Towards the Total Synthesis of Haplomyrtin

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TOWARDS THE TOTAL SYNTHESIS OF HAPLOMYRTIN

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

By

NORA E. HUNTER
B.S., Wright State University, 2007

2010
Wright State University
I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Nora E. Hunter ENTITLED Towards the Total Synthesis of Haploemyrtin BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Vice President for Research and Graduate Studies
Interim Dean, School of Graduate Studies
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.
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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.\textsuperscript{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.\textsuperscript{1,3,4}

\[
\begin{align*}
\text{1} & \quad \text{2} & \quad \text{3} & \quad \text{4} \\
\end{align*}
\]

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.\textsuperscript{5} Haplomyrtin 4, a 1-aryl-2,3-naphthalide lignan obtained from Turkish \textit{Haplophyllum myrtifolium} and \textit{Haplophyllum telephioides}\textsuperscript{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 \(\gamma\)-lactone ring.\textsuperscript{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.\textsuperscript{7}

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

\begin{center}
\begin{tabular}{lll}
Natural Product & R\textsubscript{1} & R\textsubscript{2} & Natural Product & R\textsubscript{1} & R\textsubscript{2} \\
5) Justicidin B & Me & (-CH\textsubscript{2}-) & 8) Retrojusticidin B & Me & (-CH\textsubscript{2}-) \\
6) Taiwanin C & (-CH\textsubscript{2}-) & & 9) Justicidin E & (-CH\textsubscript{2}-) & \\
7) Chinensin & (-CH\textsubscript{2}-) & Me & 10) Retrochinensin & (-CH\textsubscript{2}-) & Me
\end{tabular}
\end{center}
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.

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 Br₂ 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 Al2O3 provided ketoaldehydes 22a-b.

\[ \text{R}_1\text{O}\text{CHO} \xrightarrow{\text{Br}_2, \text{AcOH}} \text{R}_1\text{O}\text{Br} \xrightarrow{\text{NaBH}_4} \text{R}_1\text{O}\text{CH}_2\text{OH} \]

18a) \( \text{R}_1 = \text{Me} \)
18b) \( \text{R}_1 = \text{CH}_2 \)
19a) \( \text{R}_1 = \text{Me} \) (80%)
19b) \( \text{R}_1 = \text{CH}_2 \) (86%)
20a) \( \text{R}_1 = \text{Me} \) (86%)
20b) \( \text{R}_1 = \text{CH}_2 \) (89%)

\[ \text{R}_1\text{O}\text{CHO} \xrightarrow{\text{PCC on Al}_2\text{O}_3} \text{R}_1\text{O}\text{CHO} \]

18a) \( \text{R}_2 = \text{Me} \)
18b) \( \text{R}_2 = \text{CH}_2 \)
21a) \( \text{R}_1 = \text{Me} \) \( \text{R}_2 = \text{CH}_2 \) (69%)
21b) \( \text{R}_1 = \text{CH}_2 \) \( \text{R}_2 = \text{Me} \) (81%)
22a) \( \text{R}_1 = \text{Me} \) \( \text{R}_2 = \text{CH}_2 \) (61%)
22b) \( \text{R}_1 = \text{CH}_2 \) \( \text{R}_2 = \text{Me} \) (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).
Table 1. Conditions of Tandem Horner-Emmons-Claisen condensation.

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

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 LiAlH4 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 BaMnO4, although the presence of the regioisomeric lactones was significant.

\[
\begin{align*}
25 & \quad \text{25a-c} \\
\text{a)} \ R_1=\text{Me}, \ R_2=\text{CH}_2, \ R=\text{Et} & \quad (93\%) \\
\text{b)} \ R_1=R_2=\text{CH}_2, \ R=\text{Et} & \quad (98\%) \\
\text{c)} \ R_1=\text{CH}_2, \ R_2=\text{Me}, \ R=\text{Et} & \quad (97\%)
\end{align*}
\]

\[
\begin{align*}
26 \text{ a-f} & \\
\text{a)} \ R_1=\text{Me}, \ R_2=\text{CH}_2 & \quad (75\%) \\
\text{b)} \ R_1=R_2=\text{CH}_2 & \quad (83\%) \\
\text{c)} \ R_1=\text{CH}_2, \ R_2=\text{Me} & \quad (74\%)
\end{align*}
\]

\[
\begin{align*}
28 & \\
\text{a)} \ R_1=\text{Me}, \ R_2=\text{CH}_2 & \quad (75\%) \\
\text{b)} \ R_1=R_2=\text{CH}_2 & \quad (83\%) \\
\text{c)} \ R_1=\text{CH}_2, \ R_2=\text{Me} & \quad (74\%)
\end{align*}
\]

<table>
<thead>
<tr>
<th>Natural Product</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5) Justicidin B</td>
<td>Me</td>
<td>(-CH(_2)-)</td>
</tr>
<tr>
<td>6) Taiwanin C</td>
<td>(-CH(_2)-)</td>
<td></td>
</tr>
<tr>
<td>7) Chinensin</td>
<td>(-CH(_2)-)</td>
<td>Me</td>
</tr>
</tbody>
</table>
Table 2. Conditions and yields for the conversion of 26a-f to natural products 5-10.

<table>
<thead>
<tr>
<th>Condition A with 25</th>
<th>Yield (%)</th>
<th>Condition C with 28</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5 (97%)</td>
<td>A</td>
<td>8 (34%)</td>
</tr>
<tr>
<td>B</td>
<td>6 (87%)</td>
<td>B</td>
<td>9 (59%)</td>
</tr>
<tr>
<td>C</td>
<td>7 (97%)</td>
<td>C</td>
<td>10 (91%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition B with 25</th>
<th>Yield (%)</th>
<th>Condition D with 28</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>8 (67%) + 5 (28%)</td>
<td>A</td>
<td>5 (12%) + 8 (86%)</td>
</tr>
<tr>
<td>B</td>
<td>9 (57%)</td>
<td>B</td>
<td>6 (14%) + 9 (71%)</td>
</tr>
<tr>
<td>C</td>
<td>10 (72%)</td>
<td>C</td>
<td>7 (19%) + 10 (80%)</td>
</tr>
</tbody>
</table>

A: BH₃, SMe₂, HCl; B: NaH, LiBH₄, HCl; C: MnO₂, DCM, rt.; D: BaMnO₄, 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. 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 199415 provided a new method of constructing biaryl compounds like C using a Ni⁰- catalyzed [2+2+2] cocyclization of compounds like A and two molecules of acetylene or from diynes like B and one molecule of acetylene.
In 2004, Sato, et al.\textsuperscript{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\textsuperscript{6}, and Tawanin E\textsuperscript{29} in 9 and 10 steps respectively, and established the sequence of steps for the synthesis of Chinensin\textsuperscript{7}, Justicidin B\textsuperscript{5}, and Diphyllin\textsuperscript{30}. 

![Diagram](image-url)
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.
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 Tf₂O to give 39 in 83% yield over three steps.

The Taiwanin core 40 was constructed by Pd⁰- 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.
$$\text{O}$$

$$\text{O}$$

$$\text{TMS}$$

$$\text{OTf}$$

$$\text{O}$$

$$\text{O}$$

$$\text{H}_3\text{C}-\text{N}$$

$$\text{OCH}_3$$

5 mol % $[$Pd$_2$(dba)$_2]$  
40 mol % $[$P(o-tol)$_2]$  
CsF (6.0 equiv.) 
$\text{CH}_3\text{CN}$, rt., 4h  

$$\text{N}$$

$$\text{O}$$

$$\text{CH}_3$$

$$\text{O}$$

$$\text{O}$$

$$\text{O}$$

$$\text{O}$$

$$\text{O}$$

NaH/CH$_3$OH 
$\text{CH}_2\text{Cl}_2$, rt.

$$\text{NaBH}_4$$  
$\text{CH}_3\text{OH}$  
0°C to rt.

$$\text{PCC}$$  
M.S. 4A  
$\text{CH}_2\text{Cl}_2$  
0°C

$$\text{CHO}$$

45 (89%)
Formation of the B ring in the arylnapththalene 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. 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. 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.
A similar Diels-Alder reaction involving an isobenzofuran and dimethyl acetylenedicarboxylate (DMAD) was utilized by Plaumann\textsuperscript{19} and Patil, et al.\textsuperscript{20} to form the B ring of the arylnaphthalene lignan core. In the synthesis of the 1-arylnaphthalene lignan precursor of Tawainin E \textsuperscript{29} and Diphyllin \textsuperscript{30}, Plaumann achieved the isobenzofuran from the crude hydroxyl acetals \textsuperscript{51a-b} by refluxing in benzene in the presence of a trace amount of pTSA. The Diels-Alder reaction produced the diester \textsuperscript{52a} in 65\% yield and \textsuperscript{52b} in comparable yield.
Patil, et al.\textsuperscript{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-arylnaphthalan 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.
**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.

\[ \begin{align*}
56 & \xrightarrow{\text{Ac}_2\text{O}, \text{pyr}, \Delta} 57(85\%) \xrightarrow{\text{Br}_2, \text{HAc}} 58 (48\%)
\end{align*} \]
Later, Schaaf 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 bromoacetal 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.
Some modifications to the individual steps of the synthesis were also reported by Chirisa. 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.
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

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 Ac₂O (3.4 mL) in Et₂O (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 °C (lit,23 mp 75-76 °C); IR (film) cm⁻¹ 3570, 3360, 3110, 3070, 3030, 1770, 1700, 1600, 1510; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

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 NaHCO₃. The organic layer was dried over MgSO₄ and concentrated to give 59 as a colorless solid (3.01 g, 79.5%): mp 173.8-175.9 °C (lit., mp 174-75 °C); IR (film) cm⁻¹ 3210 (O-H), 2910 (aromatic C-H), 1680 (C=O), 1201 (C-O), 1040 (C-O); ¹H NMR (300 MHz, CDCl₃) δ 3.37 (s, 1H), 3.83 (s, 3H), 7.10 (s, 1H), 7.33 (s, 1H), 10.00 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 189.8, 153.7, 124.6, 119.4, 119.1, 111.5, 55.7.

2-bromo-5-methoxy-4-(4-methoxybenzyloxy)benzaldehyde 68

A solution of 59 (0.996 g, 3.65 mmol, 1 eq), K₂CO₃ (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 N₂. 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 190.8, 159.8,
Phosphorous tribromide (3.5 mL) was added dropwise to a solution of 4-methoxybenzyl alcohol (12.8 mL) in dichloromethane (150 mL) at 0°C and stirred for 24 h. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and extracted with CHCl₃. Removal of the solvent in vacuo from the organic phase gave the product as a clear oil. (16.948 g, 84%). ¹H NMR (300 MHz, CDCl₃) 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-methoxybenzyl oxy)-2-bromo-5-methoxyphenyl)-1,3-dioxolane 69

To a solution of 68 (3.31 g, 9.43 mmol, 1 eq) and a catalytic amount of p-toluenesulfonic acid (pTSA) (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 MgSO₄ 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; ¹H NMR (300 MHz, CDCl₃) 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), ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₁₉BrO₅: C, 54.70 %; H, 4.85 %. Found: C, 64.05 %; H, 6.53 %.
5-bromo-4-(1,3-dioxolan-2-yl)-2-methoxyphenol 70\textsuperscript{21}

To 59 (1.52 g, 6.6 mmol, 1 eq) 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\textsuperscript{17} mp 97-98 °C (EtOAc-hexanes); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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\textsuperscript{26}

Vanillin 56 (5.076 g, 33.4 mmol, 1 eq), K\textsubscript{2}CO\textsubscript{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\textsubscript{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\textsuperscript{-1} 3083, 3007, 2968, 2938, 2871, 1670; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 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\textsubscript{16}H\textsubscript{16}O\textsubscript{4}: C, 70.57%; H, 5.92%. Found: C, 71.03%; H, 6.15%.
4-(3-bromo-4-methoxybenzyloxy)-2-bromo-5-methoxybenzaldehyde\textsuperscript{72} and 4-(3-bromo-4-methoxybenzyloxy)-3-methoxybenzaldehyde\textsuperscript{73}\textsuperscript{26}

To a solution of \textbf{71} (1.209 g, 4.55 mmol, 1 eq), and sodium acetate (1.279 g, 15.59 mmol, 3.4 eq) in acetic acid (11 mL) was added Br\textsubscript{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\textsubscript{4}, filtered and concentrated to yield a powdery solid as a mixture of products, \textbf{72} (0.031 g, 1.6%) and \textbf{73} (0.54 g, 28%).

\textbf{Compound 72}: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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);

\textbf{73}: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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), 7.66 (d, 1H, J=2.0 Hz).

2-(4-(benzyloxy)-2-bromo-5-methoxyphenyl)-1,3-dioxolane \textbf{74}

To a solution of \textbf{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\textsubscript{4} filtered and concentrated to provide \textbf{74} as a yellow solid (5.05 g, 13.9 mmol, 87.6%): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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), \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 149.4, 149.2, 136.3,
Dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-7-(4-methoxybenzyloxy)-4-hydroxy-6-methoxynapththalene-2,3-dicarboxylate 75

Method 1: PMB acetal 69 (0.50 g, 1.3 mmol, 1 eq) was dissolved in THF (4 mL) and cooled to -78°C under N₂ 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 H₂O (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 MgSO₄, 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°C for 1 h. The reaction mixture was cooled to RT. The mixture was washed with 10% CaCO₃ (aq) and extracted with ether. The organic layers were combined, dried over MgSO₄, 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 ¹H 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 ¹H NMR.
**Method 2:**\textsuperscript{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\textsubscript{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\textsubscript{2}O (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\textsubscript{4}, filtered, and concentrated. The crude product, DMAD (0.28 mL, 2 mmol, 2 eq) and a catalytic amount of pTSA were dissolved in toluene (50 mL) and heated at reflux for 2 h. No coupling product was detected by TLC or \textsuperscript{1}H NMR.

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

**General reaction:**\textsuperscript{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\textsubscript{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\textsubscript{2}O (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 MgSO₄, filtered, and concentrated. The crude product, DMAD (0.28 mL, 2 mmol, 2 eq) and a catalytic amount of pTSA 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\(_3\)) \(\delta\) 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, \(J=1.32\)Hz), 6.55 (dd., 1H, \(J_1=7.84\) Hz, \(J_2=1.96\) Hz), 6.58 (d., 1H, \(J=1.23\)Hz), 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\(_3\)) \(\delta\) 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 electrophilic 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\textsuperscript{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).

\[ \text{56} \xrightarrow{\text{NaOH (aq)}} \text{57} \ (96\%) \]

Bromination and subsequent deacetylation\textsuperscript{24} to yield 59 was indicated by the reappearance 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).
Methoxybenzyl Protective Group

The addition of the C ring through lithium-halogen exchange and coupling with piperonal, required that the bromovanillin $\mathbf{59}$ 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$^2^{1}$’s thesis work showed the Bn phenol $\mathbf{61}$ 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 $\mathbf{59}$ was treated with 4-methoxybenzyl bromide in DMF to provide $\mathbf{68}$ in 80.4% yield. This transformation was indicated in the $^1$H NMR of $\mathbf{68}$ 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).  

The p-methoxylbenzyl protective group proved to be problematic in acetal formation. The cyclic dioxolane in 69\textsuperscript{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 \textsuperscript{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 \textsuperscript{1}H NMR at 10 ppm and the \textsuperscript{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\textsuperscript{-1} (Figure 11). A time dependent study of the reaction was performed and the results are summarized in Table 3.
Table 3. Acetal formation results.

<table>
<thead>
<tr>
<th>Trial #</th>
<th>68 (mmol)</th>
<th>pTSA (mmol)</th>
<th>Time (days)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.8</td>
<td>0.05</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>2.6</td>
<td>0.05</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>9.4</td>
<td>0.15</td>
<td>5</td>
<td>48</td>
</tr>
</tbody>
</table>

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\(_2\)CO\(_3\) to carbonic acid in the reaction although it is surprising that the concentration of acid produced was high enough to catalyze the removal the acid labile acetal.

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 \textit{para} substitution on the phenyl ring in \textbf{Figure 16}. Two methods of bromination were explored. The first method employed KBr (aq), and Br\textsubscript{2}.\textsuperscript{22} This method seemed promising because the product should be insoluble in water and could be easily isolated. Benzyl ether \textbf{71} did not undergo bromination apparently because of reaction condition incompatibility. In the second method,\textsuperscript{26} C2 bromination was attempted using a method employing AcOH/AcONa and Br\textsubscript{2}. Bromination did occur, but compound \textbf{68} was not produced. The two products appear to show substitution on the PMB ether ring at the 3’ position as seen in compound \textbf{73} and \textbf{72} shows bromination at the C2 positions on the A ring. Compound \textbf{72} was characterized by $^1\text{H}$ 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) (\textbf{Figure 18}). Compound \textbf{73} was also characterized by $^1\text{H}$ 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) (\textbf{Figure 19}).
In order to address the isobenzofuran cycloaddition in a timely fashion, the focus returned to the original 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).

**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.\textsuperscript{17,18,19,20}

Initially, the PMB derivative 69 was subject to the Gilmore\textsuperscript{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.\textsuperscript{20} There were five trials of the coupling/Diels-Alder reaction run; the results are summarized in Table 4.

**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 pTSA 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.

<table>
<thead>
<tr>
<th>Trial #</th>
<th>74 (mmol)</th>
<th>nBuLi (mmol)</th>
<th>Yield (%) 63</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.37</td>
<td>1.60</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>1.36</td>
<td>1.92</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>1.34</td>
<td>1.60</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>1.52</td>
<td>1.82</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>1.37</td>
<td>1.60</td>
<td>10</td>
</tr>
</tbody>
</table>

**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 $\delta$ 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 $\rho$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).
Spectral Analysis of 63

In general, the infrared spectrum obtained for 63 lacks the strong OH stretch that was previously reported for the diester. Yet intramolecular hydrogen bonding affects the frequencies of phenolic OH stretch causing a reduction of the absorption frequency. As stated by Silverstein et al., 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 ¹H NMR (300 MHz, CDCl₃)

The ¹H 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 D₂O 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 $\delta \sim 7.5-4.0$. When a carbonyl function is ortho to the phenol, as in compound 63, a six-membered ring will form due to intramolecular hydrogen bonding. Hydrogen bonding shifts the absorption of the phenolic proton to the range of $\delta \sim 12.0-10.0$.

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 benzyl hydrogens and an absorption from 7.18-7.25 ppm corresponds to the benzyl 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 Ac₂O/ Et₂O in basic solution. The solid 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 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 pTSA, toluene and two equivalents of DMAD instead of AcOH and twenty equivalents of DMAD.\textsuperscript{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 $^{13}\text{C}$ NMR Spectrum (CDCl$_3$) of 57

Figure 5. 300 MHz $^1\text{H}$ NMR Spectrum (DMSO) of 59.
Figure 6. 75 MHz $^{13}$C NMR Spectrum (DMSO) of 59.

Figure 7. 300 MHz $^1$H NMR Spectrum (CDCl₃) 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$_3$) of 70.

Figure 15. IR Spectrum (NaCl) of 71.
**Figure 16.** 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 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$_2$O) 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
REFERENCES

5. Gilmore, T., M.S. Thesis, Wright State University, June 1996.


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.