TOWARDS THE TOTAL SYNTHESIS OF HAPLOMYRTIN

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

By

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WRIGHT STATE UNIVERSITY

SCHOOL OF GRADUATE STUDIES

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Nora E. Hunter ENTITLED Towards the Total Synthesis of Haplomyrtin BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science .

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ABSTRACT

Hunter, Nora E. M.S., Department of Chemistry, Wright State University, 2010. Towards the total synthesis of haplomyrtin.

Haplomyrtin, a 1-aryl-2,3-naphthalide lignan obtained from Turkish *Haplophyllum myrtifolium* and *Haplophyllum telephioides* offers a number of synthetic challenges with the incorporation of two aromatic hydroxyl groups at positions C4 and C7 on the naphthalene ring system and regiospecific condensation of the γ-lactone ring. Improvements towards the total synthesis of haplomyrtin were pursued with commercially available vanillin and piperonal in a total of 8 separate steps. All steps have excellent reproducibility. This strategy includes bromination of protected vanillin to yield 2-(4-(4-methoxybenzyloxy)-2-bromo-5-methoxyphenyl)-1,3-dioxolane and 2-(4-(benzyloxy)-2-bromo-5-methoxyphenyl)-1, 3-dioxolane in 48% and 88% yield respectively, and incorporation of the fully functionalized pendant aryl ring through a lithium-halogen exchange followed by coupling with piperonal. The C4 hydroxyl group is placed by the in-situ formation of an isobenzofuran and subsequent Diels-Alder reaction with DMAD to yield the diester precursor to haplomyrtin, Dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-7-(benzyloxy)-4-hydroxy-6-methoxynaphthalene-2,3-dicarboxylate, in 52% yield.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (CONTINUED)

Page

LIST OF FIGURES

Figure Page

LIST OF FIGURES (CONTINUED)

Figure Page

LIST OF TABLES

Table Page

DEDICATION

I want to thank my parents William and Karen Hunter for the personal sacrifices they made to ensure my education and that of all my siblings. To my father for the strong work ethic he instilled in me through example. To my mother, I thank you for fostering my creativity as a child and being my close friend. My brothers who have taught me many things in ways only brothers can. To my brother William for his perseverance and kindness that has propelled me through the toughest times. Timothy's lightheartedness and laughter made these years a joy. Don's vitality and creativity reminds me to look at each new endeavor with the potential to learn. To my sister and brother-in-law, Alia and Jason, for your support and advice throughout the years. My nephew, Alexander for being a joy to teach and watch grow.

ACKNOWLEDGMENTS

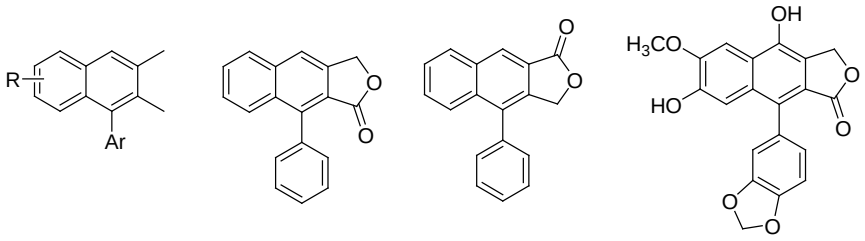
I would like to give special thanks to my mentor Dr. Feld, for the support and guidance he has shown throughout the years. You've given me a lot of freedom to learn and develop my projects and express my creativity in the area of science.

To my committee members, Dr. Fossum and Dr. Turnbull, for your guidance and advice throughout my Masters program I thank you. To the faculty, staff, and students in the Chemistry Department at Wright State University for all the memories. To Dr. Pavel and the officers of Women in Pursuit of Science (past and present) for coming along by my side and helping bring this vision to life. Thank you for helping create a group that has already touched so many in such a positive way.

Lastly, for the members of the WAF group (past and present) for your insight, help, and humor. It has been a pleasure working with you all I wish you the best. Thank you for sharing this experience with me.

INTRODUCTION

Lignans were isolated 400-600 years ago from the root extracts of Podophyllum perennials. They were used medicinally by both natives of the Himalayas and what is now Maine as a carthartic, poison, and suicide agent.[1,2] Early phytochemical studies linked lignans to their use in the treatment of venomous snake bites, arthritis, and gastric ulcers. They are currently known to exhibit a broad range of biological activities that includes antimicrobial, antiviral, enzyme inhibitory, and antimitotic capabilities.[1,3, 4]



1 **2** **3** **4**

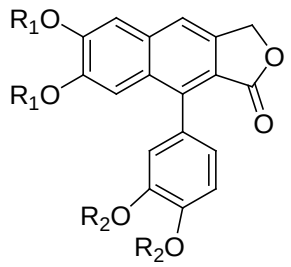
The arylnaphthalene lignan subgroup has been identified as constituents of bark and plants used in folkloric medicine. Arylnaphthalene lignans have the core structure **1** and appear 90% of the time in the form **3**. The retro lactone **2** is less commonly found in nature.[5] Haplomyrtin **4**, a 1-aryl-2,3-naphthalide lignan obtained from Turkish *Haplophyllum myrtifolium* and *Haplophyllum telephioides*[6] offers a number of synthetic challenges with the incorporation of two aromatic hydroxyl groups at positions 4 and 7 on the naphthalene ring system and regiospecific condensation of the γ-lactone ring.[7] Investigating the use of 4-methoxybenzyl bromide as a protecting group, addressing the instability of the coupling product and the poor yield of the Diels-Alder reaction product are the goals of this project.

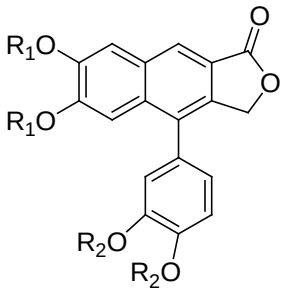
HISTORICAL

Syntheses of the arylnaphthalene ring system

The arylnaphthalene ring system has been the focus of several studies over the years. These lignans have no stereocenters but may exist as atropisomers, meaning they are chiral, existing in one enantiomeric form due to the hindered rotation around a carbon-carbon bond of the phenyl-naphthalene bond.[7]

Flanagan, et al. at The University of Southampton developed a new benzannulation reaction to allow the multiple parallel syntheses of six arylnaphthalene lignans.[8] Their approach, using a tandem Horner-Emmons-Claisen condensation sequence, has allowed the synthesis of Justicidin B **5** and the following arylnaphthalene derivatives Taiwan C **6**, and Chinensin **7** as well as their retrolactones Retrojusticidin B **8**, Justicidin E **9**, and Retrochinensin **10**.

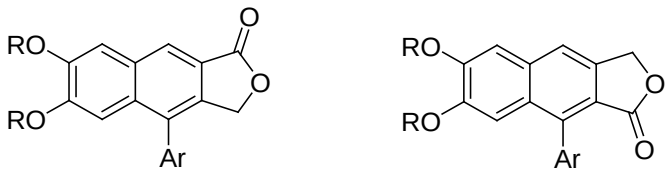




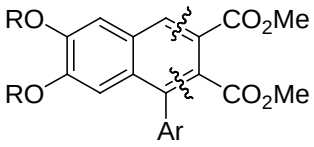
Natural Product	R^1	R^2
5) Justicidin B	Me	$(-CH_2-)$
6) Taiwanin C	$(-CH_2-)$	
7) Chinensin	$(-CH_2-)$	Me

Natural Product	R^1	R^2
8) Retrojusticidin B	Me	$(-CH_2-)$
9) Justicidin E	$(-CH_2-)$	
10) Retrochinensin	$(-CH_2-)$	Me

Construction of the arylnaphthalene core was accomplished via diester **13** resulting from the condensation of a ketoaldehyde **14** and a succinate derivative such as **15-17**.



11 **12**



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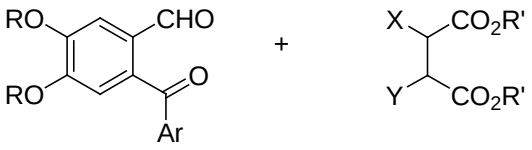
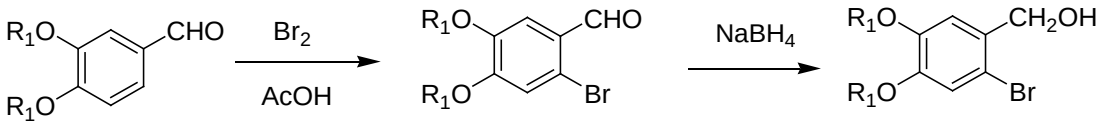


14

15) X=Y=H
16) X=Y= CO_2H
17) X=Y=$PO(OR')_2$

The ketoaldehydes **14** were synthesized in four steps. Veratraldehyde **18a** was used as the starting material for the synthesis of lignans **5** and **8** and commercially available piperonal **18b** was used for the synthesis of lignans **6**, **7**, **9**, and **10**. Aldehydes **18a-b** were brominated at position six using Br_2 and acetic acid. Each aldehyde was then reduced with sodium borohydride to produce the alcohols **20a-b**. Diols **21a-b** were

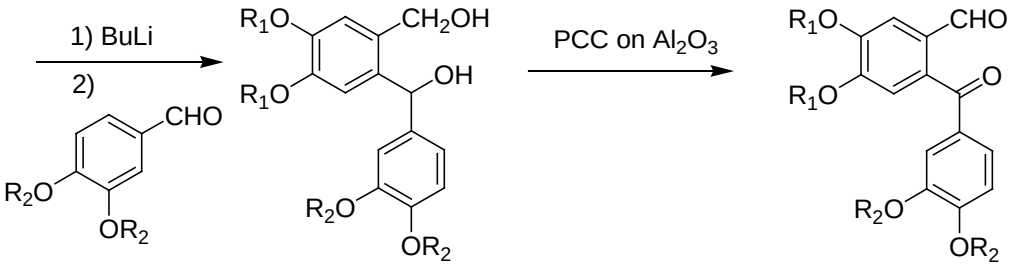
generated by a lithium-halogen exchange on **20a-b** followed by coupling with aldehydes **18a-b**. Oxidation of **21a-b** with PCC on Al_2O_3 provided ketoaldehydes **22a-b**.



18a) R_1= Me
18b) R_1=CH_2

19a) R_1= Me (80%)
19b) R_1= CH_2 (86%)

20a) R_1= Me (86%)
20b) R_1= CH_2 (89%)

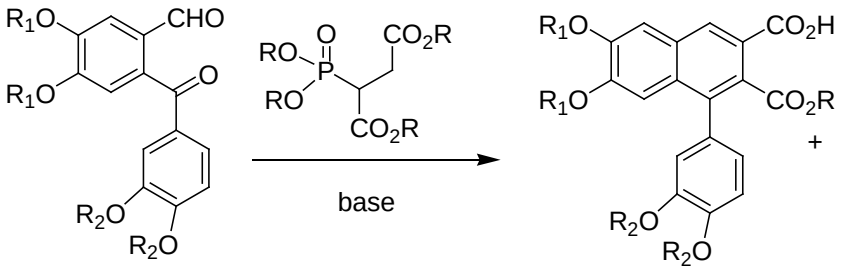


18a) R_2= Me
18b) R_2=CH_2

21a) R_1=Me R_2=CH_2 (69%)
21b) R_1= CH_2 R_2=Me (81%)

22a) R_1=Me R_2=CH_2 (61%)
22b) R_1= CH_2 R_2=Me (75%)

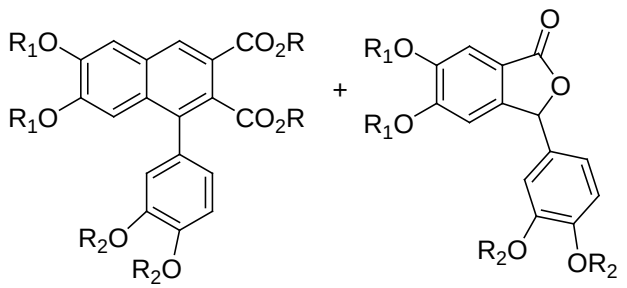
The naphthalene ring was formed via a tandem Horner-Emmons-Claisen condensation sequence. The condensation products included the acid-esters **25a-c** and the diesters **26a-f** as well as intramolecular Cannizzaro lactones **27a-c**. Solvent and base were modified to determine if the desired aromatic annulations product yields could be increased (**Table 1**).



23
a) R_1=Me, R_2=CH_2
b) R_1=R_2=CH_2
c) R_1= CH_2, R_2=Me

24
a) R=Me
b) R=Et

25
a) R_1=Me,R_2=CH_2,R=Et
b) R_1=R_2=CH_2, R=Et
c) R_1= CH_2,R_2=Me, R=Et
d) R_1=R=Me, R_2= CH_2
e) R_1=R_2=CH_2, R=Me



26

a) R_1=Me, R_2=CH_2,R=Et
b) R_1=R_2=CH_2, R=Et
c) R_1= CH_2,R_2=Me, R=Et
d) R_1=R=Me, R_2= CH_2
e) R_1=R_2=CH_2, R=Me
f) R_1= CH_2, R_2=R=Me

27

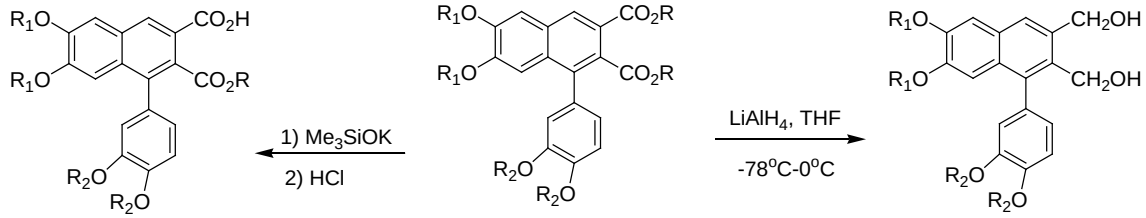
a) R_1=Me, R_2=CH_2
b) R_1=R_2=CH_2
c) R_1= CH_2, R_2=Me

Table 1. Conditions of Tandem Horner-Emmons-Claisen condensation.

Ketoaldehyde	Phosphate	Reaction Conditions	Yields
23a	**24a**	NaOMe, MeOH, THF, 0°C, 3 h	**26d** (56%), **25d** (15%), **27a** (11%)
		DBU, LiCl, MeCN, rt., 16 h	**26d** (70%)
	24b	NaOEt, EtOH, THF, 0°C, 5 h	**26a** (68%), **25a** (5%)
23b	**24a**	NaOMe, MeOH, THF, 0°C, 3 h	**26e** (84%), **25e** (5%), **27b** (4%)
		DBU, LiCl, MeCN, rt., 16 h	**26e** (60%)
	24b	NaOEt, EtOH, THF, 0°C, 3 h	**26b** (67%), **25b** (3%), **27b** (5%)
23c	**24a**	NaOMe, MeOH, THF, 0°C, 3 h	**26f** (65%)
		DBU, LiCl, MeCN, rt., 16 h	**26f** (49%)
	24b	NaOEt, EtOH, THF, 0°C, 2 h	**26c** (46%), **25c** (19%), **27c** (9%)

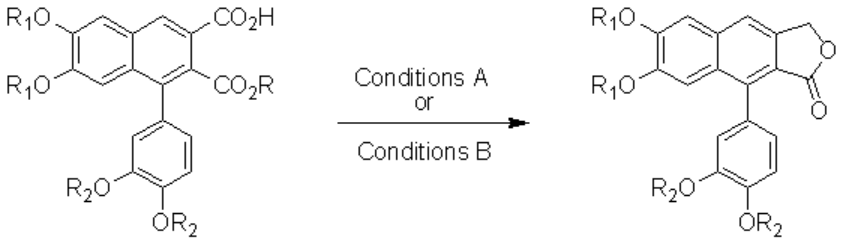
Once the arylnaphthalene cores **26a-f** were prepared, Flanagan followed a method developed by Padwa, et al.[9,10,11,12] to generate the natural products. The lactone core was produced by saponification of the diesters **26a-c** with potassium trimethylsilanoate to produce the corresponding half acids **25a-c.** Subsequently, **25a-c** were reduced with borane dimethyl sulfide to yield natural products **5-7**. The corresponding retrolactone

core was produced via deprotonation of the half acids **25a-c** with sodium hydride, reduction of the acid function with lithium borohydride, and acid mediated lactonisation (Conditions A and B, **Table 2**). The corresponding retrolactones were also achieved by reduction of the diesters **26a-f** with $LiAlH_4$ to the corresponding diols **28a-c** and subsequent oxidation of the less hindered alcohol followed by condensation to afford the less hindered retrolactone in the natural products **8-10** using either manganese(IV) oxide or barium manganate(VI) (Conditions C and D, Table 2). Product yields were reported to be higher with $BaMnO_4$, although the presence of the regioisomeric lactones was significant.



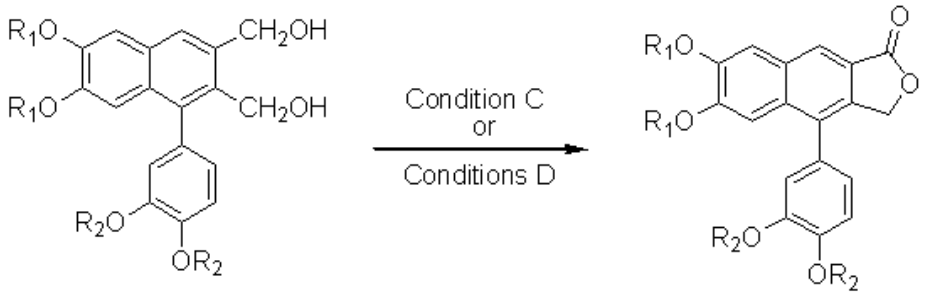
25 **26 a-f** **28**

a) R_1=Me, R_2=CH_2,R=Et (93%) **a)** R_1=Me, R_2=CH_2 (75%)
b) R_1=R_2=CH_2, R=Et (98%) **b)** R_1=R_2=CH_2 (83%)
c) R_1= CH_2, R_2=Me, R=Et (97%) **c)** R_1= CH_2, R_2=Me (74%)



25a-c

Natural Product	R^1	R^2
5) Justicidin B	Me	(-CH_2-)
6) Taiwanin C	(-CH_2-)	
7) Chinensin	(-CH_2-)	Me



28a-c

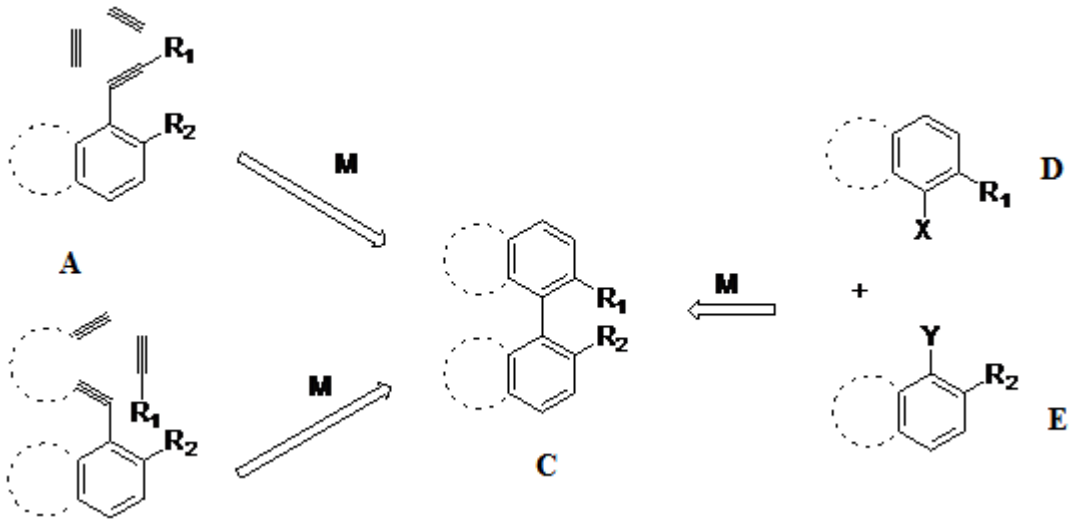
	Natural Product	R^1	R^2
8)	Retrojusticidin B	Me	($-CH_2-$)
9)	Justicidin E	($-CH_2-$)	
10)	Retrochinensin	($-CH_2-$)	Me

Table 2. Conditions and yields for the conversion of **26a-f** to natural products **5-10**.

Condition A with **25**	Yield (%)	Condition C with **28**	Yield (%)
A	**5** (97%)	**A**	**8** (34%)
B	**6** (87%)	**B**	**9** (59%)
C	**7** (97%)	**C**	**10** (91%)
Condition B with **25**	Yield (%)	Condition D with **28**	Yield (%)
a	**8** (67%) +**5** (28%)	**A**	**5** (12%) + **8** (86%)
B	**9** (57%)	**B**	**6** (14%) + **9** (71%)
C	**10** (72%)	**C**	**7** (19%) + **10** (80%)

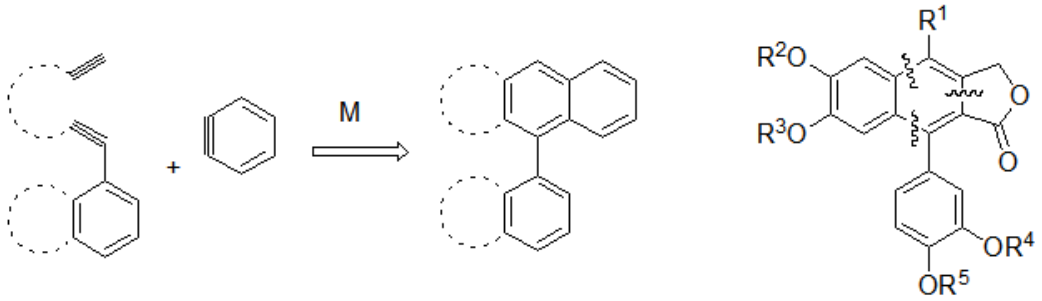
A: BH_3, SMe_2, HCl; B: NaH, $LiBH_4$, HCl; C: MnO_2, DCM, rt.; D: $BaMnO_4$, DCM, rt.

It is known that biaryl molecules like **C** can be synthesized using aryl-aryl coupling reactions using molecules like **D** and **E**. The utilization of transition metal (**M**) catalyzed [2+2+2] cocyclization was also developed to obtain biaryl molecules **C**.[13,14] The synthetic advances of Sato, et al. in 1994[15] provided a new method of constructing biaryl compounds like **C** using a Ni^0- catalyzed [2+2+2] cocyclization of compounds like **A** and two molecules of acetylene or from diynes like **B** and one molecule of acetylene.

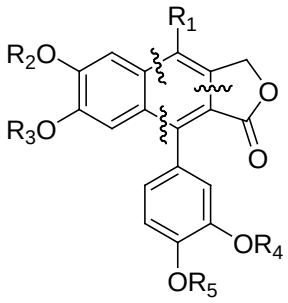


B (R_1=H)

In 2004, Sato, et al.[16] accessed the arylnaphthalene core **H** using a Pd^0- catalyzed [2+2+2] cocyclization of diynes like **F** and arynes **G**. This method also allowed for the incorporation of a hydroxyl group at the C7 position R_1 on the arylnaphthalene lignan core **I** within a few steps using three C-C bond-forming reactions. By utilizing the appropriate arynes and diynes, Sato accomplished the convergent synthesis of Tawanin C **6**, and Tawanin E **29** in 9 and 10 steps respectively, and established the sequence of steps for the synthesis of Chinensin **7**, Justicidin B **5**, and Diphyllin **30**.



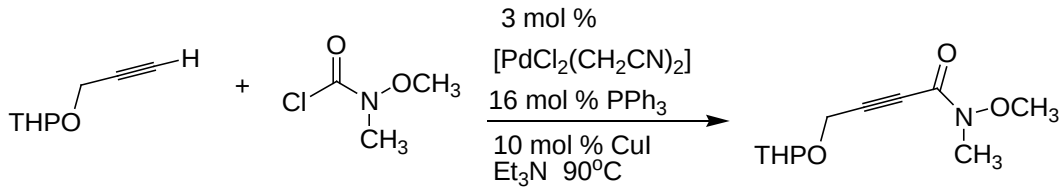
F aryne **G** arylnaphthalene derivative **H** **I**



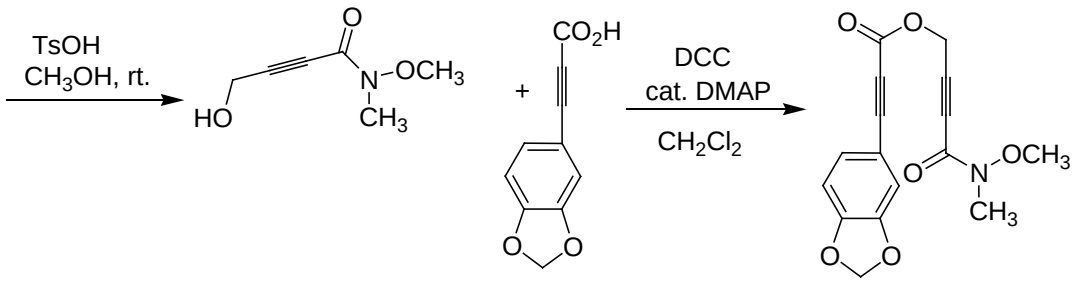
I

Natural Product	R_1	R_2/R_3	R_4/R_5
7) Chinensin	H	$-CH_2-$	CH_3
5) Justicidin B	H	CH_3	$-CH_2-$
30) Diphyllin	OH	CH_3	$-CH_2-$
6) Tawanin C	H	$-CH_2-$	$-CH_2-$
29) Tawanin E	OH	$-CH_2-$	$-CH_2-$

Construction of the Taiwanins began with the synthesis of the diyne and benzyne substrates. Diyne **31** was prepared bearing an N-methoxy-N-methylcarboxamide moiety (Weinreb amide) by DCC-mediated esterification of carboxylic acid **32** with the corresponding propargylic alcohol **33** containing the Weinreb amide moiety. Propargylic alcohol **33** was prepared by the Pd-catalyzed coupling of **34** and **35** with subsequent cleavage of the THP protecting group in **36**. Integration of the Weinreb amide into diyne **31** allows for the later installation of the C7 hydroxyl group.

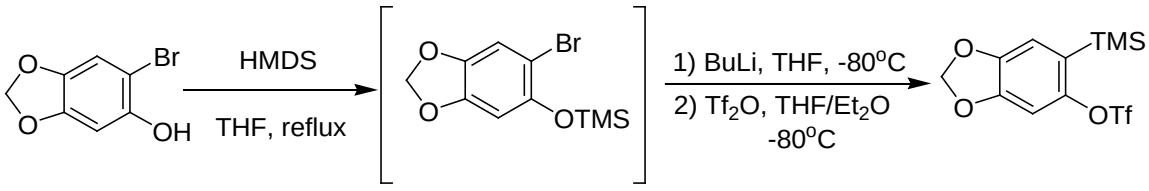


34 **35** **36** (60%)



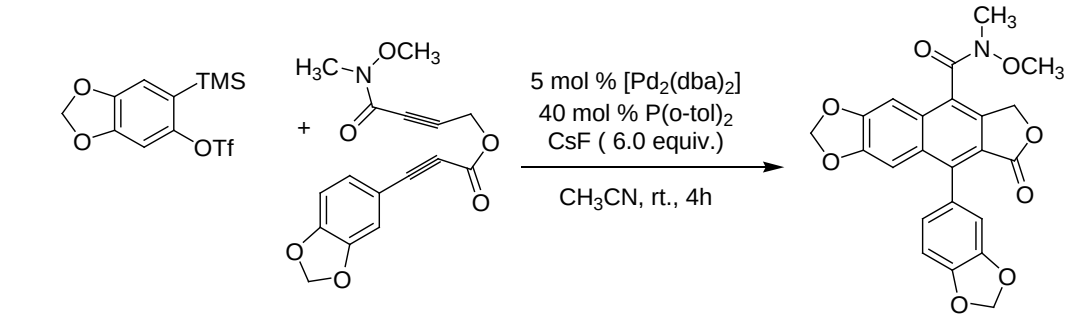
33 (86%) **32** **31** (86%)

Benzyne precursor **39** was prepared by the reaction of **37** with hexamethyldisilazane (HMDS) resulting in the TMS ether **38**. Subsequently, **38** was reacted with BuLi and the resulting silyl-migration product was treated with Tf_2O to give **39** in 83% yield over three steps.

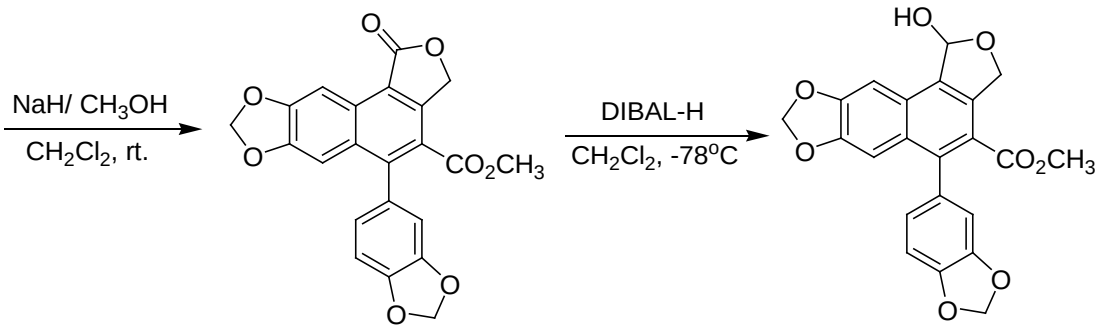


37 **38** **39** (83%)

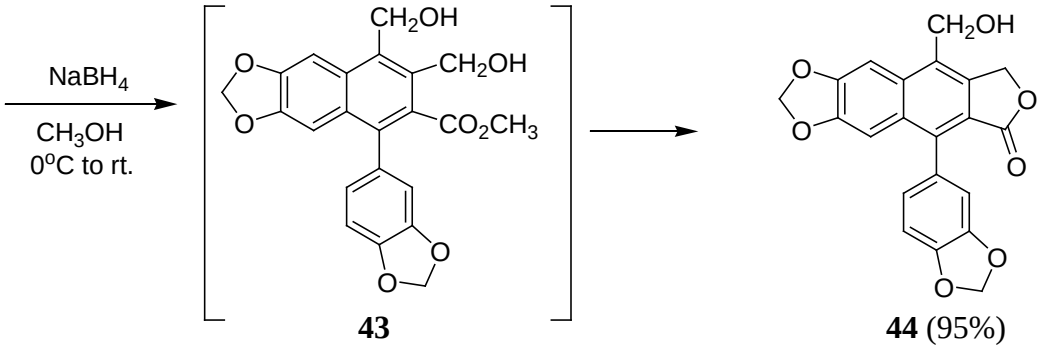
The Taiwanin core **40** was constructed by Pd^0- catalyzed [2+2+2] cocyclization of diynes **31** and the benzyne precursor **37**. Conversion of **40** to both Taiwanin C and E began with the ring opening of **40** with sodium methoxide in dichloromethane at room temperature followed by rearrangement to the lactone ester **41**. The chemoselective reduction of **41** with DIBAL-H produced the lactol **42.** Treatment of **42** with sodium borohydride produced the alcohol lactone **44**. Oxidation of **44** with PCC produced the aldehyde **45**. Taiwanin E **46** was obtained via a Baeyer-Villager oxidation of **45** with MCPBA with subsequent hydrolysis of the formate. Taiwanin C **6** was obtained via a decarbonylation reaction with the Wilkinson catalyst.



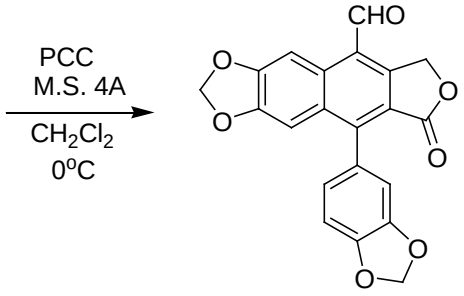
39 **31** **40** (61%)



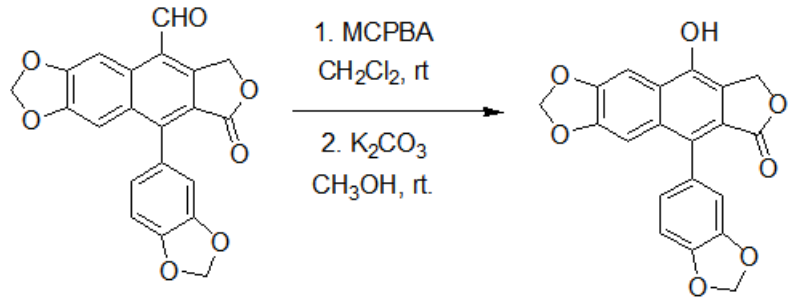
41(78%) **42** (63%)



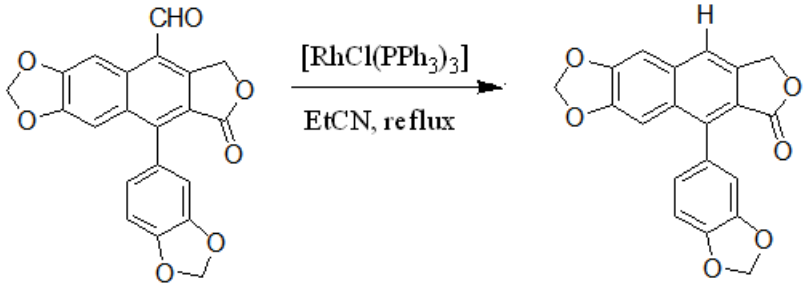
43 **44** (95%)



45 (89%)

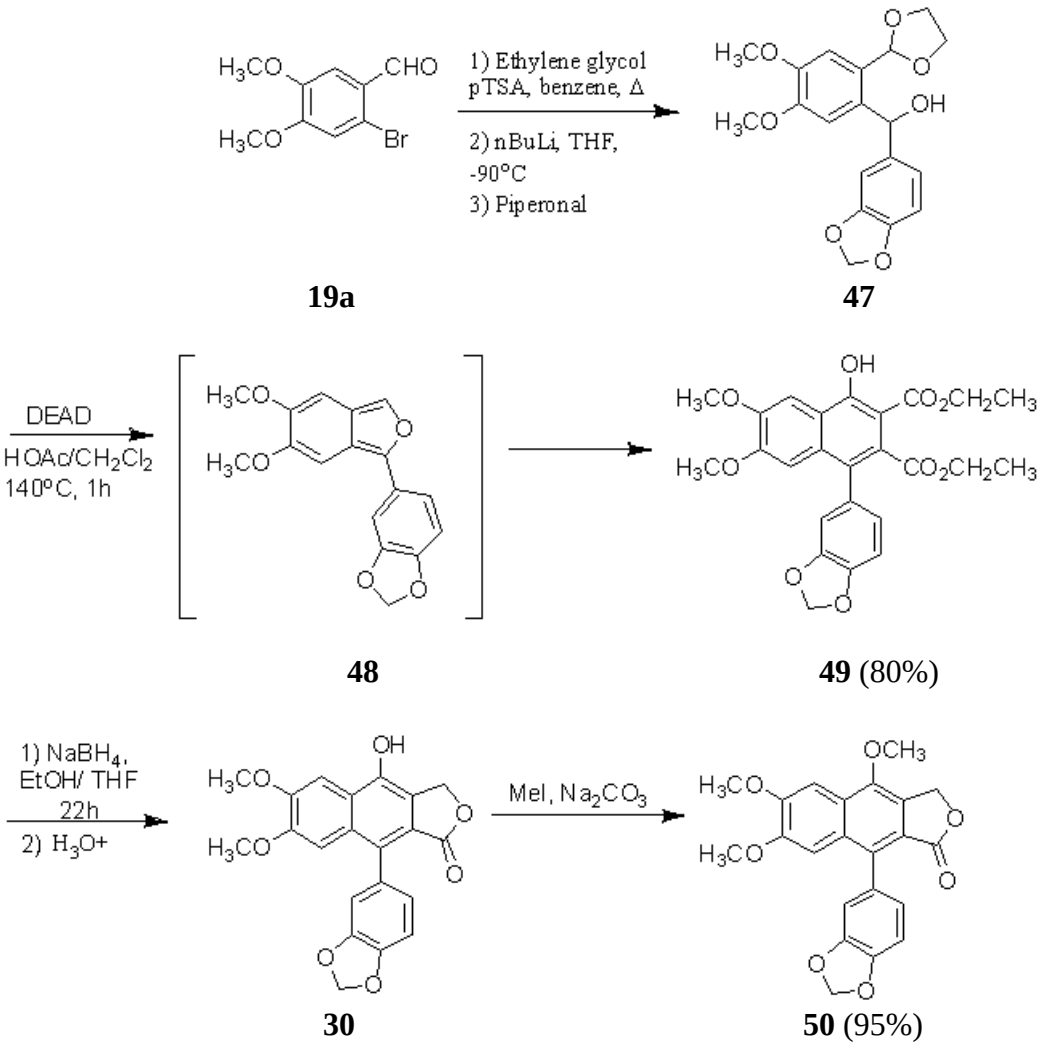


45 **46** (88%)



45 **6** (64%)

Formation of the B ring in the arylnaphthalene lignan core has been achieved through a Diels-Alder reaction of an isobenzofuran and diethyl acetylenedicarboxylate (DEAD) as reported by Charlton, et al. in 1996.[17] Justicidin A **52** was synthesized from commercially available **19a** and piperonal **18b**. The hydroxy acetal **47** was formed using the method reported by Keay, et al.[18] The aldehyde **19a** was initially protected by refluxing with ethylene glycol and pTSA in benzene under a dean stark trap to afford the bromoacetal. Lithium-halogen exchange of the bromo acetal was accomplished in dry THF at -78°C with nBuLi, followed by coupling with piperonal **18b** to afford **47**. The hydroxy acetal **47** was unstable; therefore, it was directly dissolved in acetic acid/ methylene chloride to form an isobenzofuran **48** *in situ*. The isobenzofuran was used in the Diels-Alder reaction with DEAD to produce **49** in 80% yield. Reduction of the diester with sodium borohydride formed the lactone moiety and the natural product diphyllin **30**. Methylation of the phenol produced Justicidin A **50** in 95% yield.

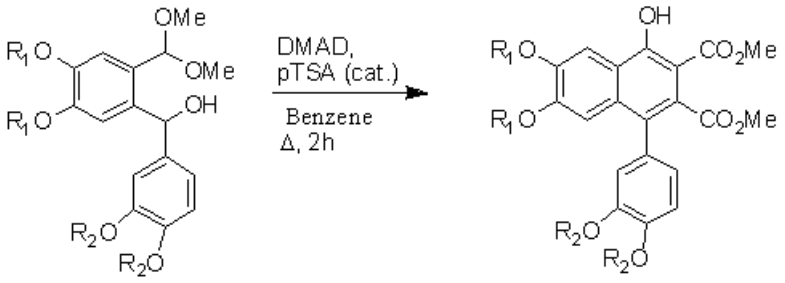


19a **47**

48 **49** (80%)

30 **50** (95%)

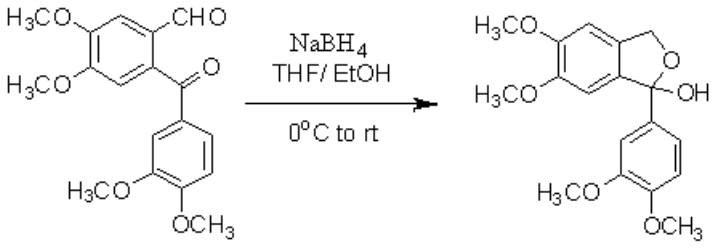
A similar Diels-Alder reaction involving an isobenzofuran and dimethyl acetylenedicarboxylate (DMAD) was utilized by Plaumann[19] and Patil, et al.[20] to form the B ring of the arylnaphthalene lignan core. In the synthesis of the 1-arylnaphthalene lignan precursor of Tawainin E **29** and Diphyllin **30**, Plaumann achieved the isobenzofuran from the crude hydroxyl acetals **51a-b** by refluxing in benzene in the presence of a trace amount of pTSA. The Diels-Alder reaction produced the diester **52a** in 65% yield and **52b** in comparable yield.



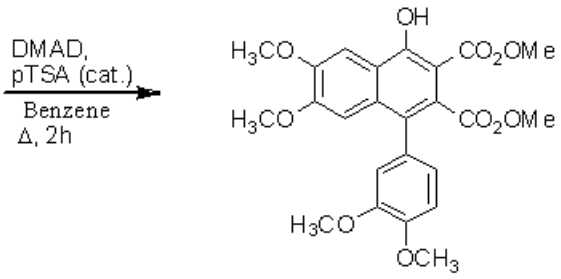
51
a) R_1= OMe
b) R_2= CH_2

52
a) R_1= OMe (65%)
b) R_2= CH_2

Patil, et al.[20] achieved the isobenzofuran from a 1-hydroxy-1-arylnaphthalan **54**. The o-formylbenzophenone **53** was obtained by hydrolysis of the corresponding keto-acetal. Selective reduction of **53** with sodium borohydride afforded the 1-hydroxy-1-arylphthalan **54**. Compound **54** was dissolved in benzene in the presence of pTSA and utilized immediately in the Diels-Alder reaction with DMAD to afford the diester **55** in 60% yield.



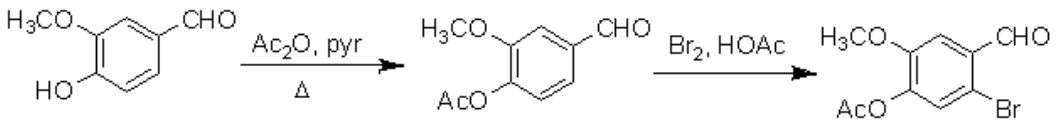
53 **54**



55 (60 %)

Progress towards Haplomyrtin at Wright State

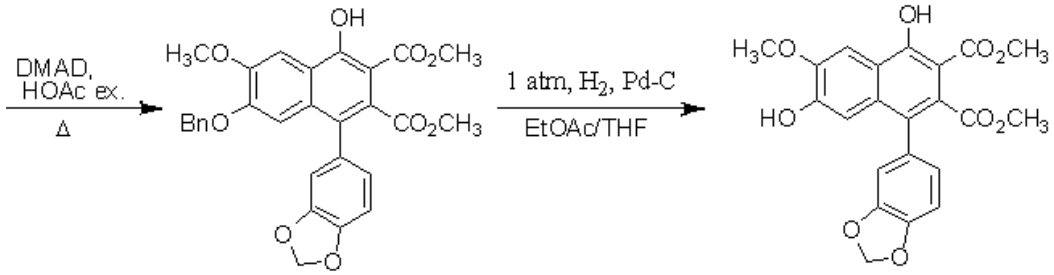
Significant progress has been made locally towards the total synthesis of haplomyrtin **4**. A synthetic route to build the arylnaphthalene lignan core system of haplomyrtin **4** starting from commercially available vanillin **56** was reported by Gilmore[5] in 1996. In order to brominate vanillin **56** para to the methoxy group, the phenol function needed to be deactivated. Vanillin **56** was acetylated using acetic anhydride in pyridine to afford the acetoxy compound **57** in 85% yield. Bromination with Br_2 and acetic acid followed by deprotection gave brominated vanillin **59** in 40% yield in two steps. The brominated product was benzylated to afford **60** in 97% yield. Acetal halogen-lithium exchange on **61** with nBuLi in THF followed by coupling with piperonal afforded the secondary alcohol **62** in 66% yield. Product **62** was dissolved in acetic acid with DMAD and the solution was refluxed to afford the diester Diels-Alder product **63** in 74% yield. Hydrolysis of the benzyl group afforded the diol **64** in 81% yield. Reduction of the ester which is ortho to the C4 phenolic function in **64** led to the in-situ formation of a lactone potentially **65**. The product was similar to **4** but was thought to retain boron moieties possibly on the C 4 and/or C7 hydroxyl groups. This synthesis allowed for the arylnaphthalene lignan core of haplomyrtin to be obtained. The shortcomings to this sequence were 1) the overall number of steps, 2) the overall poor yield of the first five steps – 31%, 3) the repeated use of protection and deprotection reactions, 4) the lack of purification of haplomyrtin, and 5) the difficulty of purifying **63**.



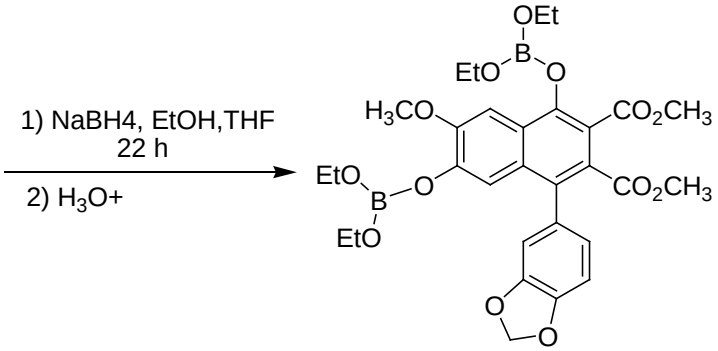
56 **57**(85%) **58** (48%)

59 (84%) **60** (97%)

61 (97%) **62** (66%)



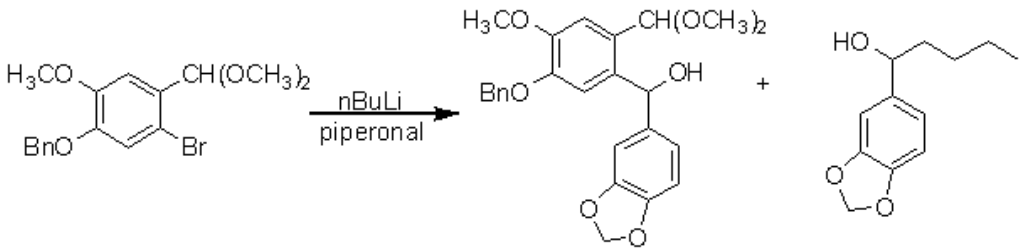
63 (74%) **64** (81%)



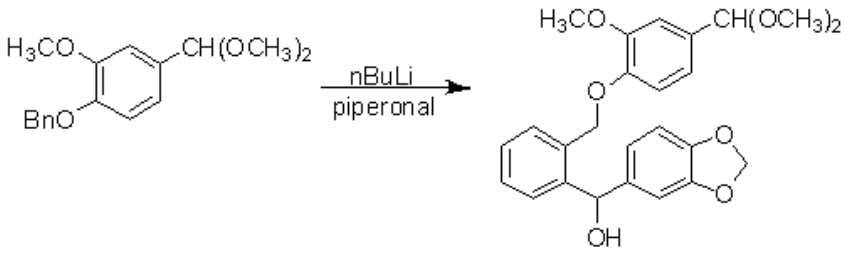
65 (85%)

Later, Schaaf[21] explored the halogen-metal exchange reaction as well as reducing the overall number of steps in the synthesis. In the halogen-lithium exchange and coupling step with **61**, a mixture of products was produced which included **62** and **66,** produced by the alkylation of piperonal by butyl lithium. Schaaf also attempted to directly form a lithium salt from the non-brominated compound **67**. It was found that

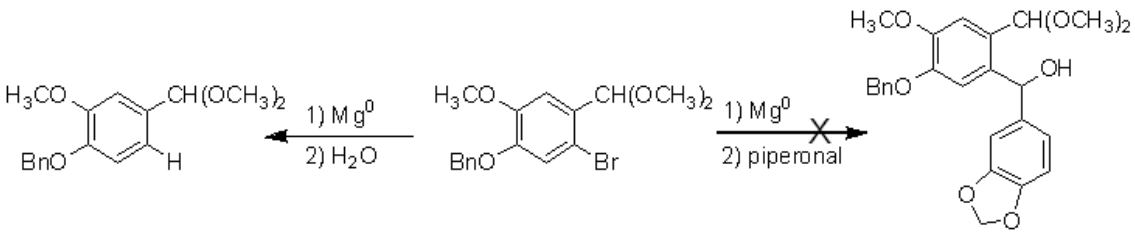
deprotonation of the aromatic hydrogens of the benzyl group occurred and coupling with piperonal was proposed to give rise to **68**. An attempt was made to convert the bromo acetal **61** into a Grignard reagent and perform a coupling with piperonal to obtain **62**. The reaction did not yield **62**. To determine the efficiency of the Grignard reaction, **61** was treated with magnesium and quenched with water to yield **67**. Clearly the Grignard product was being formed but was unable to couple with piperonal. It was proposed that the steric hindrance that the dimethoxy acetal groups imposed on the ortho position of the ring hinder the coupling with piperonal. Schaaf then removed the acetylation and deacetylation steps from the overall route by directly protecting vanillin **56** with benzyl chloride followed by bromination to yield **60**.



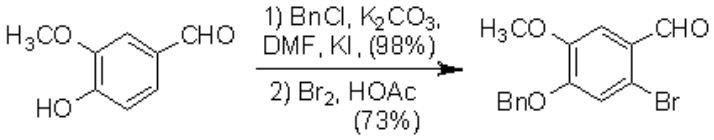
61 **62** **66**



67 **68**

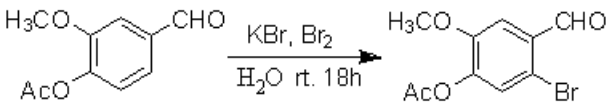


67 **61** **62**



56 **60**

Some modifications to the individual steps of the synthesis were also reported by Chirisa.[22] The yield of the bromination step (**57** > **58**) was nearly doubled by the addition of bromine in an aqueous solution of potassium bromide. The Diels-Alder reaction product from the dimethyl acetylenedicarboxylate reaction, **63**, was isolated by base extraction followed by acidification. The large amounts of aqueous base used in the extraction were thought to decrease the yield significantly. The final product resembles haplomyrtin, being spectroscopically similar yet elementally variant.



57 **58**

Experimental

Chemicals and Instrumentation

All melting points were obtained using an Electrothermal capillary melting point apparatus and are uncorrected. Nuclear Magnetic Resonance (NMR) spectra were obtained using a Bruker Avance 300 spectrometer. All samples were run in deuterated chloroform. Infrared spectra (IR) were recorded with a Genesis II FTIR spectrometer using NaCl plates. Starting materials and reagents were purchased from Aldrich Chemical Company and used without further purification.

4-formyl-2-methoxyphenyl acetate 57[23]

Vanillin **56** (4.99 g, 32.8 mmol, 1 eq) was dissolved in a NaOH soln (1.35 g NaOH in 25 mL of water). Sodium salt formation was marked by a yellow solution color. At 0° C, a solution of Ac_2O (3.4 mL) in Et_2O (50 mL) was added to the well-stirred salt mixture. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h or until the ether layer evaporates. The white solid product was filtered off and washed with water until all yellow salt solution was rinsed away. The solid was air dried for two days to give **57** as a white solid (5.622 g, 89%): mp 114-116 ^oC (lit,[23] mp 75-76 ^oC); IR (film) cm^{-1} 3570, 3360, 3110, 3070, 3030, 1770, 1700, 1600, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.97 (s, 3H), 7.20 (s, 1H), 7.51 (d, J=1.2 Hz, 1H), 7.48 (d, J=1.8 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 168.2, 151.9, 144.9, 135.2, 124.6, 123.4, 110.8, 56.1, 20.5.

2-Bromo-4-hydroxy-5-methoxybenzaldehyde 59[24]

To a suspension of **57** (3.23 g, 16.7 mmol) in a KBr solution (6.67 g, 55 mmol, 3.5 eq in 80 mL water) was added bromine (0.94 mL, 2.94 g, 18.4 mmol, 1.1 eq) dropwise. The reaction mixture was stirred for 18 h at room temperature and then filtered. The precipitate was suspended in 6 N HCl (80 mL) at 90 °C for 20 h. The reaction mixture was cooled, filtered and the resulting solid was dissolved in EtOAc and the solution was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to give **59** as a colorless solid (3.01 g, 79.5%): mp 173.8-175.9 °C (lit,[5] mp 174-75 °C); IR (film) cm^{-1} 3210 (O-H), 2910 (aromatic C-H), 1680 (C=O), 1201 (C-O), 1040 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (s, 1H), 3.83 (s, 3H), 7.10 (s, 1H), 7.33 (s, 1H), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 153.7, 147.8, 124.6, 119.4, 119.1, 111.5, 55.7.

2-bromo-5-methoxy-4-(4-methoxybenzyloxy)benzaldehyde 68[22]

A solution of **59** (0.996 g, 3.65 mmol, 1 eq), K_2CO_3 (0.79 g, 1.6 eq), and a catalytic amount of KI (0.002g, 0.0005 eq) were dissolved in DMF (5.3 mL). The reaction mixture was purged with N_2. The reaction solution was warmed to 80°C followed by the dropwise addition of 4-methoxybenzyl bromide (0.5 mL, 4.02 mmol, 1.1 eq). The reaction was stirred for an additional 18 h. The mixture was cooled, added to 200 mL distilled water and stirred for 18 h. The mixture was filtered and dried in vacuo. to yield **68** as a white, powdery solid (1.15 g, 2.92 mmol, 80%): mp 173.8-175.9°C ; IR (film) cm^{-1} 3339, 3070, 3031, 2965, 2932, 2872, 1677; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.90 (s, 3H), 5.13 (s, 2H), 6.95 (d, 2H, J=8.70 Hz), 7.12 (s, 1H), 7.37 (d. 2H, J=8.67 Hz), 7.42 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 159.8,

153.8, 149.4, 129.9, 129.7, 129.3, 127.3, 126.64, 120.1, 117.21, 114.2, 110.8, 71.1, 56.1, 55.3. Anal. Calcd. for $C_{16}H_{15}BrO_4$: C, 54.72 %; H, 4.31 %. Found: C, 56.11 %; H, 4.49%.

4-methoxybenzyl bromide[25]

Phosphorous tribromide (3.5 mL) was added dropwise to a solution of 4-methoxybenzyl alcohol (12.8 mL) in dichloromethane (150 mL) at 0^{o}C and stirred for 24 h. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and extracted with $CHCl_2$. Removal of the solvent in vacuo from the organic phase gave the product as a clear oil. (16.948 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.43 (s, 2H), 6.89 (d, 1H, J=8.7 Hz), 7.35 (d, 1H, J=8.7 Hz).

2-(4-(4-methoxybenzyloxy)-2-bromo-5-methoxyphenyl)-1,3-dioxolane 69[17]

To a solution of **68** (3.31 g, 9.43 mmol, 1 eq) and a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) (20 mg, 0.1 mmol) in toluene (250 mL) was added ethylene glycol (0.85 mL). The reaction mixture was heated under reflux for 3 days under Dean-Stark conditions. The contents were cooled to room temperature and washed for 2 h with 80 mL of 10% sodium bisulfite solution. The organic layer was dried over $MgSO_4$ filtered and concentrated to provide **69** as a yellow oil (1.78 g, 4.50 mmol, 48%): IR (film) cm^{-1} 3457, 3000, 2934, 2860, 2836; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75-3.80 (m, 4H), 3.82 (s, 3H), 4.51 (s, 2H), 6.88-6.93 (m, 3H), 7.28-7.30 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 159.2, 132.01, 130.44, 130.13, 129.7, 129.5, 129.4, 129.3, 114.2, 113.9, 113.8, 72.9, 72.9, 71.1, 69.2, 61.9, 55.3. Anal. Calcd. for $C_{18}H_{19}BrO_5$: C, 54.70 %; H, 4.85 %. Found: C,64.05 %; H, 6.53 %.

5-bromo-4-(1,3-dioxolan-2-yl)-2-methoxyphenol 70[21]

To **59** (1.52 g, 6.6 mmol, 1eq) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) in toluene (80 mL) was added ethylene glycol (1.24 g, 20 mmol) and the reaction mixture was heated under reflux for 18 h in a Dean-Stark apparatus. The contents were cooled to room temperature, concentrated and washed with water (3 x 30 mL) to provide **70** as a colorless solid (1.15 g, 5.37 mmol, 81%): mp 127.6-132.4 °C, (lit,[17] mp 97-98 °C (EtOAc-hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.98-4.12 (m, 4H), 5.63 (s, 1H), 5.91 (s, 1H), 7.04 (s, 1H), 7.05 (s, 1H).

4-(4-methoxybenzyloxy)-3-methoxybenzaldehyde 71[26]

Vanillin **56** (5.076 g, 33.4 mmol, 1 eq), K_2CO_3 (4.495 g, 1.0 eq) and a catalytic amount of KI were dissolved in DMF (30 mL). The reaction vessel was purged with N_2. The solution turned a bright yellow color at room temperature which was indicative of the formation of the sodium salt of vanillin. The solution was warmed to 80°C followed by the dropwise addition of 4-methoxybenzyl bromide (4.9 mL, 33.4 mmol, 1 eq). The dull yellow solution was stirred for 18 h. The mixture was cooled, added to 600 mL distilled water and stirred for 72 h. The mixture was filtered and the precipitate was dried in vacuo to yield **71** as a white, powdery solid (7.88 g, 28.94 mmol, 86.8%): IR (film) cm^{-1} 3083, 3007, 2968, 2938, 2871, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.95 (s, 3H), 5.19 (s, 2H), 6.91-7.04 (m, 3H), 7.37-7.44 (m, 4H), 9.85(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 159.7, 159.2, 153.7, 150.1, 130.5, 130.3, 129.7, 129.4, 129.04, 128.04, 126.5, 114.1, 113.8, 112.5, 109.44, 71.5, 70.7, 56.0, 55.3. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57%; H, 5.92%. Found: C, 71.03%; H, 6.15%.

4-(3-bromo-4-methoxybenzyloxy)-2-bromo-5-methoxybenzaldehyde72 and **4-(3-bromo-4-methoxybenzyloxy)-3-methoxybenzaldehyde73**[26]

To a solution of **71** (1.209 g, 4.55 mmol, 1 eq), and sodium acetate (1.279g, 15.59 mmol, 3.4 eq) in acetic acid (11 mL) was added Br_2 (0.58 mL, 11.4 mmol, 2.5 eq) dropwise. The reaction mixture was heated at 40°C overnight. The reaction was cooled to room temperature and poured into 200 mL distilled water. The product was filtered, dissolved in DCM and washed with a saturated aqueous sodium bicarbonate solution. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to yield a powdery solid as a mixture of products, **72** (0.031g, 1.6%) and **73** (0.54 g, 28%). Compound **72**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 5.00 (s, 2H), 6.84 (d, 1H, J=8.4 Hz), 7.01 (s, 1H), 7.27 (d.d., 1H, J=1.77 Hz, J=8.4), 7.35 (s, 1H), 7.56 (d, 1H, J=1.74 Hz); **73**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.96 (s, 3H), 5.15 (s, 2H), 6.93 (d, 1H, J=8.4 Hz), 7.0 (d, 1H, J=8.1 Hz), 7.35 (d.d., 1H, J= 8.0 Hz, J = 2.0 HZ), 7.43 (d.d., 1H, J= 10.4 Hz, J = 2.1 Hz), 7.45 (d, 1H, J = 2.1 Hz), 7.66 (d, 1H, J=2.0 Hz).

2-(4-(benzyloxy)-2-bromo-5-methoxyphenyl)-1,3-dioxolane 74

To a solution of **60** (5.02 g, 15.7 mmol, 1 eq) and a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) (20 mg, 0.1 mmol) in toluene (200 mL) was added ethylene glycol (1.7 mL). The reaction mixture was heated under reflux for 24 h under Dean-Stark conditions. The contents were cooled to room temperature and washed for 2 h with 80 mL of 10% sodium bisulfite solution. The organic layer was dried over $MgSO_4$ filtered and concentrated to provide **74** as a yellow solid (5.05 g, 13.9 mmol, 87.6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.97-4.11 (m, 4H), 5.03 (s, 2H), 5.89 (s, 1H), 6.97-7.05 (m, 2H), 7.22-7.30 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 149.2, 136.3,

136.4, 128.8, 128.8, 128.1, 127.4, 127.3, 126.8, 120.1, 117.9, 117.2, 113.2, 110.8, 102.6, 71.3, 65.3,63.7, 56.17.

Dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-7-(4-methoxybenzyloxy)-4-hydroxy-6-methoxynaphthalene-2,3-dicarboxylate 75

Method 1:[5] PMB acetal **69** (0.50 g, 1.3 mmol, 1 eq) was dissolved in THF (4 mL) and cooled to -78°C under N_2 atmosphere. A solution of 1.6 M solution of n-butyllithium in hexanes (1 mL, 1.6 mmol, 1.2 eq) was added dropwise and stirred for 10 min. at -78°C. A solution of piperonal (0.205 g, 1.3 mmol, 1 eq), dissolved in THF (6 mL), was added dropwise to the reaction. The reaction mixture was allowed to stir at -78°C for 30 min. The reaction mixture was warmed to RT and quenched with H_2O (12.5 mL). The reaction mixture was extracted with ether (25 mL). The organic layer was washed with a 10% solution of sodium bisulfite (25 mL) for 2 h at RT to remove excess piperonal. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was combined with DMAD (2.84 mL, 23.20 mmol, 20 eq) and acetic acid (2.3 mL) and stirred at 130^{o}C for 1 h. The reaction mixture was cooled to RT. The mixture was washed with 10% $CaCO_3$ (aq) and extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in DCM (70 mL) and washed with 5% NaOH (aq) solution (50 mL). The organic layer showed the presence of DMAD and piperonal by ^{1}H NMR. The aqueous layer was acidified with 10% solution of HCl (aq) until a pH of 2 was reached. No solid precipitated from the aqueous layer. The aqueous layer was extracted with DCM (50 mL) and concentrated to show the presence of **56** in trace amounts by ^{1}H NMR.

Method 2:[20] PMB acetal **69** (0.50 g, 1.3 mmol, 1 eq) was dissolved in THF (4 mL) and cooled to -78°C under N_2 atmosphere. A solution of 1.6 M solution of n-butyllithium in hexanes (1 mL, 1.6 mmol, 1.2 eq) was added dropwise and stirred for 10 min at -78°C. A solution of piperonal (0.205 g, 1.3 mmol, 1 eq) dissolved in THF (6 mL) was added dropwise to the reaction. The reaction mixture was allowed to stir at -78°C for 30 min. The reaction mixture was warmed to RT and quenched with H_2O (12.5 mL). The reaction mixture was extracted with ether (25 mL). The organic layer was washed with a 10% solution of sodium bisulfite (25 mL) for 2 h at RT to remove excess piperonal. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product, DMAD (0.28 mL, 2 mmol, 2 eq) and a catalytic amount of *p*TSA were dissolved in toluene (50 mL) and heated at reflux for 2 h. No coupling product was detected by TLC or ^{1}H NMR.

Dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-7-(benzyloxy)-4-hydroxy-6-methoxynaphthalene-2,3-dicarboxylate 63

General reaction:[20] Benzylacetal **74** (0.50 g, 1.3 mmol, 1 eq) was dissolved in THF (4 mL) and cooled to -78°C under a N_2 atmosphere. A solution of 1.6 M solution of n-butyllithium in hexanes (1.0 mL, 1.6 mmol, 1.2 eq) was added dropwise and stirred for 10 min at -78°C. A solution of piperonal (0.20 g, 1.3 mmol, 1 eq), dissolved in THF (6 mL), was added dropwise to the reaction. The reaction mixture was allowed to stir at -78°C for 30 min. The reaction mixture was warmed to RT and quenched with H_2O (12.5 mL). The reaction mixture was extracted with ether (25 mL). The organic layer was washed with a 10% solution of sodium bisulfite (25 mL) for 2 h at RT to remove excess

piperonal. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product, DMAD (0.28 mL, 2 mmol, 2 eq) and a catalytic amount of *p*TSA were dissolved in toluene (50 mL) and heated at reflux with for 2 h. The reaction turned a dark brown. The residue was purified by flash chromatography on silica gel (ethyl acetate / hexane 50:50) to yield a red oil.

Trial 1: Benzylacetal **74** (1.37 mmol) was combined with butyllithium (1.60 mmol) and piperonal, then, reacted with DMAD (0.28 mL), and pTSA (0.05 mmol) and refluxed 2 h to give a 52.5% yield of **63**.

Trial 2: Benzylacetal **74** (1.36 mmol) was combined with butyllithium (1.92 mmol) and piperonal, then, DMAD (0.28 mL),) and pTSA (0.05 mmol) and refluxed 2 h to give a 17.4% yield of **63**.

Trial 3: Benzylacetal **74** (1.34 mmol) was combined with butyllithium (1.60 mmol), and piperonal, then, DMAD (0.28 mL), and pTSA (0.05 mmol) and refluxed 2 h to give a 39.7% yield of **63**.

Trial 4: Benzylacetal **74** (1.52 mmol) was combined with butyl lithium (1.82 mmol), and piperonal, then, DMAD (0.28 mL), and pTSA (0.05 mmol) and refluxed 2 h to give a 28% yield of **63**.

Trial 5: Benzyl acetal **74** (1.37 mmol) was combined with DMAD (0.28 mL), n-butyl lithium (1.60 mmol) and pTSA (0.05 mmol) and refluxed 2 h. The crude reaction mixture was stirred twice with 5% sodium hydroxide solution for 18 h, the aqueous layer was acidified to a pH of 1 and extracted with chloroform to give a 10% yield of **63** as a mixture of products.

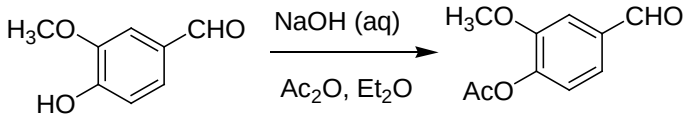
Trial 3 gave the best spectral data: IR (film) cm^{-1} 3423.8, 3005.9, 2950.5, 1735.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.5 (s, 3H), 3.84 (s, 3H), 3.98 (s, 3H), 4.97 (s, 2H), 5.95 (d, 1H, J=1.32 Hz), 6.01 (d., 1H, J=1.32Hz), 6.55 (dd., 1H, J1=7.84 Hz, J2=1.96 Hz), 6.58 (d., 1H, J=1.23Hz), 6.68 (s, 1H), 6.78 (d, 1H, J=7.83), 7.18-7.25 (m, 5H), 7.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.3, 159.5, 151.3, 150.2, 147.2, 147.0, 135.9, 132.0, 130.5, 128.5, 128.03, 127.7, 127.5, 126.1, 126.02, 124.13, 119.87, 111.34, 111.17, 110.97, 108.47, 108.06, 103.0, 101.1, 70.7, 56.1, 52.7, 51.9.

RESULTS AND DISCUSSION

Selected steps in the synthesis of arylnaphthalene lignan, Haplomyrtin **4** have been refined. The construction of the arylnaphthalene core was achieved by an annulation on vanillin.

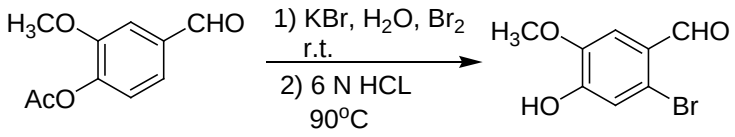
Bromination of Vanillin

Bromination at the C6 position of vanillin **56** required the deactivation of the C4 hydroxyl group to prevent electrophillic substitution at the C3 and C5. Therefore, acetylation of vanillin **56** with acetic anhydride and base was employed using a modification of a method proposed by Banerjee[23] to add a function that can exert both a steric and electronic influence in electrophilic bromination. Acetylation was noted by the appearance of a resonance at 2.36 ppm in the ^{1}H NMR of **57** (**Figure 3**) and the resonance at 20.5 and 168.3 ppm in the ^{13}C NMR of **57** (**Figure 4**) and the loss of the resonance at 6.18 ppm in the ^{1}H NMR of **56** (**Figure 2**).



56 **57** (96%)

Bromination and subsequent deacetylation[24] to yield **59** was indicated by the re-appearance resonance at 5.14 ppm, the absence of the resonance at 2.36 ppm ^{1}H NMR of **59** (**Figure 5**) and the lack of resonance at 168.3 and 20.5 ppm in the ^{13}C NMR of **59** (**Figure 6**).



57 **59** (80%)

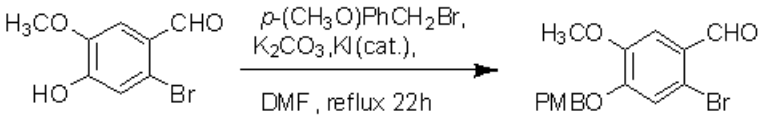
Methoxybenzyl Protective Group

The addition of the C ring through lithium-halogen exchange and coupling with piperonal, required that the bromovanillin **59** be protected with a group that could withstand basic conditions (BuLi). Both a benzyl (Bn) and a p-methoxy benzyl (PMB) protecting group were considered. Gilmore[5] and Schaaf's[21] thesis work showed the Bn phenol **61** produced a mixture of products in the lithium-halogen exchange and subsequent coupling reaction with piperonal. One of the side products of the coupling reaction indicated that deprotonation and coupling with piperonal occurred at the benzyl ring instead of at the C2 position of vanillin. This was most likely due to the acidity of the aromatic hydrogens. If the benzyl ring were to be made more electron rich, it was hypothesized that ring deprotonation would be less likely.

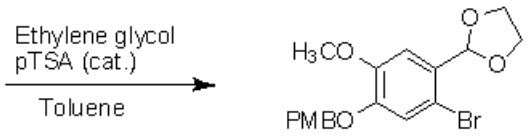
Therefore, 2-bromovanillin **59** was treated with 4-methoxybenzyl bromide in DMF to provide **68** in 80.4% yield. This transformation was indicated in the ^{1}H NMR of **68** by the appearance of the two singlets at 3.9 and 5.13 ppm and the doublets in the aromatic region at 6.9 and 7.3 ppm (**Figure 9),** the absence of an absorption at 3210 cm^{-1} in the IR spectrum **(Figure 8)**, and the appearance of the peaks at 56.1 and 71.1ppm in the ^{13}C NMR spectrum (**Figure 10**). The 4-methoxybenzyl bromide[25] was prepared by treating 4-methoxybenzyl alcohol with phosphorous tribromide. The ^{1}H NMR of the p-methoxybenzyl bromide exhibited a singlet at 3.8 ppm corresponding to the methoxy

group, an absorption at 4.4 ppm corresponds to the benzylic hydrogens and the doublets at 6.8 and 7.3 ppm corresponding to the *para* substitution on the phenyl ring (**Figure 7)**.[25]

The p-methoxylbenzyl protective group proved to be problematic in acetal formation. The cyclic dioxolane in **69**[17] was selected as a protective function because of its smaller steric profile as compared to the corresponding dimethyl acetal. The reaction of **68** with ethylene glycol was conducted for 3-5 days in toluene, under Dean-Stark conditions. The crude reaction mixture was washed with sodium bisulfite to remove excess aldehyde. The desired product, **69**, was isolated in only 48% yield as a mixture of products. In the ^{1}H NMR of **69** the multiplet from 3.75-3.80 ppm corresponds to the cyclic dioxolane (**Figure 12**). Trace amount of **68** are apparent in the ^{1}H NMR at 10 ppm and the ^{13}C NMR of **69** (**Figure 13**). The IR spectrum indicates the presence of ethylene glycol or incomplete cyclization of the dioxolane by the absorption at 3457 cm^{-1}(**Figure 11**). A time dependent study of the reaction was performed and the results are summarized in **Table 3**.



59 **68** (80.4%)

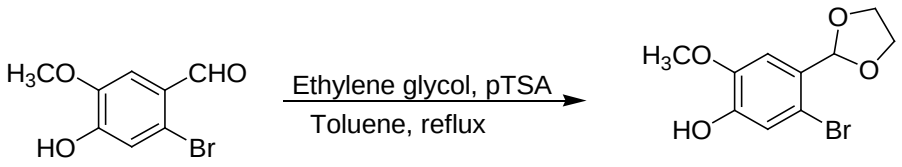


69 (48%)

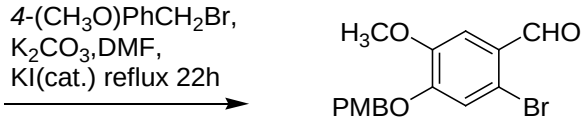
Table 3. Acetal formation results.

Trial #	**68** (mmol)	*p*TSA (mmol)	Time (days)	Yield (%)
1	5.8	0.05	2	9
2	2.6	0.05	3	48
3	9.4	0.15	5	48

Alternatively, acetal formation was conducted prior to phenol protection. The dioxolane acetal **70**[21] was prepared using **59** and ethylene glycol in the presence of pTSA in 81% yield. The ^{1}H NMR exhibited a multiplet from 3.9 to 4.1 ppm corresponding to the four hydrogens of the acetal (**Figure 14**). Reaction of the phenol with PMBBr regenerated the aldehyde **68** as determined by ^{1}H NMR, not the desired **69**. This could have been caused by the conversion of K_2CO_3 to carbonic acid in the reaction although it is surprising that the concentration of acid produced was high enough to catalize the removal the acid labile acetal.



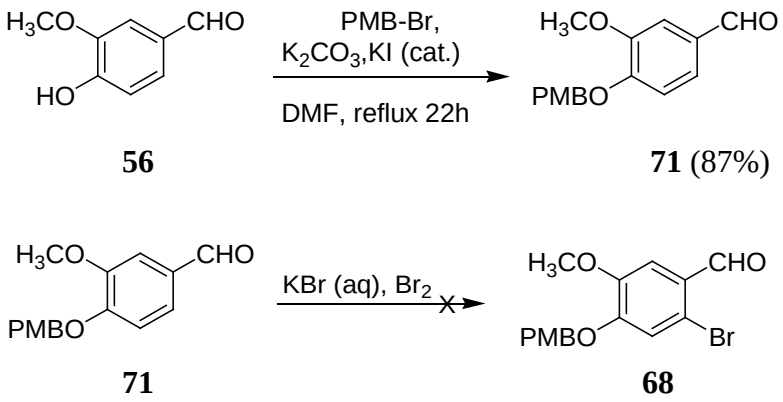
59 **70** (81%)

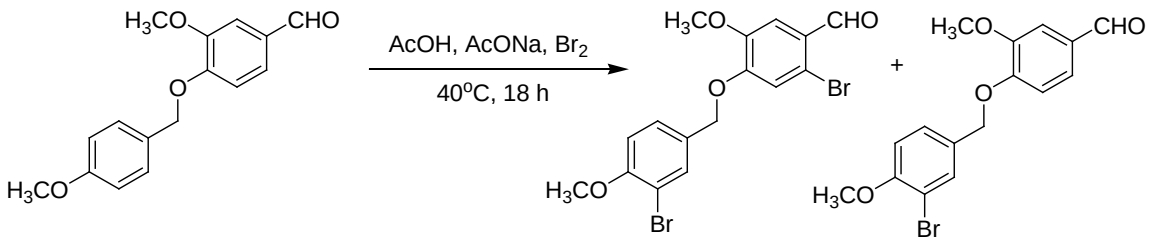


68 (71%)

A shorter synthetic sequence to **69** was also investigated. Vanillin **56** was directly protected with 4-methoxybenzyl bromide (PMBBr) to produce **71** in 87% yield.[26] This was confirmed by the presence of the singlet at 3.8 ppm corresponding to the methoxy group, the benzylic hydrogens at 4.4 ppm and the doublets at 6.8 and 7.3 ppm

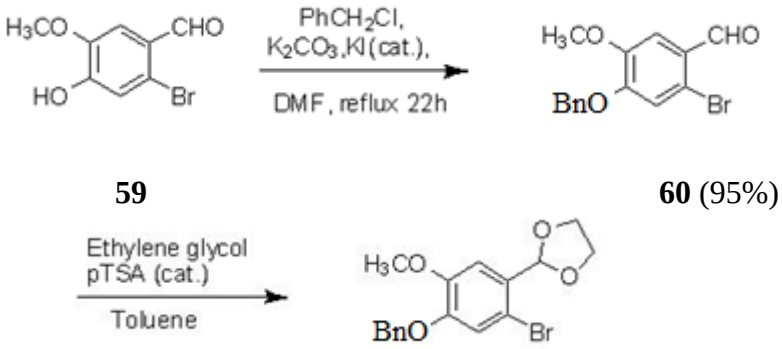
corresponding to the *para* substitution on the phenyl ring in **Figure 16**. Two methods of bromination were explored. The first method employed KBr (aq), and Br_2.[22] This method seemed promising because the product should be insoluble in water and could be easily isolated. Benzyl ether **71** did not undergo bromination apparently because of reaction condition incompatibility. In the second method,[26] C2 bromination was attempted using a method employing AcOH/AcONa and Br_2. Bromination did occur, but compound **68** was not produced. The two products appear to show substitution on the PMB ether ring at the 3' position as seen in compound **73** and **72** shows bromination at the C2 postitions on the A ring. Compound **72** was characterized by ^{1}H NMR a singlet at 3.83 ppm corresponding to six hydrogens, and a 1, 2, 4 proton coupling pattern, a doublet at 6.84 ppm (J = 8.4 Hz), a doublet of doublets at 7.27 ppm (J = 8.4 Hz, J = 1.7 Hz) and a doublet at 7.56 ppm (J = 1.7 Hz) (**Figure 18**). Compound **73** was also characterized by ^{1}H NMR: two singlets at 3.93 and 3.96 ppm corresponding to the methoxy groups, and a 1, 2, 4 proton coupling pattern, a doublet at 6.93 ppm (J = 8.4 Hz), a doublet at 7.0 ppm (J = 8.1 Hz), a doublet of doublets at 7.35 ppm (J = 8.0 Hz, J = 2.0 Hz), a doublet of doublets at 7.43 ppm (J = 10.4 Hz, J = 2.1 Hz), a doublet at7.45 ppm (J = 2.1 Hz) and a doublet at 7.66 ppm (J= 2.0 Hz) (**Figure 19**).





71 **72** (2%) **73** (28%)

In order to address the isobenzofuran cycloaddition in a timely fashion, the focus returned to the origional Bn derivative **60**. The reaction of 2-bromovanillin **59** was with benzyl chloride (BnCl) in DMF provided **60** in 95% yield. The ^{1}H NMR displayed a singlet at 5.1 corresponding to the benzylic hydrogens, in addition to an adsorption at 10.2 ppm and 4.0 ppm corresponding to the aldehyde and methoxy protons respectively, and a multiplet at 7.35 ppm corresponding to the hydrogens on the phenyl ring (**Figure 20**). Acetal formation by the 24 hour reaction of **60** with ethylene glycol provided **74** in 88% yield indicated by the diminishment of the resonance at 10.2 ppm corresponding to the proton of the aldehyde function and the appearance of the multiplets at 4.15 corresponding to the hydrogens of the cyclic dioxolane (**Figure 22**).



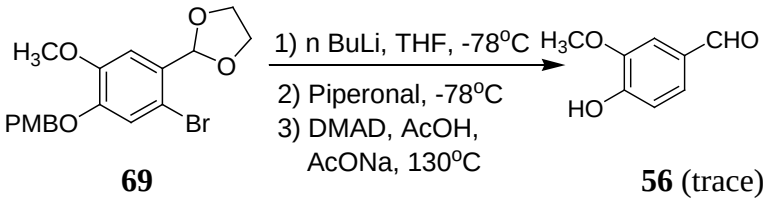
59 **60** (95%)

74 (88%)

Coupling of the C ring and Diels-Alder Reaction

With the PMB derivative **69** and the original protected bromo compound **74** in hand, attention was turned to the isobenzofuran formation and subsequent Diels-Alder

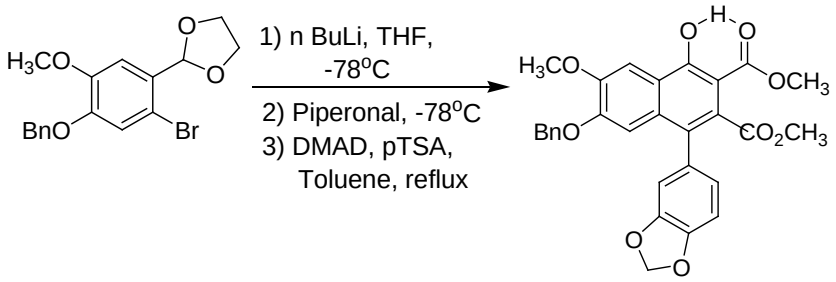
reaction. The product of the lithium-halogen exchange/ coupling reaction was known to be unstable and was generally used without purification.[17,18,19,20]



69 **56** (trace)

Initially, the PMB derivative **69** was subject to the Gilmore[5] sequence of steps. Thus, **69** was reacted with butyllithium in THF followed by the coupling of the intermediate organolithium with piperonal **18b** to provide an intermediate 2˚ alcohol that was subjected to an aldehyde deprotection/isobenzofuran formation in acetic acid followed by an in-situ Diels-Alder reaction with DMAD. Standard workup of the reaction mixture involved removal of the acetic acid and excess DMAD. Only a trace of a product, tentatively could be identified as **56** could be isolated.

Focus was returned to the use of **74**. The use of acetic acid as the catalyst and solvent for the aldehyde deprotection/isobenzofuran was abandoned in favor of a *p*-toluenesulfonic acid/toluene combination.[20] There were five trials of the coupling/ Diels-Alder reaction run; the results are summarized in **Table 4**.



74 **63** (52%)

Trial 1: After the coupling of **74** with piperonal using the usual conditions, the isobenzofuran formation/Diels-Alder reaction was performed using *p*TSA and two

equivalents of DMAD in toluene. Isolation was greatly simplified because *p*TSA could be removed by washing with water and DMAD was removed by flash chromatography. The coupling and Diels-Alder reactions gave a combined 52% yield. The reaction product appears to co-elute with an impurity. Characterization of **63** was best accomplished by IR and ^{1}H NMR (**Trial 1, Figure 1, 24-27**). The characterization data for all Trials is present later in this discussion.

Table 4: Results of diester formation.

Trial #	**74** (mmol)	nBuLi (mmol)	Yield (%) **63**
1	1.37	1.60	52
2	1.36	1.92	17
3	1.34	1.60	40
4	1.52	1.82	28
5	1.37	1.60	10

Trial 2: The coupling step between **74** and piperonal was carried out with a slightly higher amount of butyl lithium to account for any decomposition in the lithium reagent. This resulted in a greatly reduced yield in the Diels-Alder product. The Diels-Alder product was isolated by column chromatography with some slight impurities remaining in the ^{1}H NMR (**Trial 2, Figure 1, 28**).

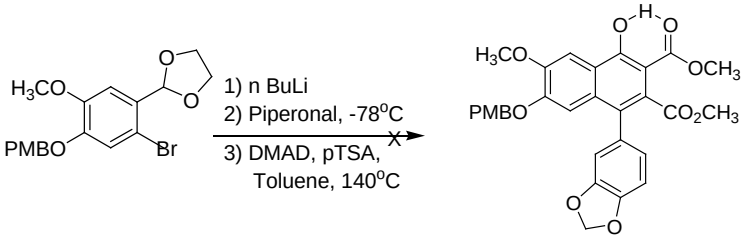
Trial 3: The coupling step was run with 1.2 equivalents of butyl lithium reagent. The Diels-Alder reaction product was isolated by flash chromatography as mostly a mixture of products but some pure diester was isolated. The yield seemed to increase

with the reduction in the amount of lithium reagent. This experiment yielded the clearest ^{1}H NMR data and is used as the basis for data analysis (**Trial 3, Figure 29-32**).

Trial 4: The coupling between **74** and **18b**, and the Diels-Alder reaction were carried out as in the first and third trial runs. The crude reaction mixture was washed with sodium bisulfite to remove, what was believed to be an aldehyde impurity from the crude reaction product indicated from a resonance at δ 10 in the ^{1}H NMR (not shown). The bisulfite wash did not remove the aldehyde. The solvent was switched to dichloromethane and the product was washed again, but the peak remained. The product was isolated by column chromatography to yield a mixture of products (**Trial 4, Figure 33-34**).

Trial 5: The coupling and Diels-Alder steps were carried out as in Trial 4. The crude reaction mixture was two spots by TLC showing only the diester and the aldehyde impurity and DMAD by ^{1}H NMR. The extraction was tried on this product. The reaction was washed twice with base for 18 hours and re-acidified to a pH of 1. The aqueous solution was extracted with chloroform. The organic layer showed the presence of both diester at 12.3 ppm and aldehyde at 9.9 ppm by ^{1}H NMR (**Figure 35**).

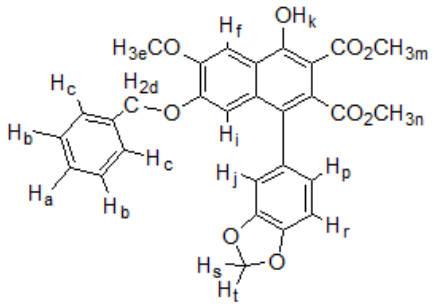
Finally, the Diels-Alder reaction was attempted with **69** using *p*TSA in toluene with DMAD. Upon examination of the crude reaction product by both TLC and ^{1}H NMR this reaction yielded no diester product **75** (**Figure 36**).



69 **75**

Spectral Analysis of 63

In general, the infrared spectrum obtained for **63** lacks the strong OH stretch that was previously reported for the diester.[5] Yet intramolecular hydrogen bonding affects the frequencies of phenolic OH stretch causing a reduction of the absorption frequency.[27] As stated by Silverstein et al.,[27] in a molecule containing an *o*-hydroxy aryl ketone, hydrogen bonding reduces the frequency of the OH stretch up to 300 $cm^{-1}$and the carbonyl stretch up to 100 cm^{-1}. Although this system involves an *o*-hydroxy aryl ester instead of a ketone moiety, the effects may be comparable. Due to the hydrogen bonding the OH stretch appears as a bulge in the baseline centered at 3200 cm^{-1}, enhancing the absorption in the aromatic CH stretching region **Figure 24, 29, 33**.



δ 3.5 (s, 3Hm), 3.84 (s, 3He), 3.98 (s, 3Hn), 4.97 (s, 2Hd), 5.95 (d, 1Hs, J=1.32 Hz), 6.01 (d., 1Ht, J=1.32Hz), 6.55 (dd., 1Hp, J1=7.84 Hz, J2=1.96 Hz), 6.58 (d., 1Hj, J=1.23Hz), 6.68 (s, 1Hi), 6.78 (d, 1Hr, J=7.83), 7.18-7.25 (m, 5Ha-c), 7.65 (s, 1Hf).

Figure 1. Proton assignments of **63** ^{1}H NMR (300 MHz, $CDCl_3$)

The ^{1}H NMR spectrum obtained in Trial 3 (**Figure 30-32**) provides the best characterization of **63**. The assignments are given in **Figure 1**.

The absorptions can be used as indicators of specific protons in **63**. The absorption at 12.3 δ in (**Figure 25**) can be assigned to the exchangeable phenolic proton.

An exchange with D_2O confirms this assignment (**Figure 26**). It is well known that exchangeable protons can fluctuate in position in chloroform depending on both concentration and temperature. Phenolic protons usually appear as a sharp singlet within the range of δ~7.5-4.0. When a carbonyl function is ortho to the phenol, as in compound **63**, a six-membered ring will form due to intramolecular hydrogen bonding.[27] Hydrogen bonding shifts the absorption of the phenolic proton to the range of δ~12.0-10.0.

The presence of the remainder of the structure of **63** can be confirmed by several obvious and highly characteristic absorptions. Three singlets at 3.5, 3.8, and 3.9 ppm correspond to the methoxy and methyl esters, the singlet at 4.9 corresponds to the benzylic hydrogens and an absorption from 7.18-7.25 ppm corresponds to the benzylic phenyl protons. The incorporation of the C ring is indicated by the doublets at 5.95 and 6.01 corresponding to the nonequivalent methylene protons of the methylenedioxy ring and a typical 1, 2, 4 proton coupling arrangement with a doublet absorption at 6.78 ppm corresponding to Hr, a doublet at 6.58 ppm corresponding to Hj and a doublet of doublets at 6.55 ppm corresponding to Hp. Finally, two singlets, one at 7.6 ppm and the other at 6.6 ppm correspond to the protons of Hf and Hi respectively.

CONCLUSIONS

This research produced four significant results. First, there were significant increases in yields of the first three reactions. The acetylation of the phenolic oxygen was carried out in a biphasic reaction using Ac_2O/ Et_2O in basic solution. The solid **57** precipitates out and is isolated by filtration in 96% yield as compared to a previous yield of 89%[1]. The bromination/deprotection to was changed to produce alcohol **59** with a combined yield of 80% vs. the previously reported combined yield of 23%.[5,21] Phenolic protection with benzyl chloride (Bn) in 97-98% yield and subsequent acetal formation in 88-95% yield completed the preparation of compound **74**.

Second, an investigation of the use of 4-methoxybenzyl bromide (PMB) for the phenolic protection was carried out with the belief that acetal **69** would be less likely to be deprotonated on the aromatic ring in the subsequent Li-halogen exchange. Unfortunately, the reactivity of the PMB protection caused a significant drop in yield from the Bn derivative (48% vs. 88%). This is thought to be due to the inherent instability of the secondary alcohol. The use of the PMB protective group was abandoned after it failed to produce diester **75** in the Diels-Alder reaction.

Third, it was found that a specific reaction sequence was necessary to produce **69**. First, acetylation, second, bromination, third, deacetylation, fourth, protection of the phenol, and fifth, acetal formation. Acetylation ensures proper directing of bromine in the bromination product. The acetal was found to be labile under the phenolic protection conditions. This sequence ensures the acetal remains intact.

Fourth, the Diels-Alder reaction procedure was changed so as to use *p*TSA, toluene and two equivalents of DMAD instead of AcOH and twenty equivalents of DMAD.[5,21,22] This allowed for both ease of isolation and conservation of materials. The new method for the Diels-Alder reaction with **74** produced **63** in 52% yield. Several trial reactions using this technique establish it as the method of choice for producing the naphthalene diester intermediate **63**. This step was repeated with the PMB acetal **69** and did not produce a coupling product.

The presence of **63** in Trials 1-5 is clearly indicated. Additional purification of the combined products should allow for the last two steps of the sequence to be accomplished. It may prove to be beneficial to reverse the directed reduction and the phenolic deprotection steps to decrease the number of alternative chelating sites for boron in the reduction step.

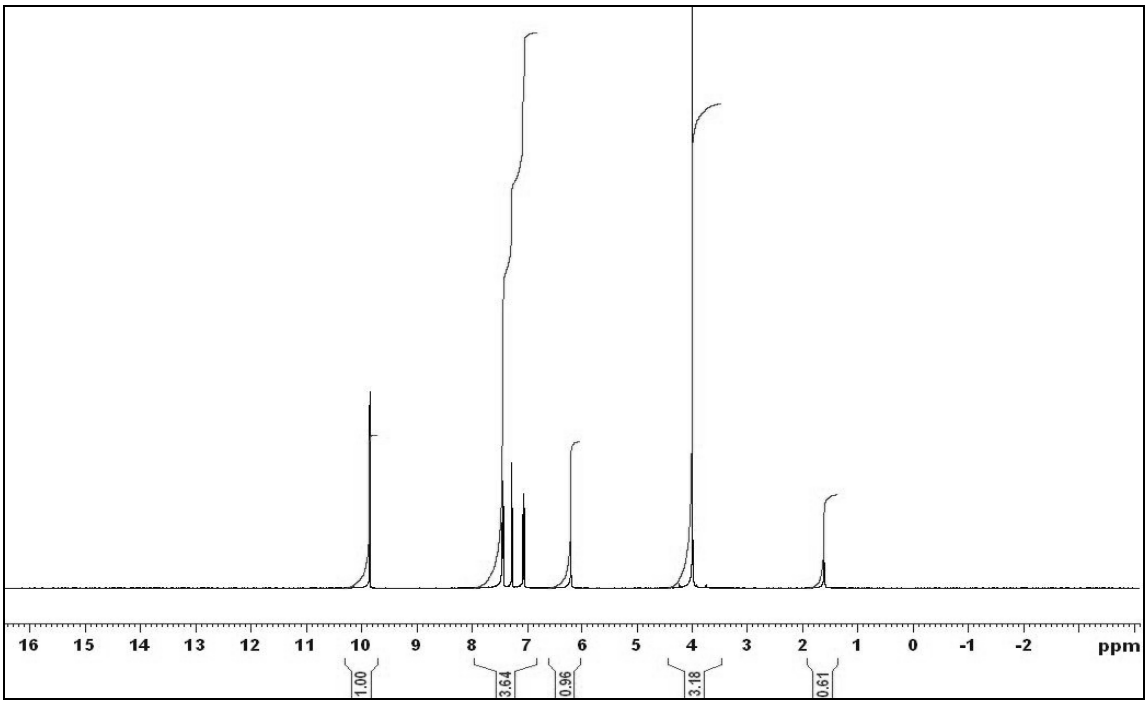


Figure 2. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **56**

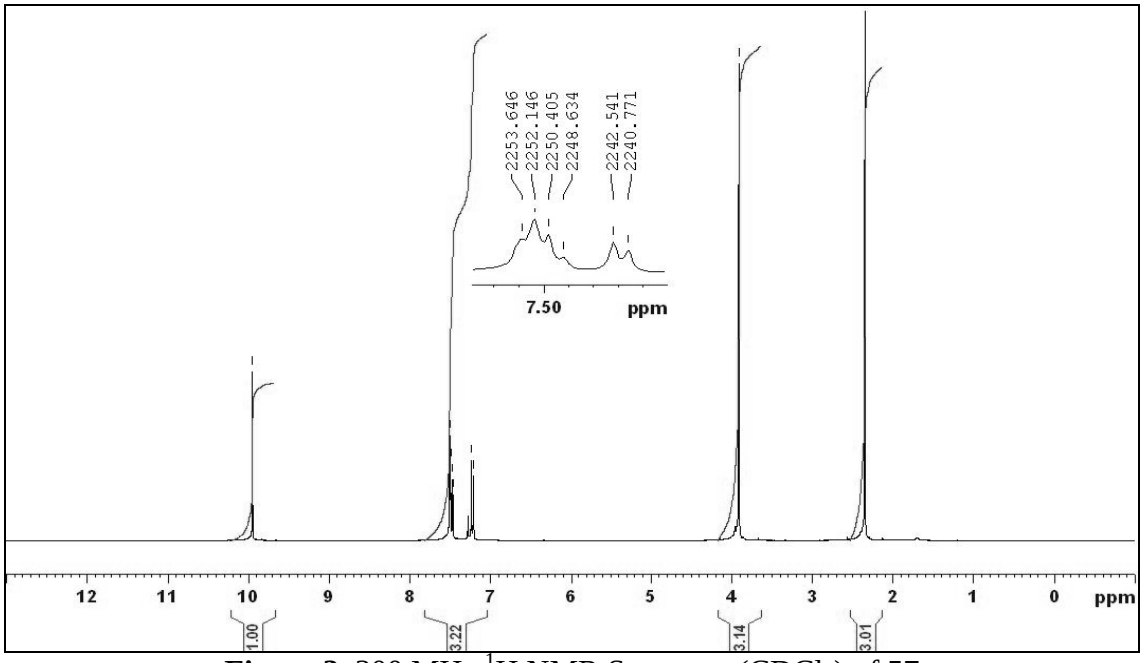


Figure 3. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **57**

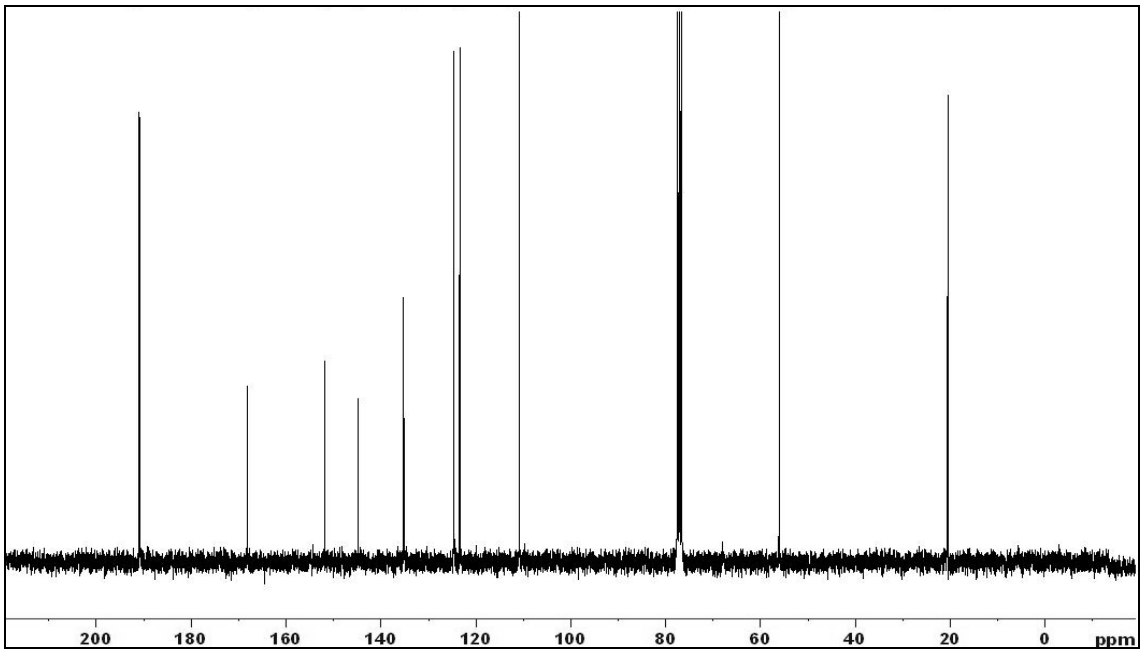


Figure 4. 75 MHZ ^{13}C NMR Spectrum ($CDCl_3$) of **57**

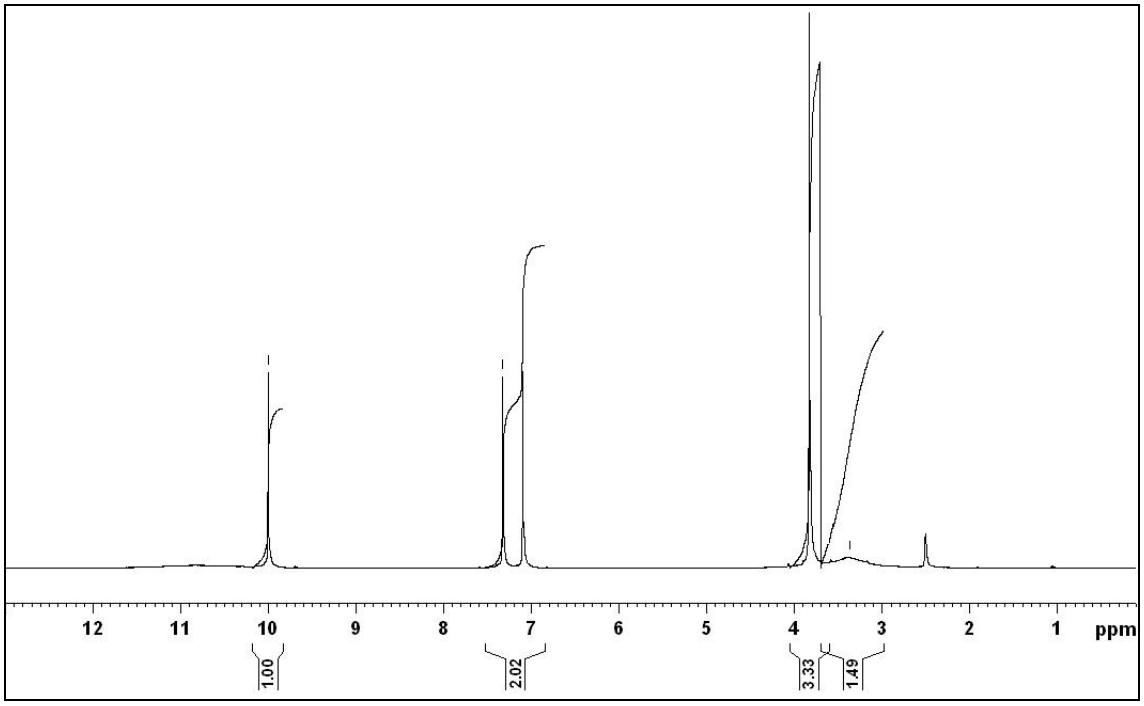


Figure 5. 300 MHz ^{1}H NMR Spectrum (DMSO) of **59**.

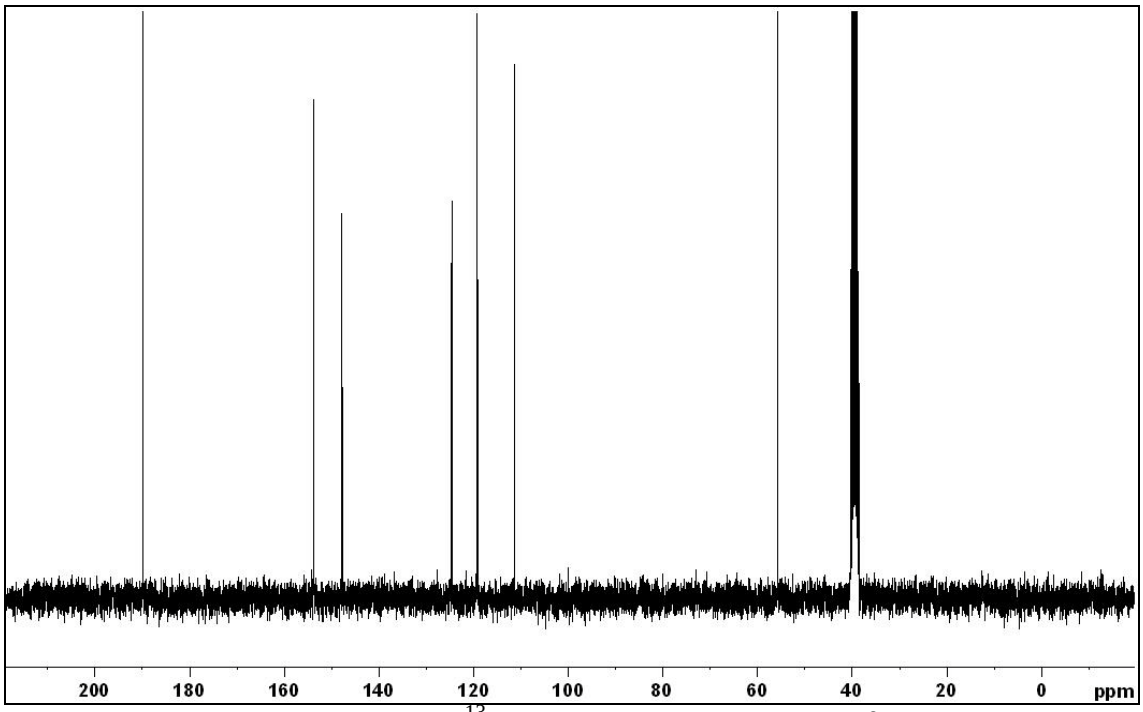


Figure 6. 75 MHz ^{13}C NMR Spectrum (DMSO) of **59**.

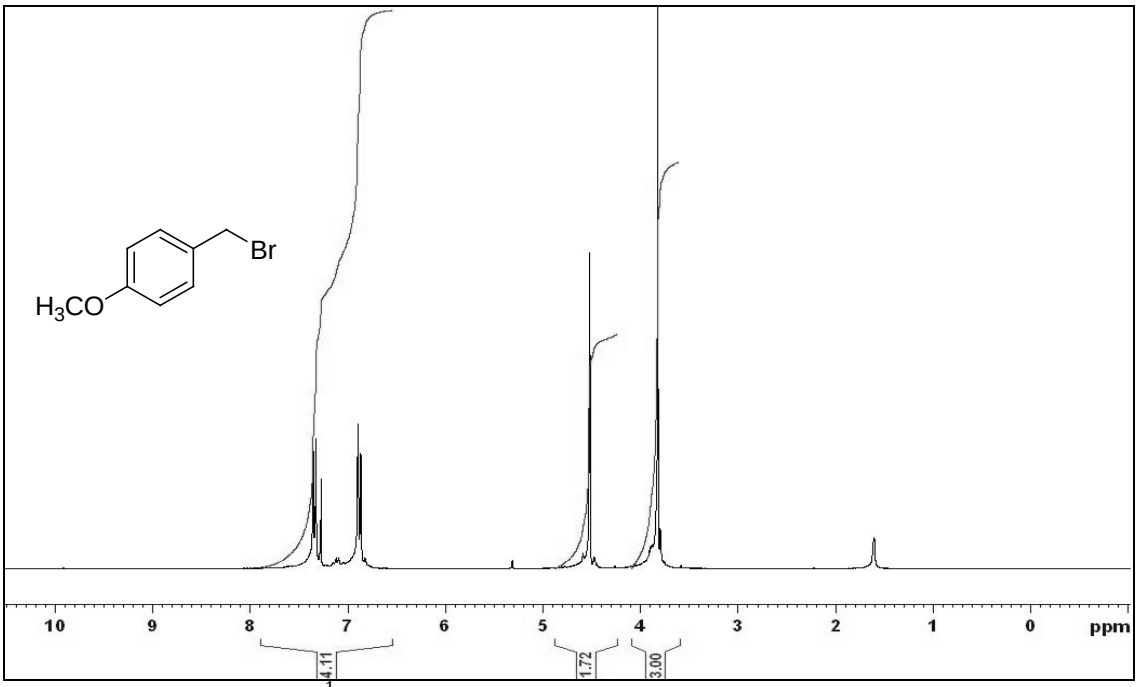


Figure 7. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of 4-methoxybenzyl bromide.

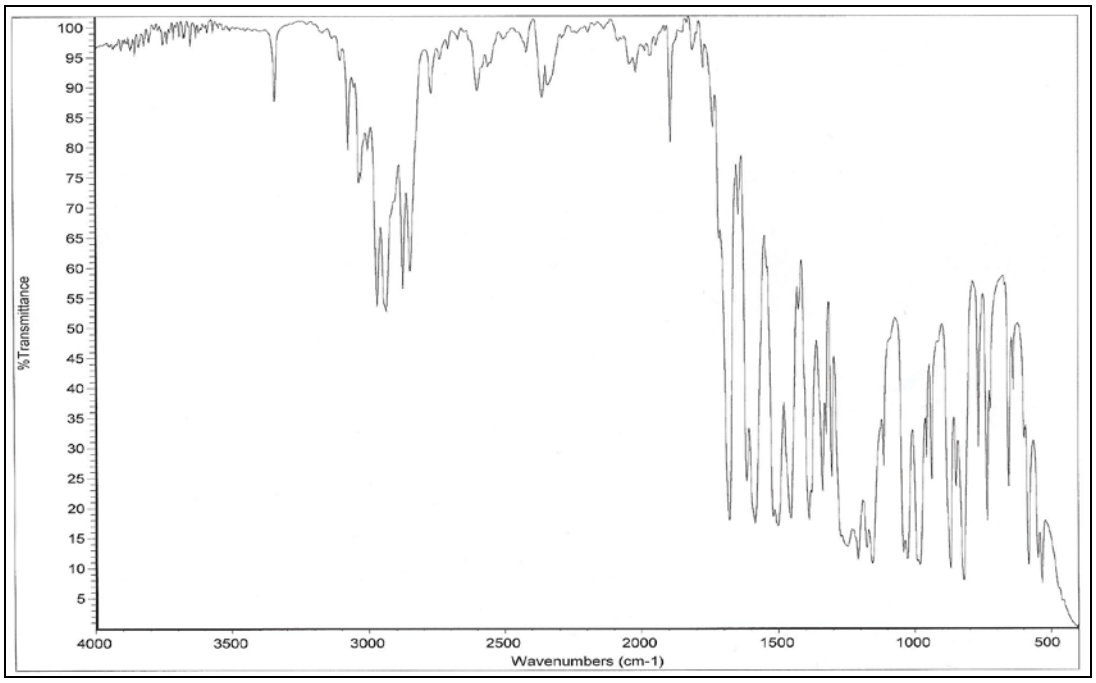


Figure 8. IR Spectrum (NaCl) of **68**.

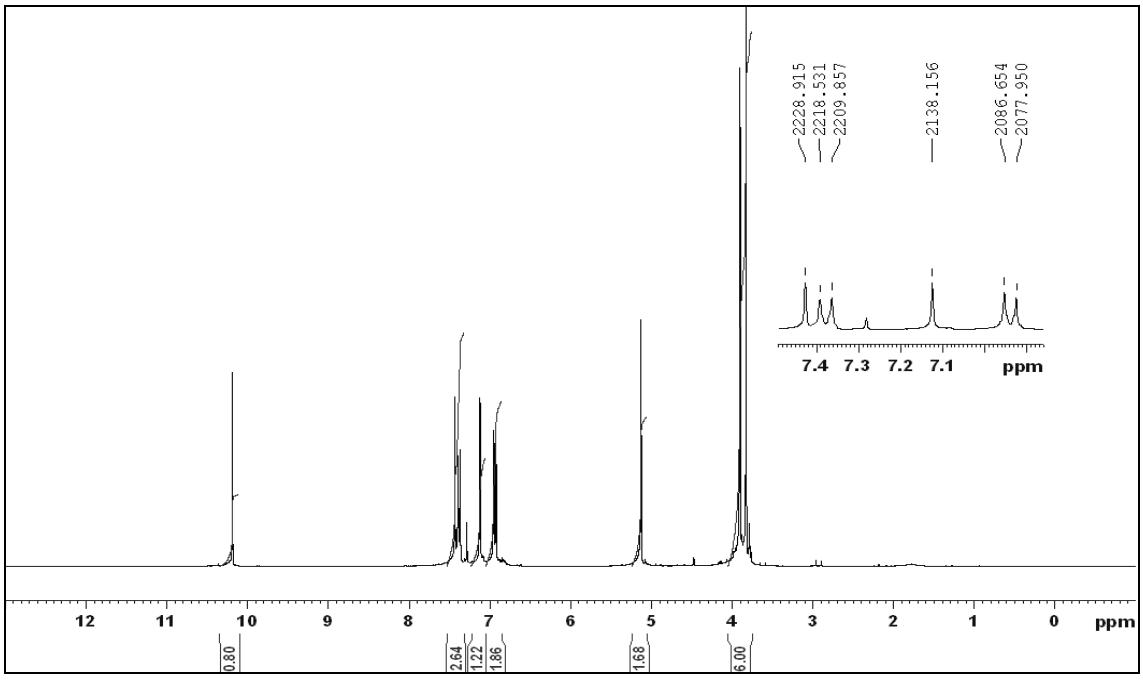


Figure 9. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **68**.

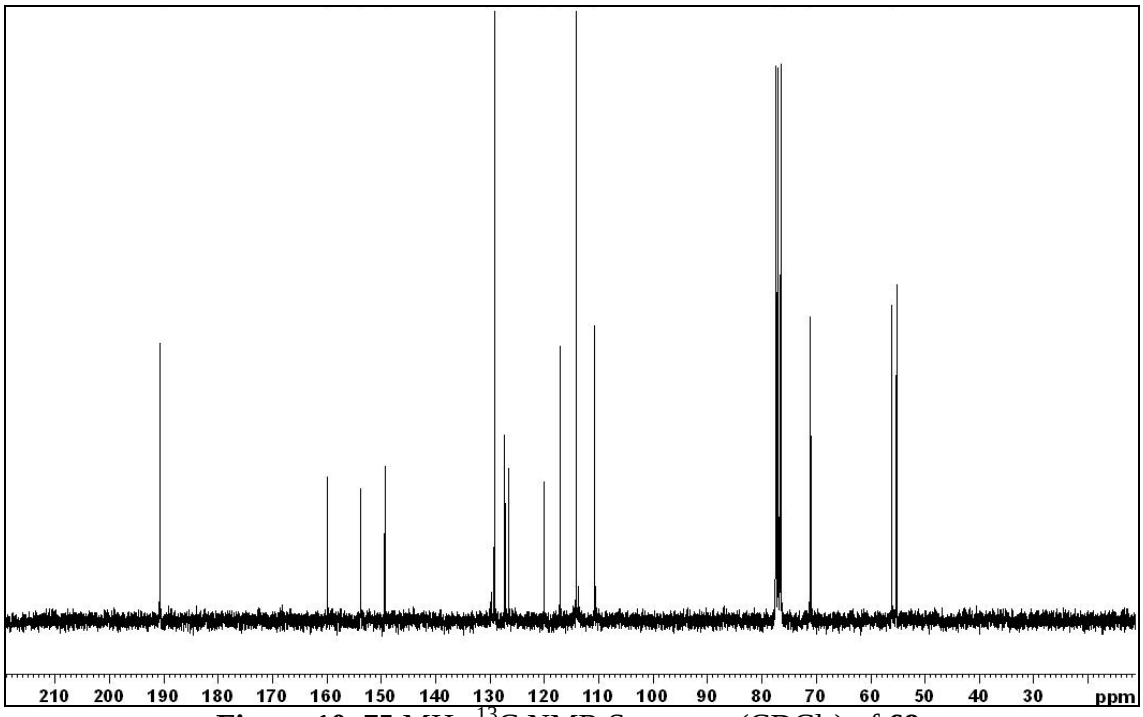


Figure 10. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of **68**.

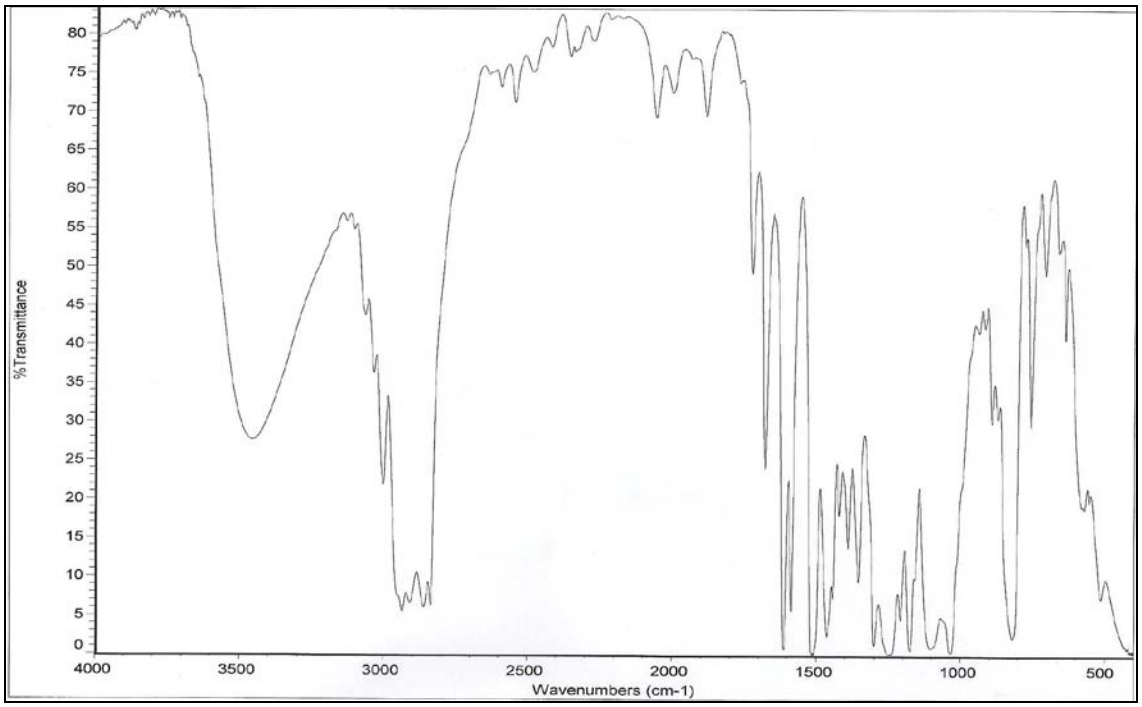


Figure 11. IR Spectrum (NaCl) of **69**.

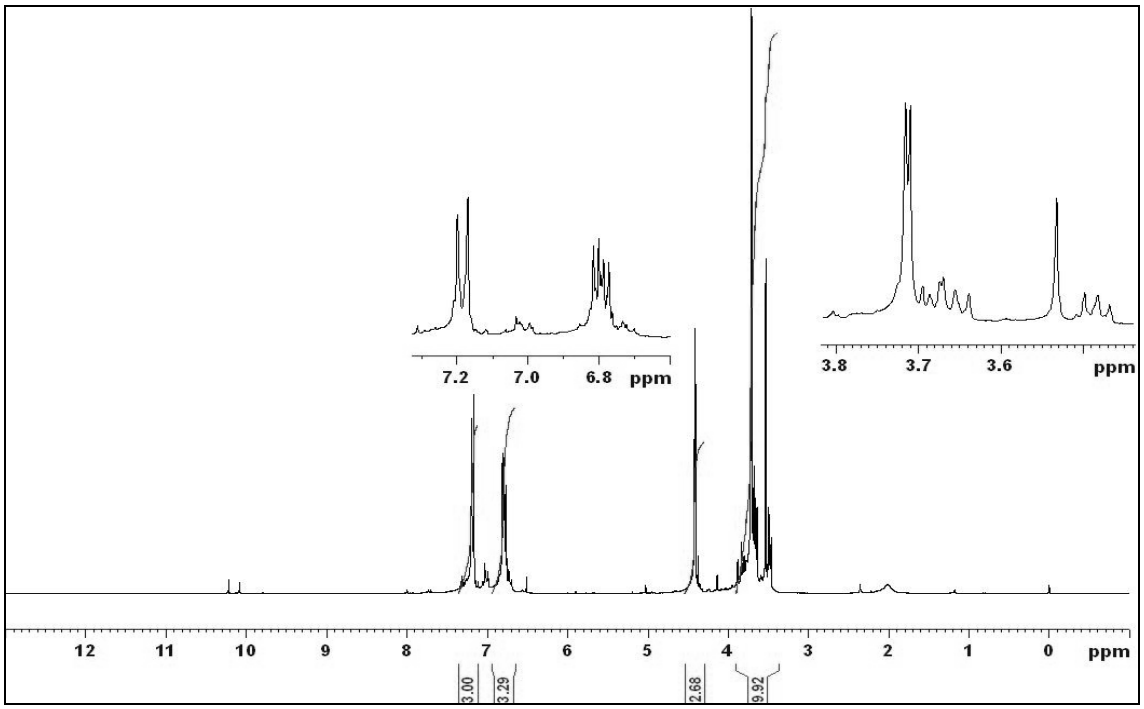


Figure 12. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **69**.

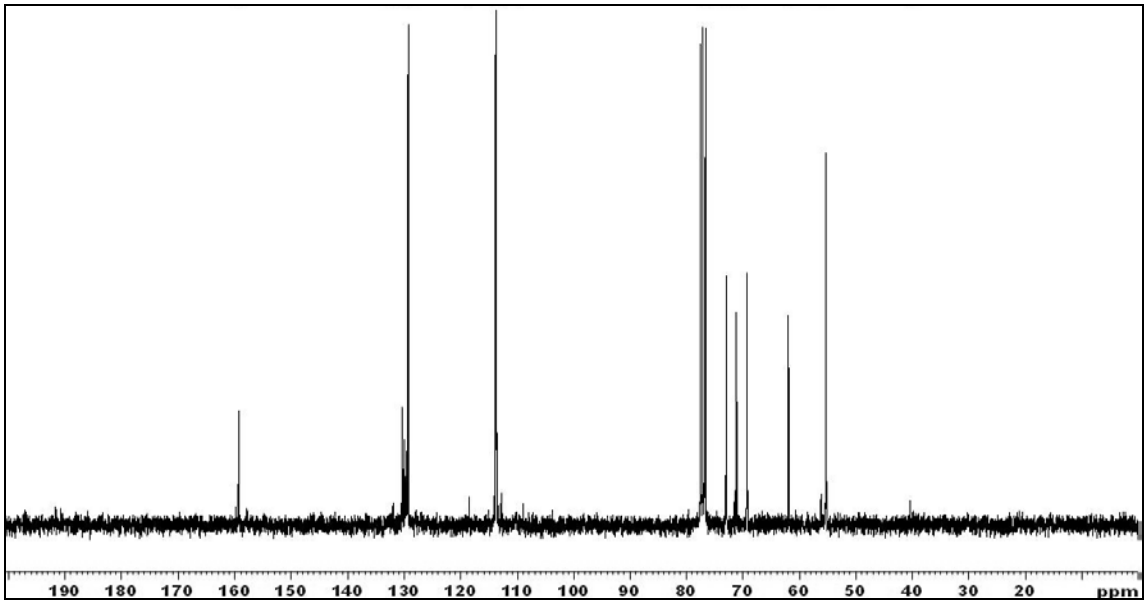


Figure 13. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of **69**.

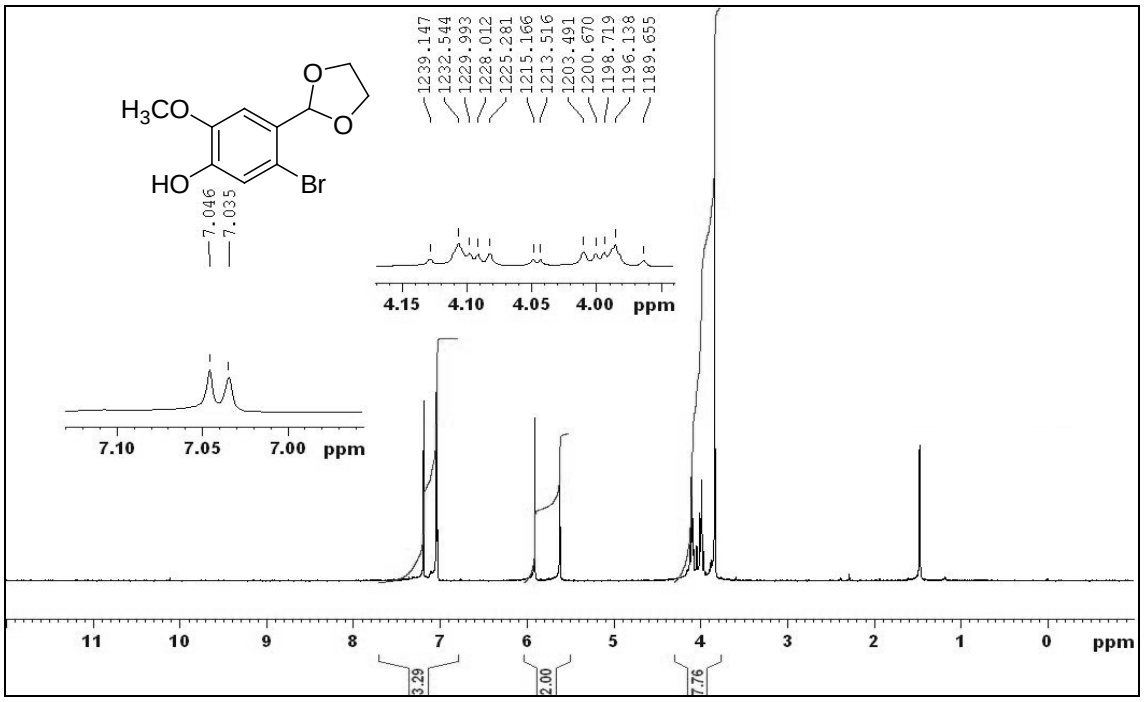


Figure 14. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) **70**.

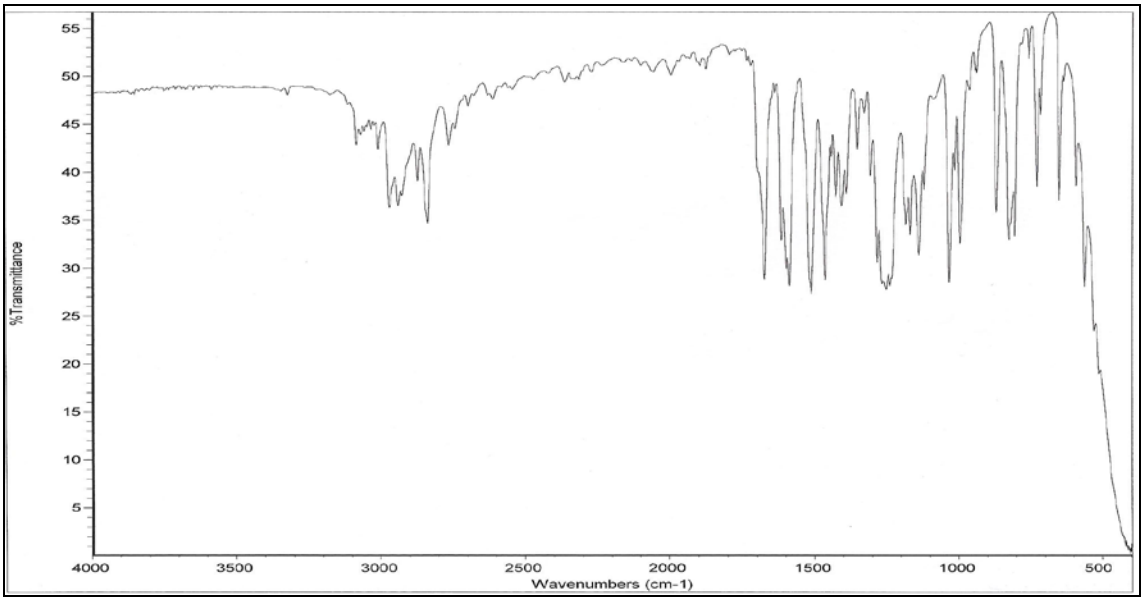


Figure 15. IR Spectrum (NaCl) of **71**.

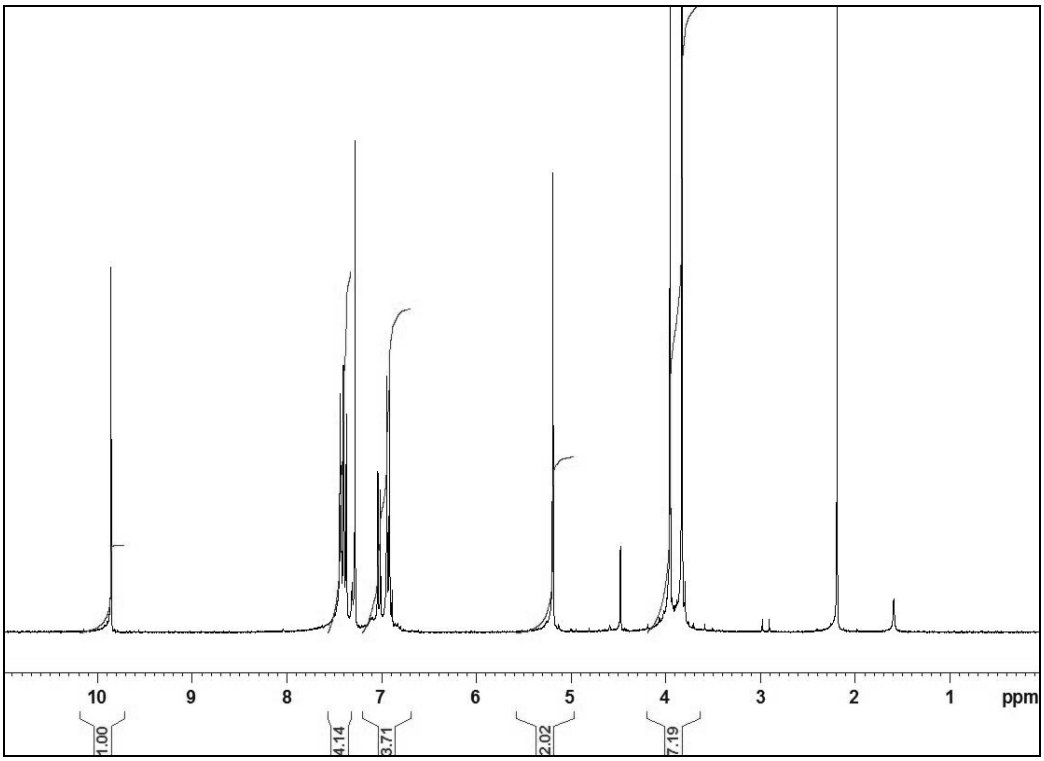


Figure 16. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) **71**.

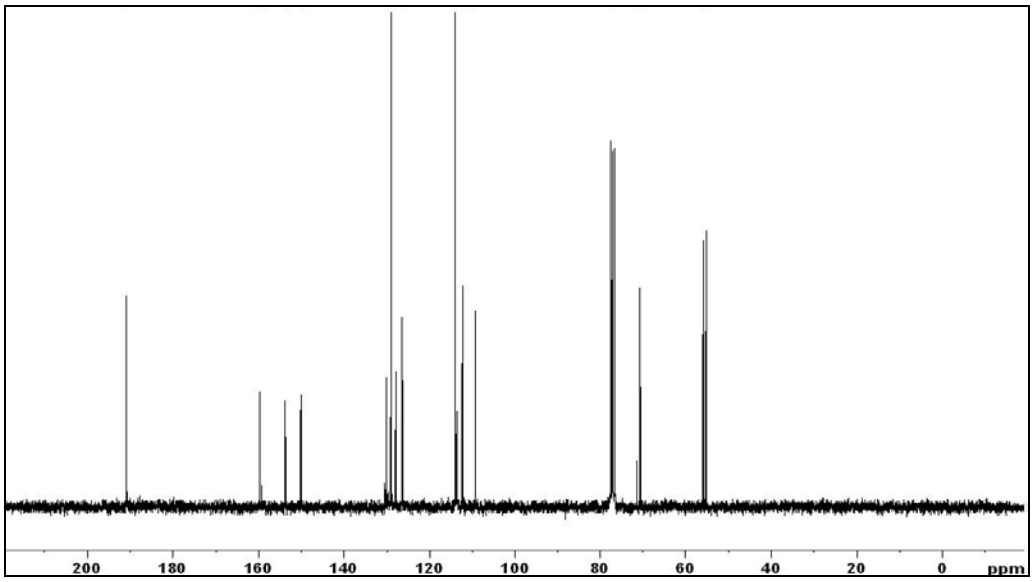


Figure 17. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of 71.

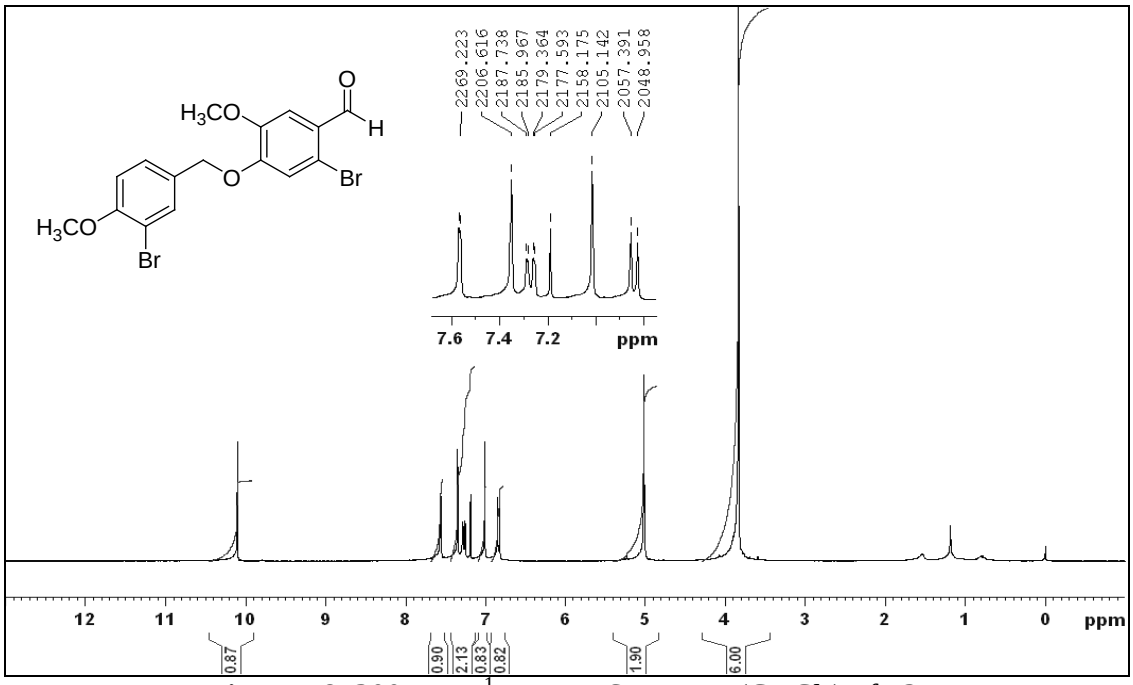


Figure 18. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **72**.

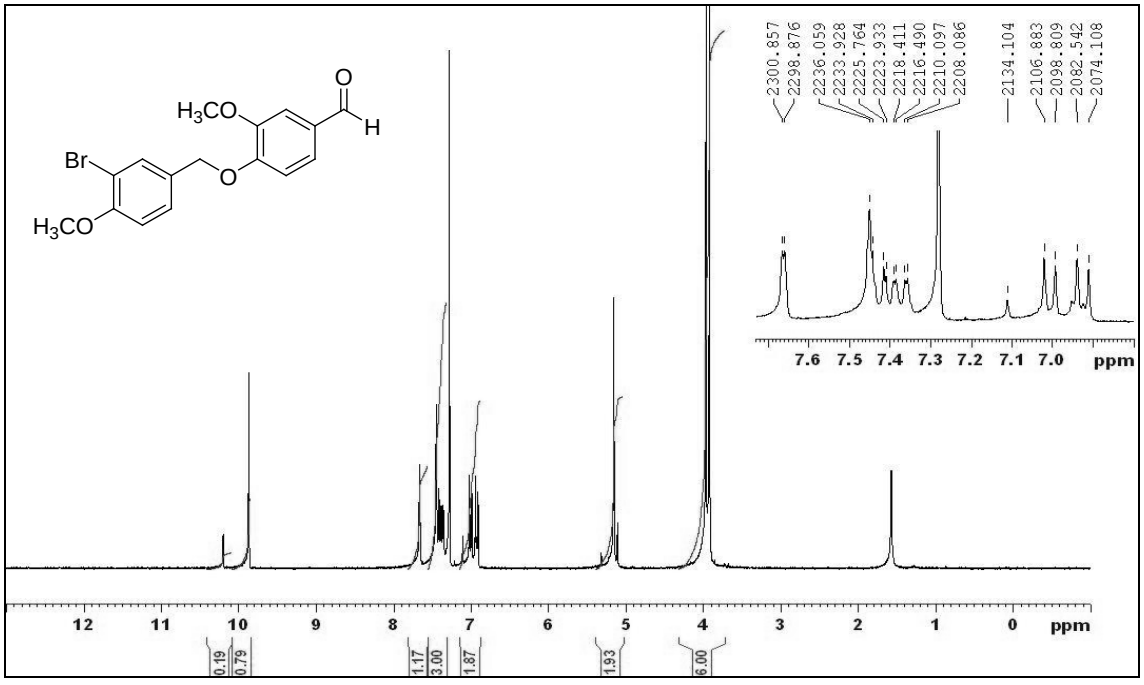


Figure 19. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **73**.

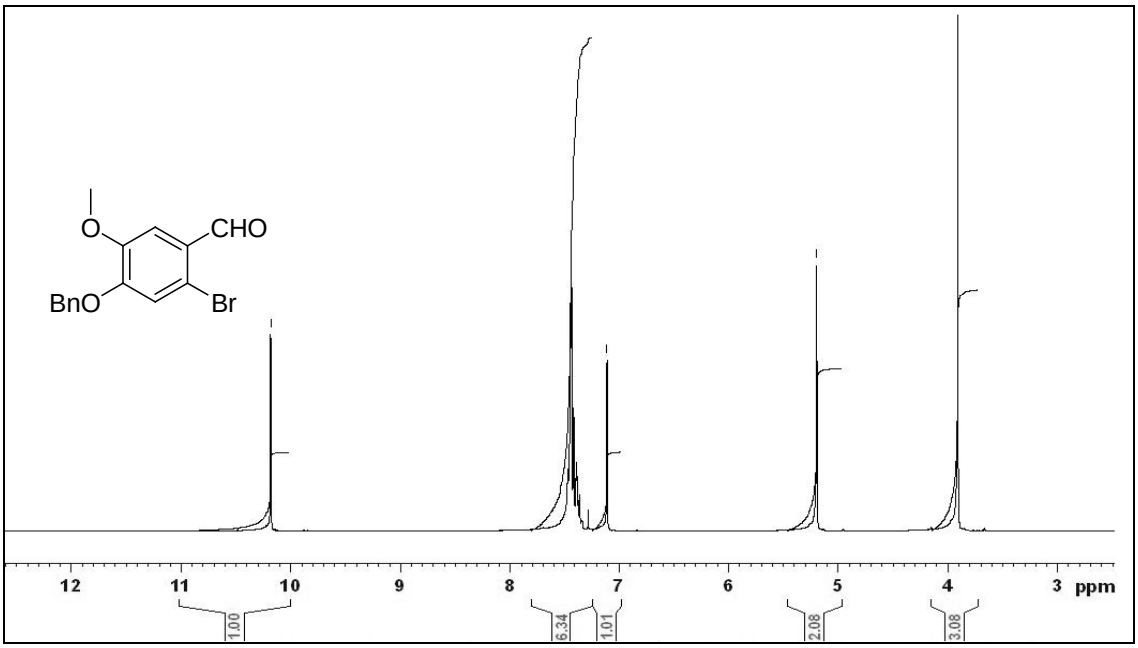


Figure 20. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **60**.

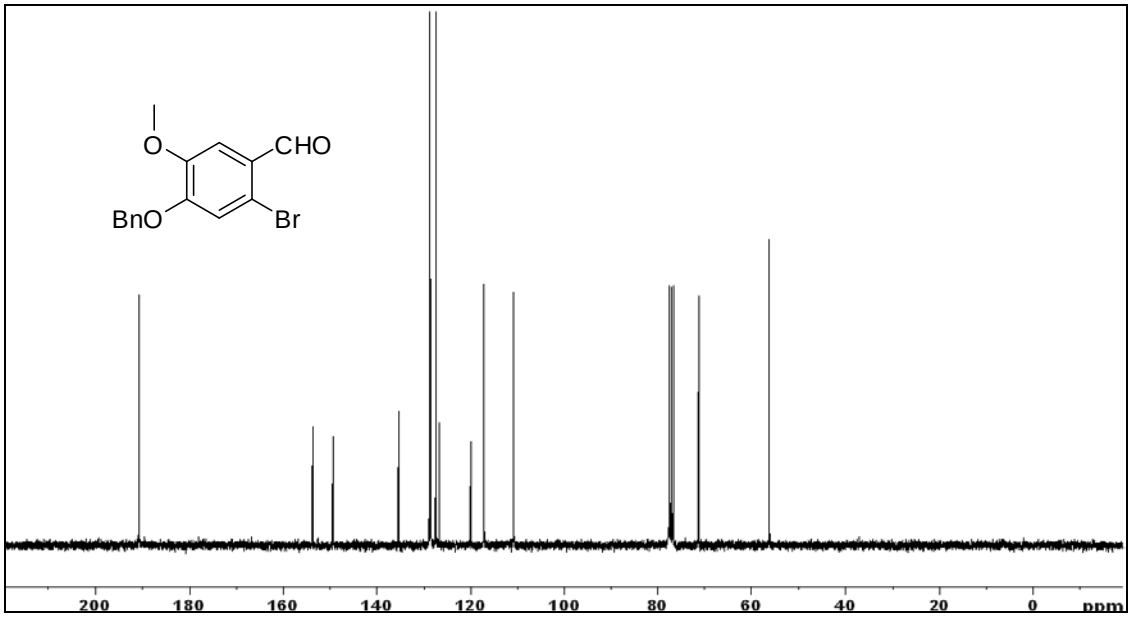


Figure 21. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of **60**.

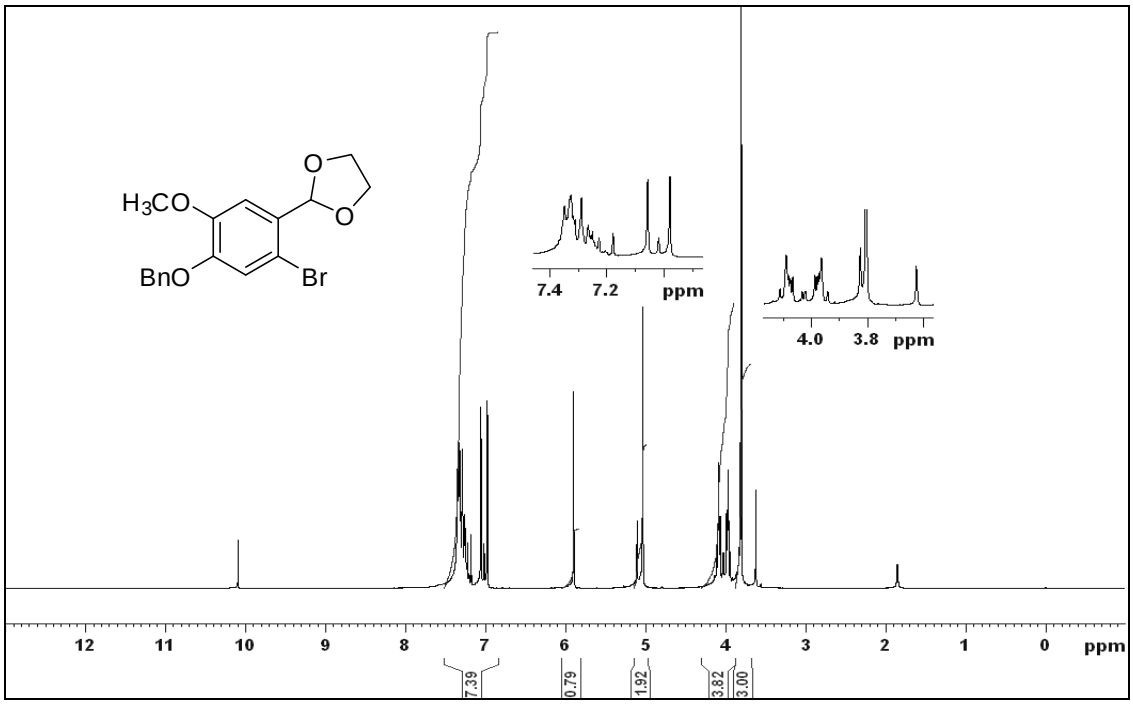


Figure 22. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of **74**.

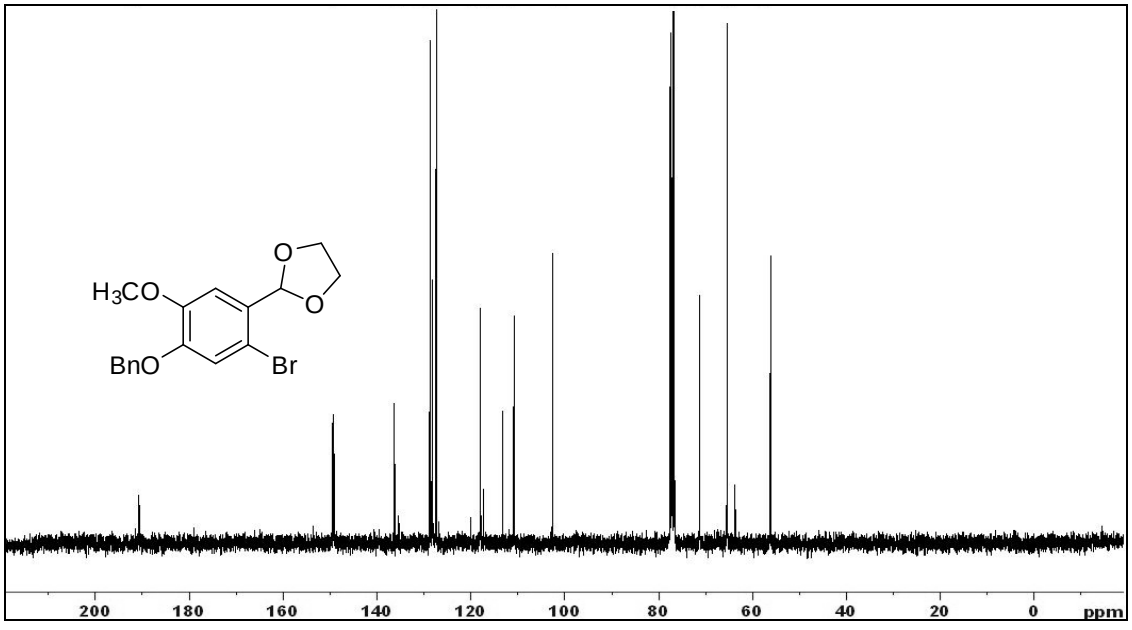


Figure 23. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of **74.**

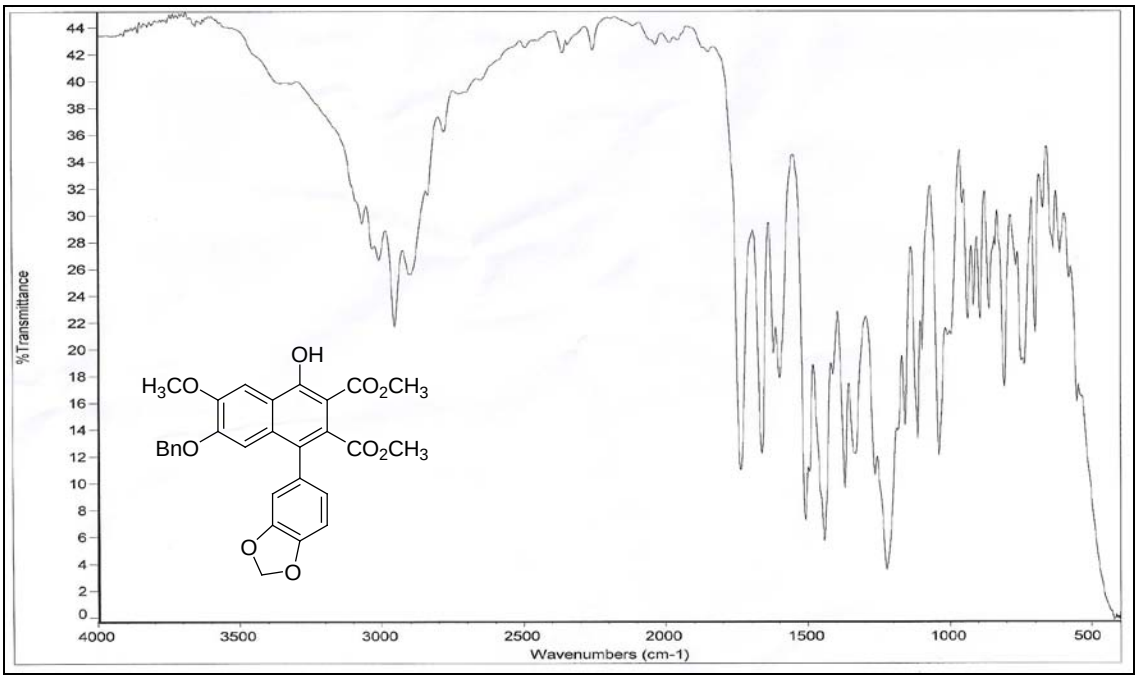


Figure 24. IR Spectrum (NaCl) of Trial 1: **63.**

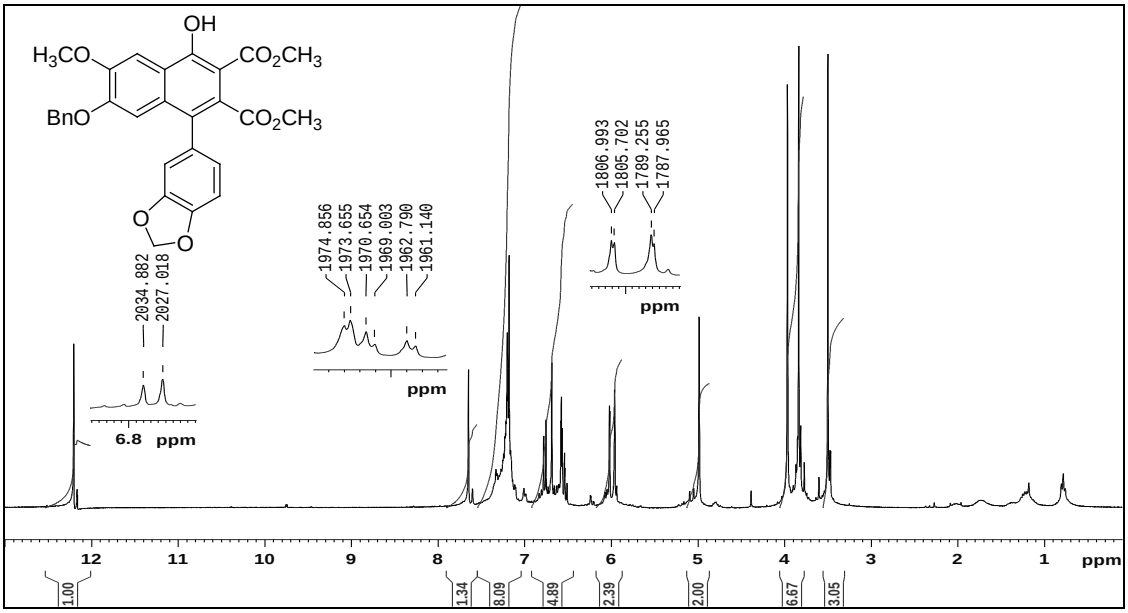


Figure 25. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trial 1 of **63.**

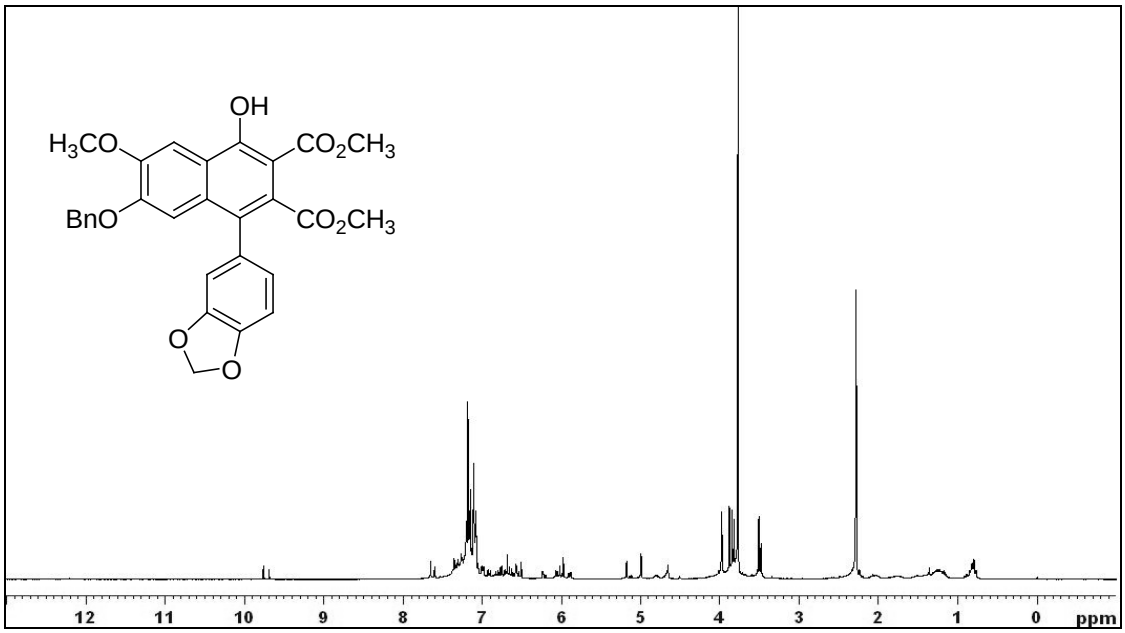


Figure 26. 300 MHz ^{1}H NMR Spectrum ($CDCl_3/D_2O$) of Trial 1 of crude **63.**

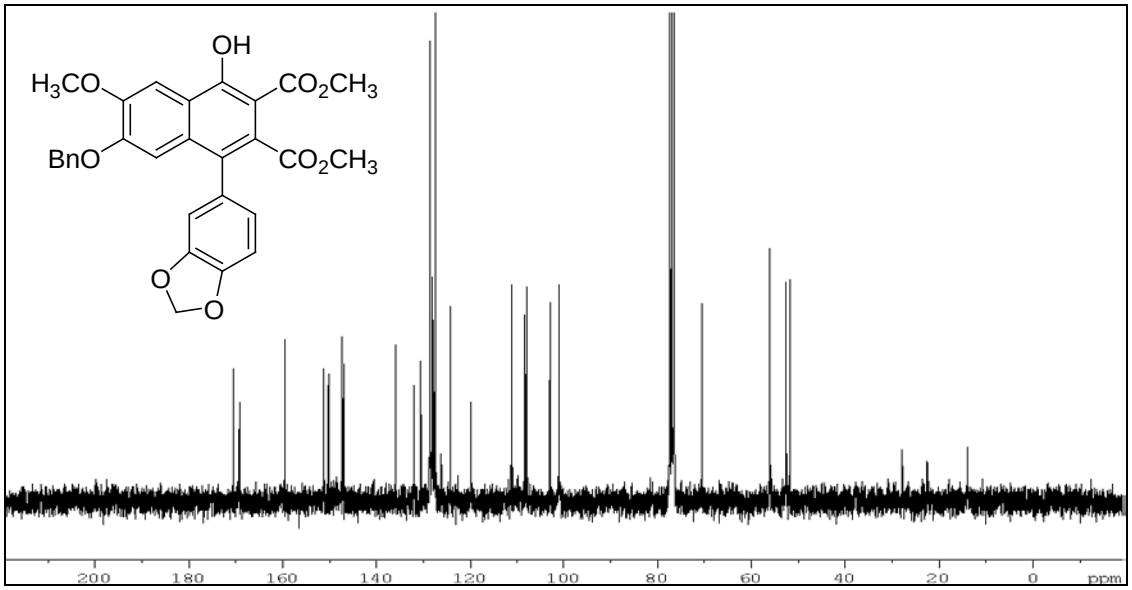


Figure 27. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) Trial 1 of **63.**

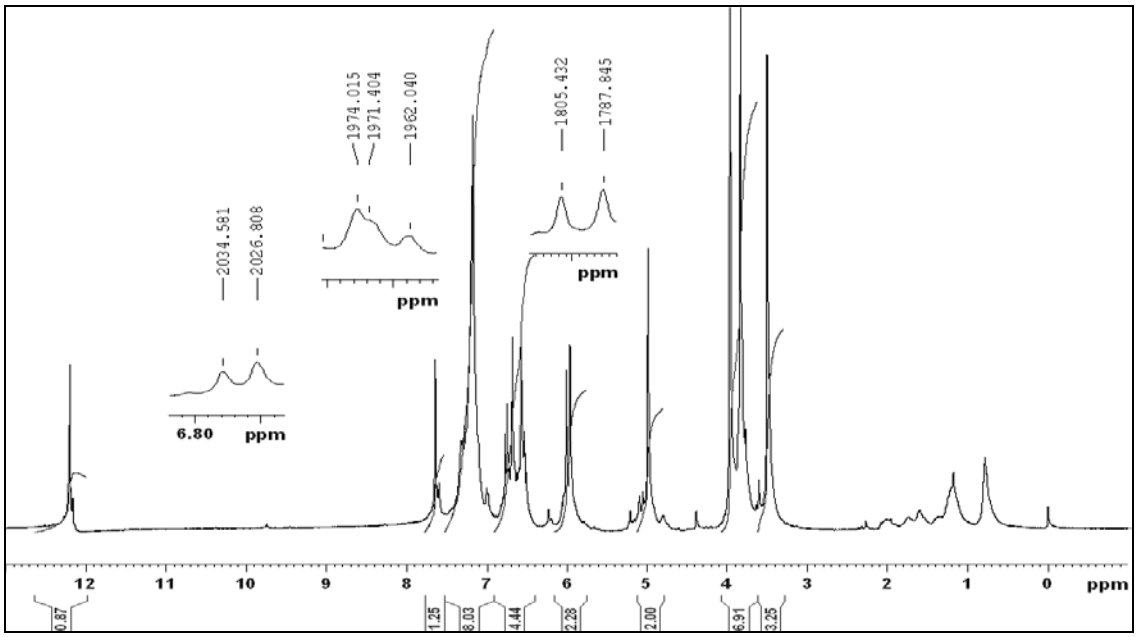


Figure 28. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trial 2: **63.**

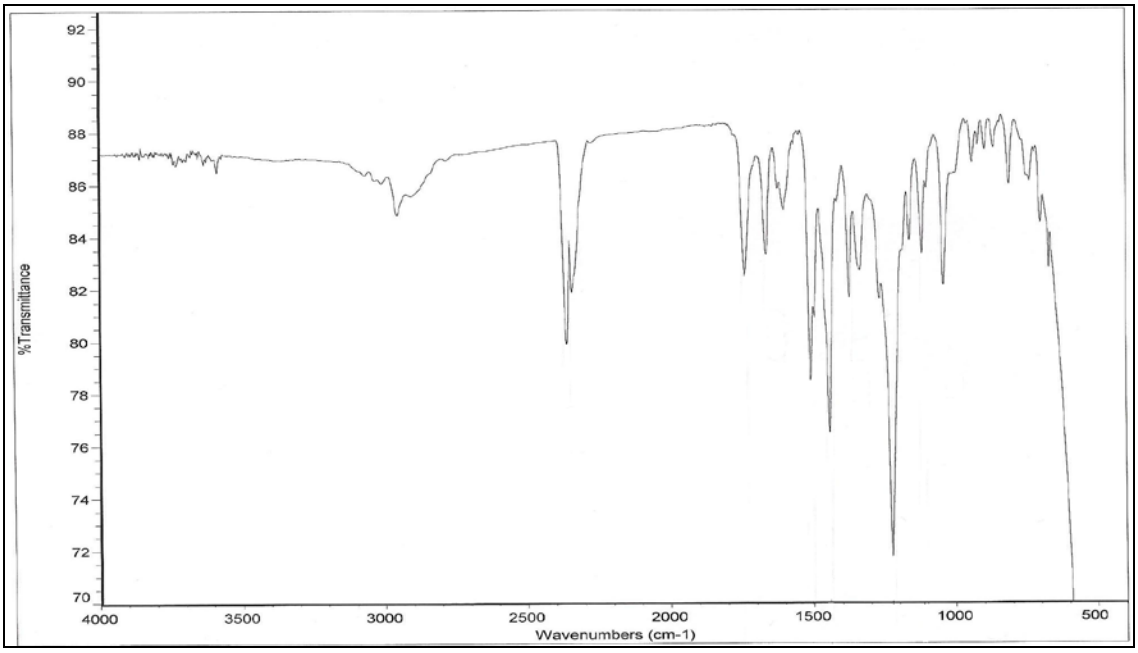


Figure 29. IR Spectrum (NaCl) of Trial 3: **63.**

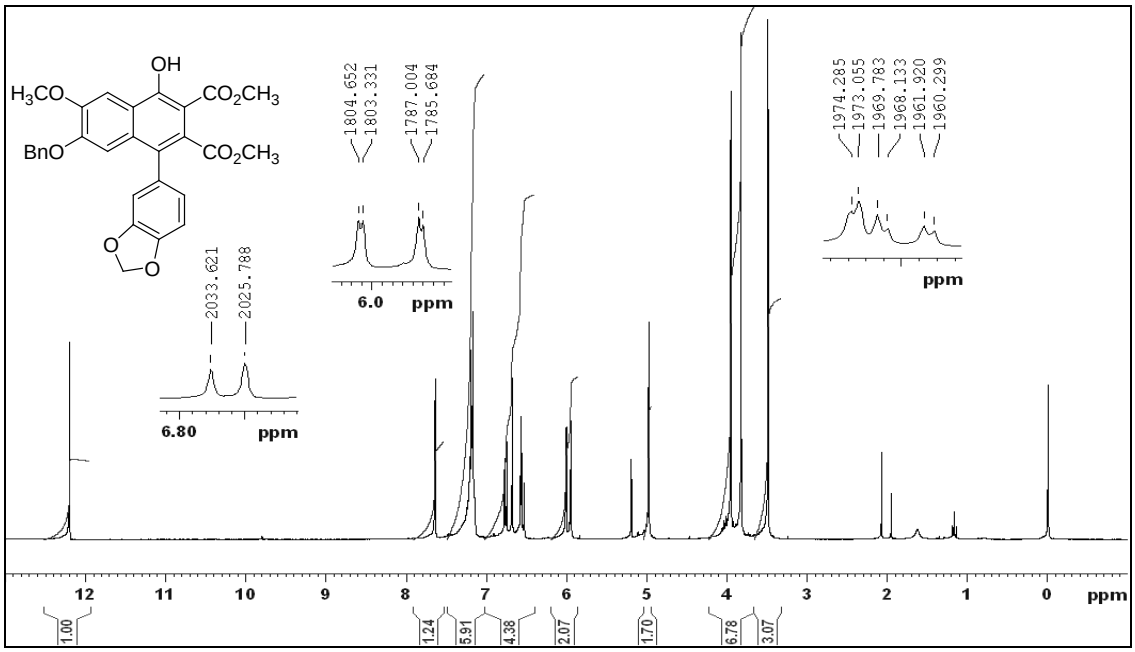


Figure 30. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trial 3: **63.**

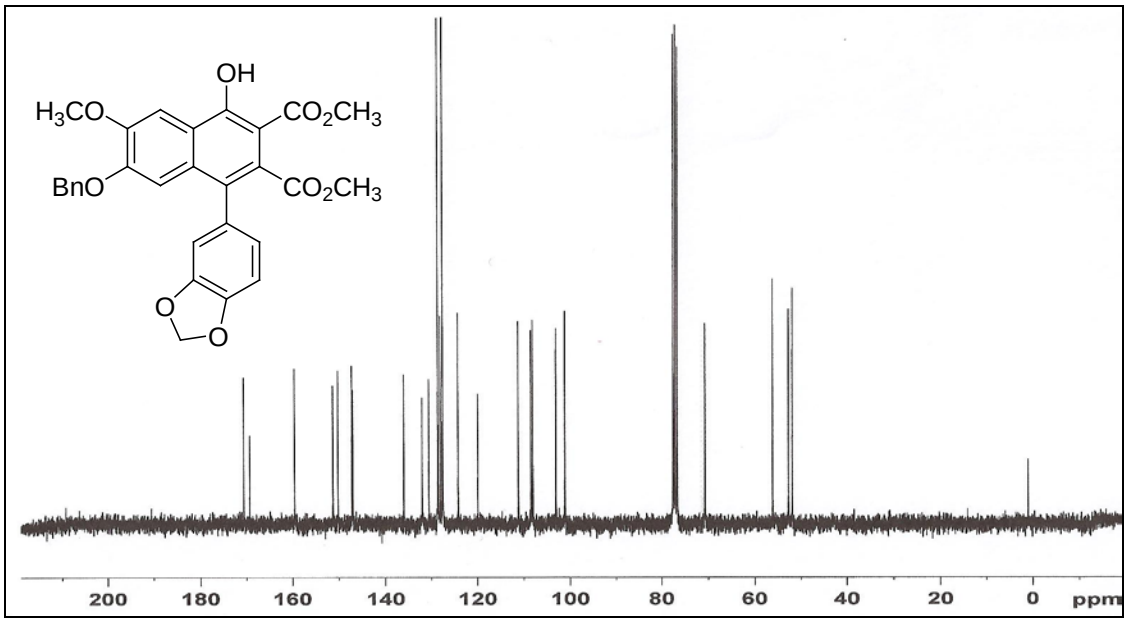


Figure 31. 75 MHz ^{13}C NMR Spectrum ($CDCl_3$) of Trial 3: **63.**

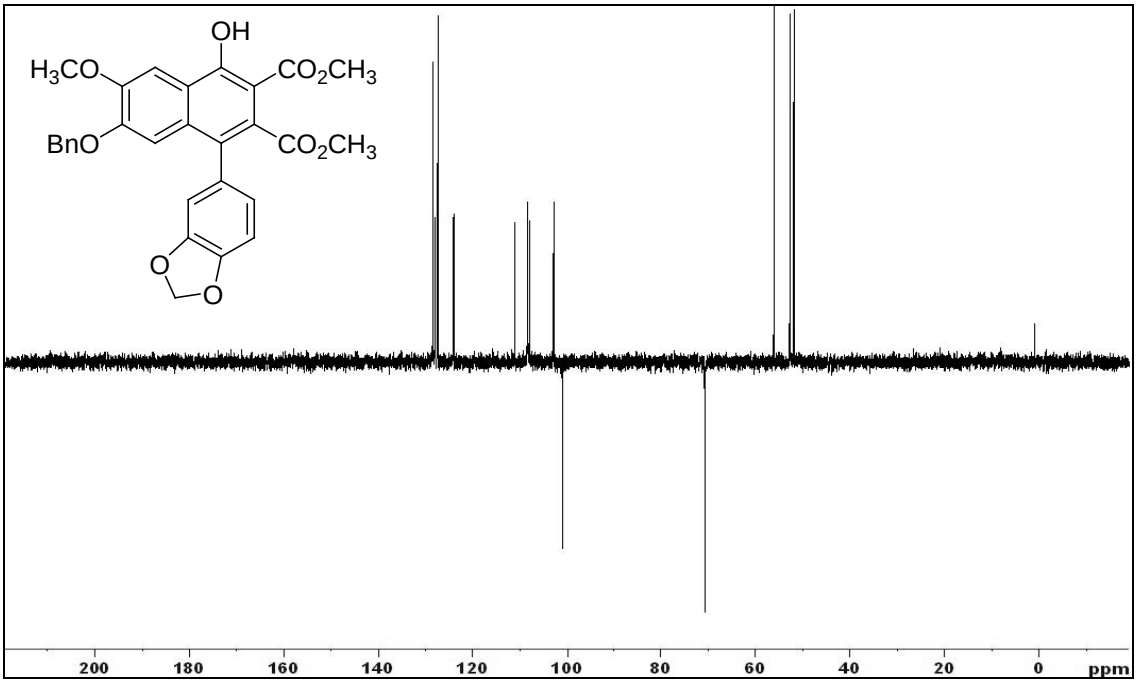


Figure 32. 75 MHz ^{13}C NMR DEPT Spectrum ($CDCl_3$) of Trial 3: **63.**

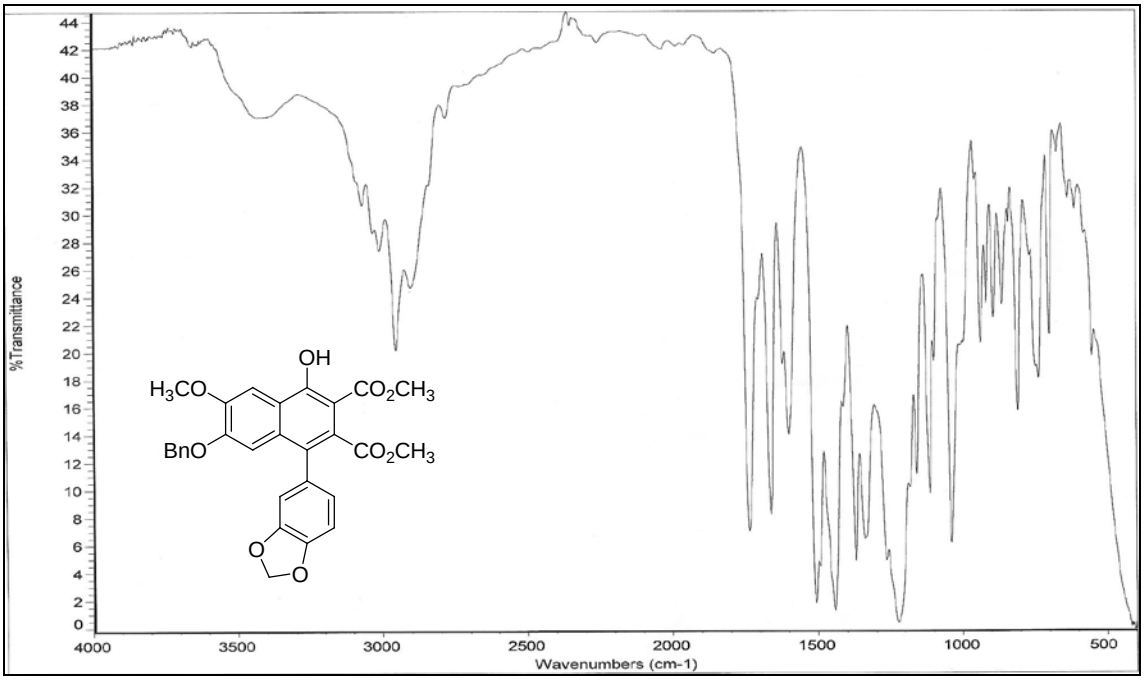


Figure 33. IR Spectrum (NaCl) of Trial 4: **63.**

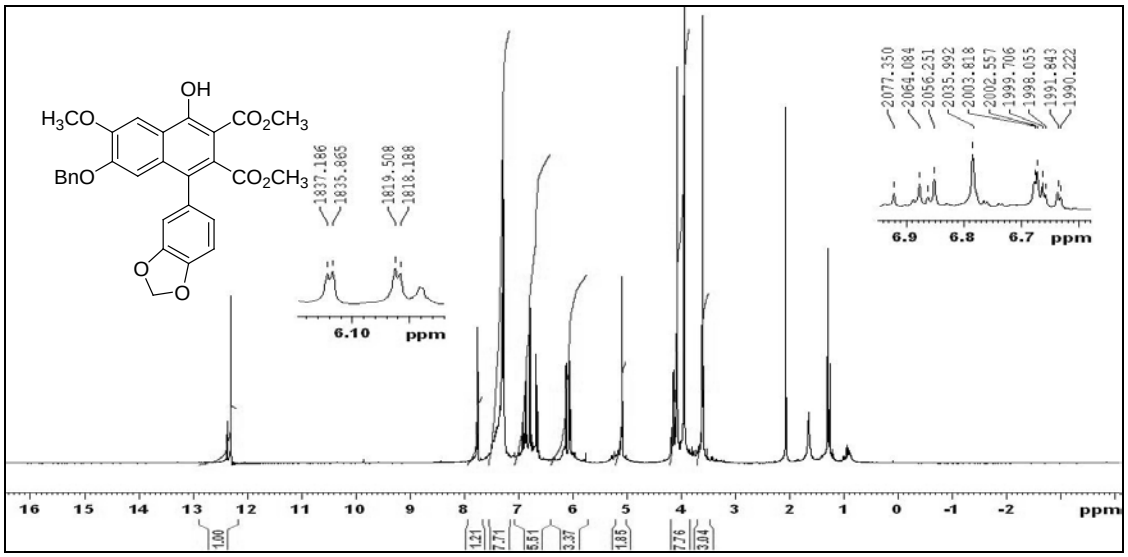


Figure 34. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trial 4: **63.**

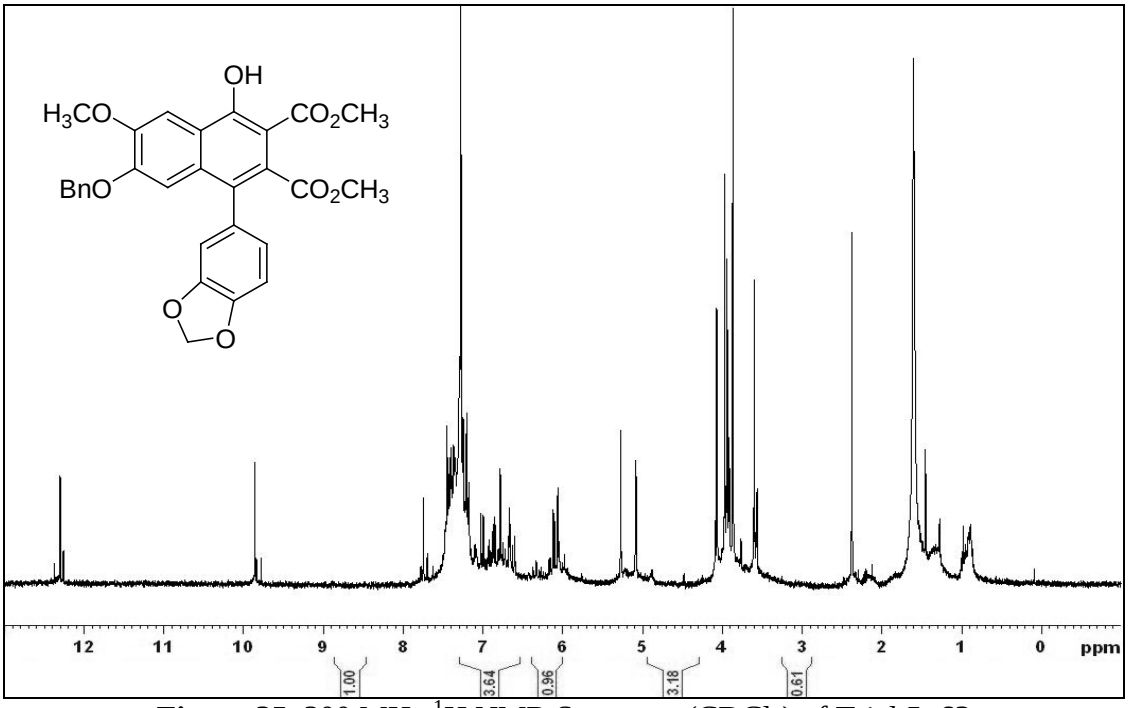


Figure 35. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) of Trial 5: **63**

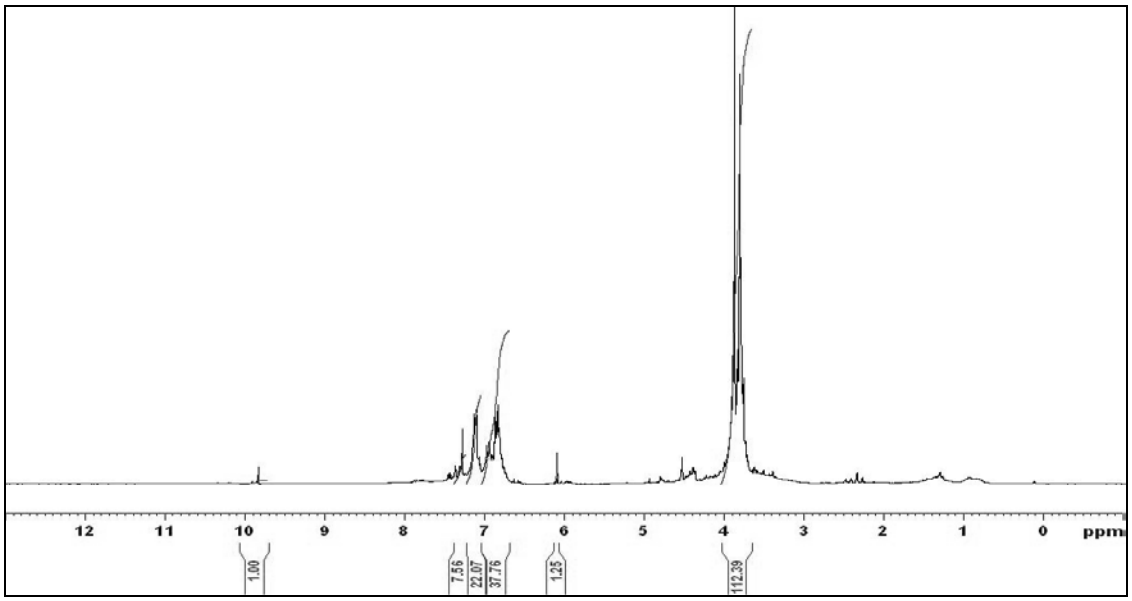


Figure 36. 300 MHz ^{1}H NMR Spectrum ($CDCl_3$) **75**

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VITA

Nora E. Hunter was born in Beavercreek, Ohio. She completed her degree at Wright State University receiving a Bachelor of Science Degree in Chemistry in June, 2007. As an undergraduate she participated in research with David Portlock, Ph. D., and William Feld, Ph. D. She received the Dubois Memorial Scholarship for the 2006-2007 Academic Year from Wright State University and the Outstanding Undergraduate Poster 2006 Dayton, Ohio ACS convention. Nora spent a year at Boston University where she was awarded the Dean's Fellow Graduate Research Fellowship 2007-2008. After this year, she decided to finish her Master of Science at Wright State University. She expects to receive her Master of Science Degree in Chemistry in June, 2010. Currently, she is enrolled in the Environmental Sciences doctoral program at Wright State University and will begin her studies in July 2010.