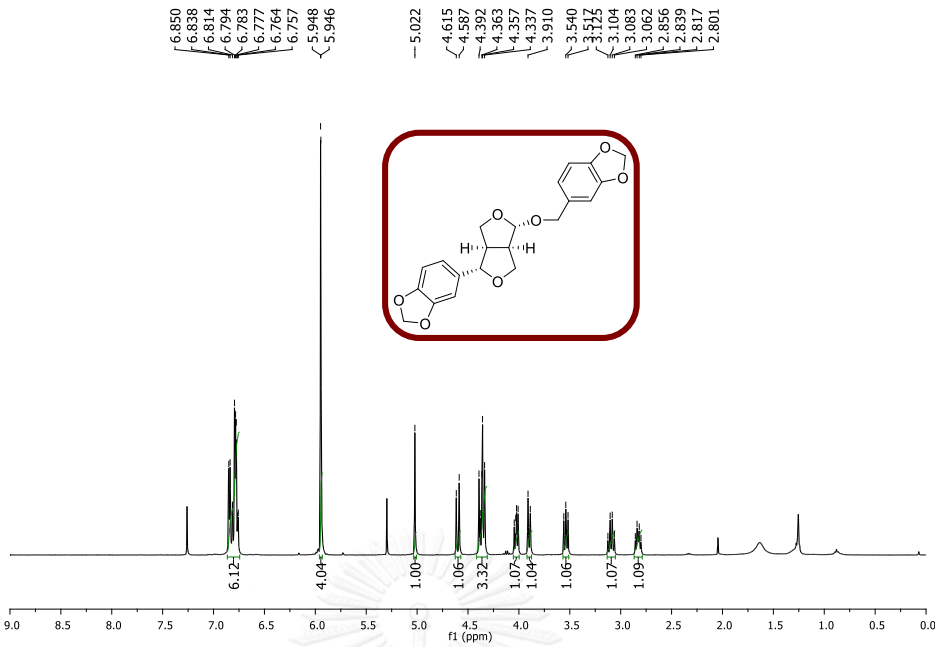

Figure 109. ^{1}H NMR spectrum of compound **3.3N** in $CDCl_3$

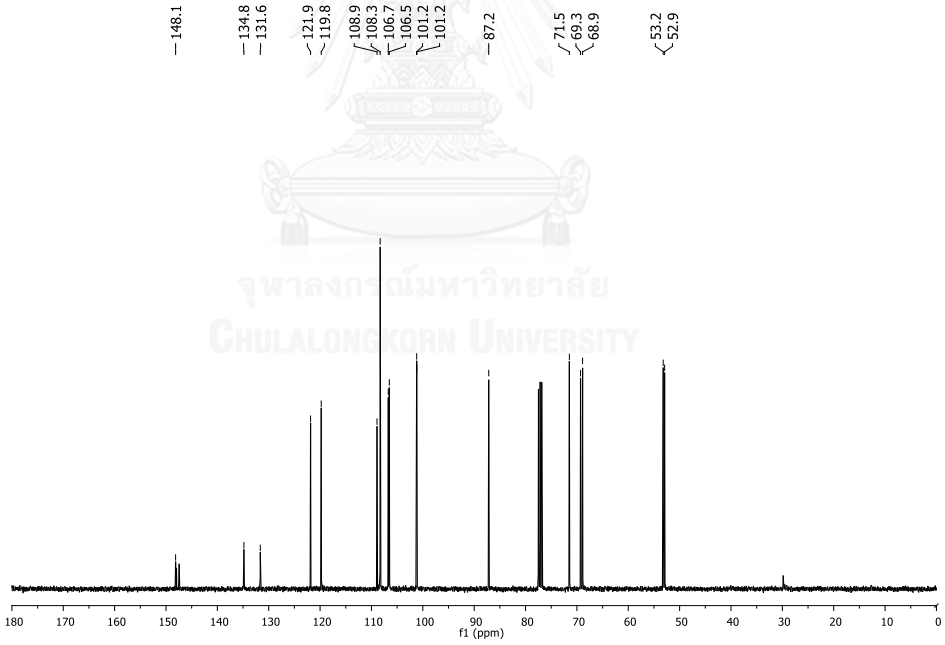

Figure 110. ^{13}C NMR spectrum of compound **3.3N** in $CDCl_3$

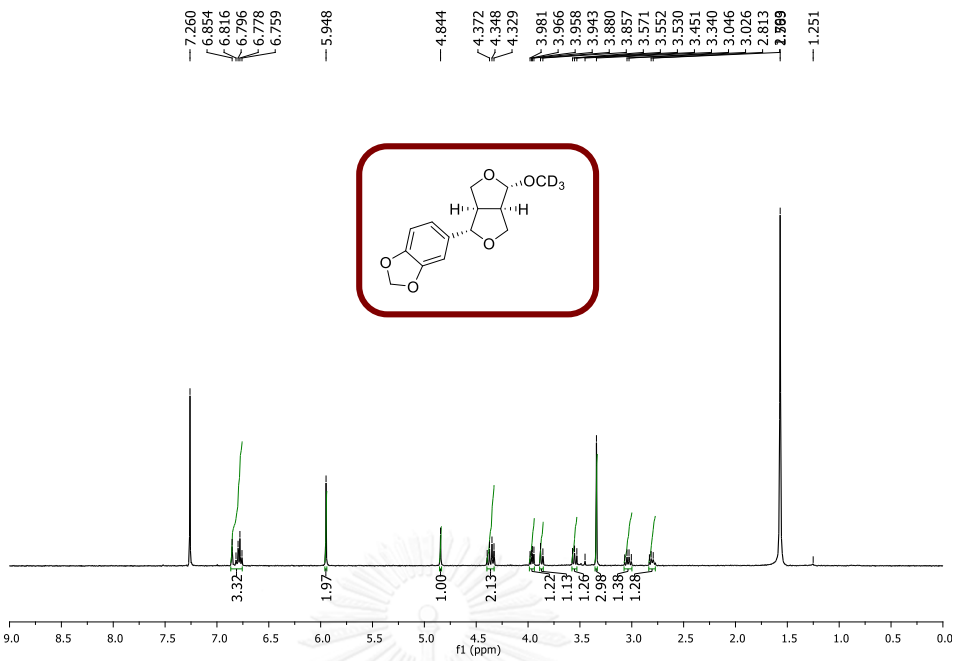

Figure 111. ^{1}H NMR spectrum of compound **4.1** in $CDCl_3$

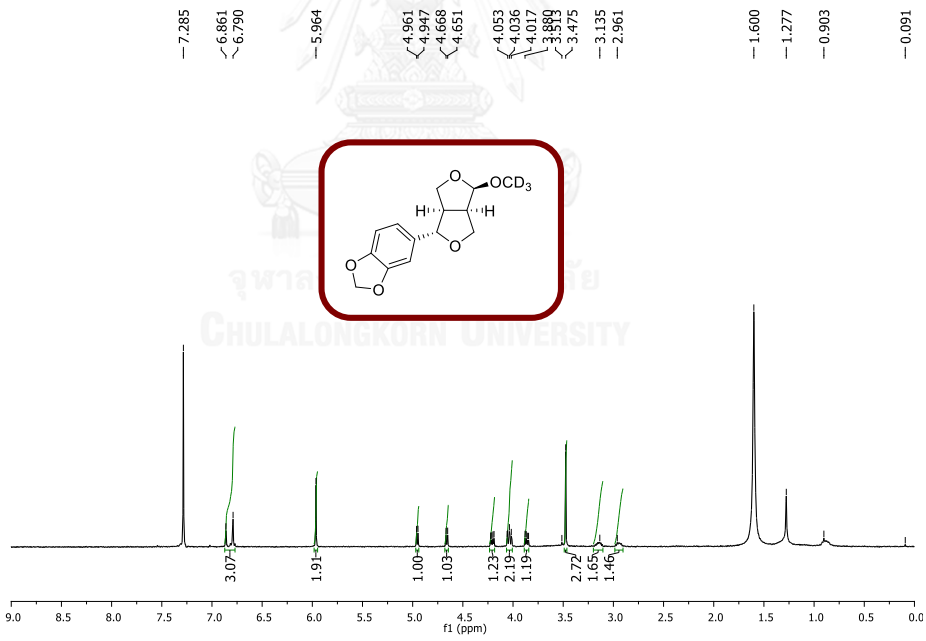

Figure 112. ^{1}H NMR spectrum of compound ***epi*-4.1** in $CDCl_3$

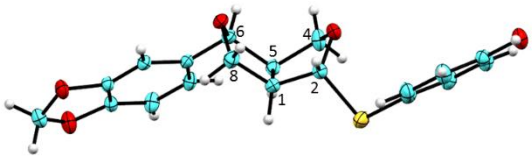

Figure 113. ORTEP plot of **3.2r**

Bond angles of **3.2r**

Number	Atom1	Atom2	Atom3	Angle
1	C2	C1	C8	113.33
2	C4	C5	C6	117.56

Torsion angles of **3.2r**

Atom1	Atom2	Atom3	Atom4	Torsion
H2	C2	C1	H1	-96.14

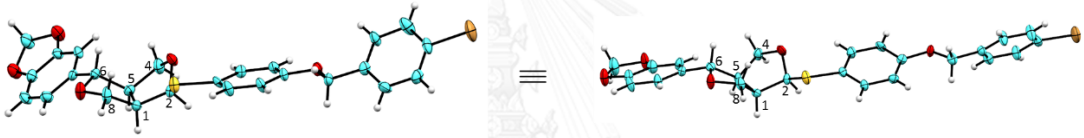

Figure 114. ORTEP plot of *epi*-3.2r-pBBE

Bond angles of ***epi*-3.2r-pBBE**

Number	Atom1	Atom2	Atom3	Angle
1	C2	C1	C8	114.01
2	C4	C5	C6	116.04

Torsion angles of ***epi*-3.2r-pBBE**

Atom1	Atom2	Atom3	Atom4	Torsion
H2	C2	C1	H1	28.01

VITA

Ms. Nantaporn Surachaitanawat was born on May 4, 1992 in Bangkok Thailand. She graduated with Bachelor's degree of Science, major in Chemistry from King Mongkut's University of Technology Thonburi in 2013 under supervised Assoc. Prof. Dr. Ploenpit Boochathum. She continued her master degree at department of chemistry, Chulalongkorn University under supervised Assoc. Prof. Dr. Preecha Phuwapraisirisan.

In the present, she lives with her family, her address is in Thungkru, Bangkok, Thailand.