The Synthesis of Haplomyrtin Utilizing The Triisopropylsilyl Protecting Group

William S. Barrow
Wright State University

Follow this and additional works at: https://corescholar.libraries.wright.edu/etd_all

Part of the Chemistry Commons

Repository Citation
https://corescholar.libraries.wright.edu/etd_all/752

This Thesis is brought to you for free and open access by the Theses and Dissertations at CORE Scholar. It has been accepted for inclusion in Browse all Theses and Dissertations by an authorized administrator of CORE Scholar. For more information, please contact library-corescholar@wright.edu.
THE SYNTHESIS OF HAPLOMYRTIN UTILIZING THE TRIISOPROPYLSILYL PROTECTING GROUP

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

By

WILLIAM S. BARROW
B.S., Wright State University, 1979

2013
Wright State University
WRIGHT STATE UNIVERSITY
GRADUATE SCHOOL

August 8, 2013


______________________________
William A. Feld, Ph.D., Director
Department of Chemistry
College of Science and Mathematics

______________________________
David A. Grossie, Ph.D., Chair
Department of Chemistry
College of Science and Mathematics

Committee on Final Examination

______________________________
Daniel M. Ketcha, Ph.D.

______________________________
Kenneth Turnbull, Ph.D.

______________________________
William A. Feld, Ph.D.

______________________________
R. William Ayres, Ph.D.
Interim Dean, Graduate School
ABSTRACT


The synthesis of the arylnapthalene lignan haplomyrtin using vanillin as a starting material is synthesized via: 1) a bromination of vanillin, 4-hydroxy-5-methoxybenzaldehyde, to produce 6-bromovanillin 2) a hydroxyl protection step of 6-bromovanillin with triisopropylsilylchloride to produce 2-bromo-4-triisopropylsilyloxy-5-methoxybenzaldehyde 3) an aldehyde protection step through a cyclic acetal formation using ethylene glycol to produce 2-(2-bromo-4-triisopropylsilyloxy-5-methoxyphenyl)-1,3-dioxolane 4) a lithium for halogen exchange of the doubly protected 6-bromovanillin leads to neucleophilic coupling with piperonal producing 1,3-benzodioxol-5-yl-[5-triisopropylsilyloxy-2-(1,3-dioxolane-2-yl)-4-methoxyphenyl]methanol and 5) an acid catalyzed intramolecular cycloaddition /Diels Alder adduct with dimethyl acetylenedicarboxylate producing dimethyl 1-(1,3-benzodioxol-5-yl)-4-hydroxy-6-methoxy-7-triisopropylsilyloxy napthalene-2,3-dicarboxylate.
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION .....................................................................</td>
<td>1</td>
</tr>
<tr>
<td>HISTORICAL .......................................................................</td>
<td>2</td>
</tr>
<tr>
<td>Gilmore Synthesis ......................................................</td>
<td>4</td>
</tr>
<tr>
<td>Schaaf Refinements .....................................................</td>
<td>6</td>
</tr>
<tr>
<td>Chirisa Refinements ...................................................</td>
<td>7</td>
</tr>
<tr>
<td>Hunter Refinements .....................................................</td>
<td>7</td>
</tr>
<tr>
<td>De Oude Refinements ...................................................</td>
<td>8</td>
</tr>
<tr>
<td>Silyl Protecting Groups ................................................</td>
<td>9</td>
</tr>
<tr>
<td>2-Bromo-5-methoxy-4-triisopropylsilyloxybenzaldehyde ..........</td>
<td>10</td>
</tr>
<tr>
<td>Lithium/Halogen Exchange Reactions ..................................</td>
<td>11</td>
</tr>
<tr>
<td>Project objectives .....................................................</td>
<td>13</td>
</tr>
<tr>
<td>EXPERIMENTAL ....................................................................</td>
<td>14</td>
</tr>
<tr>
<td>Instrumentation and Chemicals .........................................</td>
<td>14</td>
</tr>
<tr>
<td>4-Acetoxy-3-methoxybenzaldehyde ....................................</td>
<td>14</td>
</tr>
<tr>
<td>5-Bromo-4-formyl-2-methoxyphenylacetate ..........................</td>
<td>15</td>
</tr>
<tr>
<td>2-Bromo-4-hydroxy-5-methoxybenzaldehyde ........................</td>
<td>15</td>
</tr>
<tr>
<td>2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzaldehyde .......</td>
<td>15</td>
</tr>
<tr>
<td>2-(2-Bromo-4-triisopropylsiloxy-5-methoxyphenyl)-1,3-dioxolane</td>
<td>16</td>
</tr>
<tr>
<td>1,3-Benzodioxol-5-yl-[5-triisopropylsiloxy-2-(1,3-dioxolane-2-yl)-4-methoxyphenyl]methanol</td>
<td>17</td>
</tr>
</tbody>
</table>
**TABLE OF CONTENTS (CONTINUED)**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl 1-(1,3-benzodioxol-5-yl)-4-hydroxy-6-methoxy-7-triisopropylsilyloxynaphthalene-2,3-dicarboxylate</td>
<td>18</td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION</td>
<td>19</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>32</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>48</td>
</tr>
<tr>
<td>VITAE</td>
<td>50</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Imidazole catalysis of alcohol/phenol reaction with a trialkysilyl chloride</td>
</tr>
<tr>
<td>2.</td>
<td>Single electron transfer (SET) radical process</td>
</tr>
<tr>
<td>3.</td>
<td>Nucleophilic attack on halogen “ate” complex</td>
</tr>
<tr>
<td>4.</td>
<td>Four centered complex transition state</td>
</tr>
<tr>
<td>5.</td>
<td>Haplomyrtin Synthetic Scheme via a TIPS protective group</td>
</tr>
<tr>
<td>6.</td>
<td>General retrosynthetic scheme for the construction of Haplomyrtin</td>
</tr>
<tr>
<td>7.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 9 (BAV). Top Gilmore Rx. Bottom Ratton Rx</td>
</tr>
<tr>
<td>8.</td>
<td>IR Spectrum (NaCl) of 8 (AV)</td>
</tr>
<tr>
<td>9.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 8 (AV)</td>
</tr>
<tr>
<td>10.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 9 (BAV)</td>
</tr>
<tr>
<td>11.</td>
<td>IR Spectrum (NaCl) of 10 (BV)</td>
</tr>
<tr>
<td>12.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 10 (BV)</td>
</tr>
<tr>
<td>13.</td>
<td>IR Spectrum (NaCl) of 24 (TBV)</td>
</tr>
<tr>
<td>14.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 24 (TBV)</td>
</tr>
<tr>
<td>15.</td>
<td>300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 24 (TBV)</td>
</tr>
<tr>
<td>16.</td>
<td>IR Spectrum (NaCl) of 26 (TBVA)</td>
</tr>
<tr>
<td>17.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 26 (TBVA)</td>
</tr>
<tr>
<td>18.</td>
<td>300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 26 (TBVA)</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>19.</td>
<td>300 MHz $^1$H NMR spectral comparison of compound 26 reaction attempts (bottom to top is the reaction order)</td>
</tr>
<tr>
<td>20.</td>
<td>300 MHz $^{13}$C DEPT135 NMR Spectrum (CDCl$_3$) of 26 (TBVA)</td>
</tr>
<tr>
<td>21.</td>
<td>IR Spectrum (NaCl) of 27 (ROH)</td>
</tr>
<tr>
<td>22.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27 (ROH)</td>
</tr>
<tr>
<td>23.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27; expanded region 5.85 - 6.00 δ..................................</td>
</tr>
<tr>
<td>24.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27; expanded region 6.6 - 7.4 δ..................................</td>
</tr>
<tr>
<td>25.</td>
<td>300 MHz $^1$H NMR Spectra (CDCl$_3$) of the six 28 reaction attempts – spectrum 4 is D$_2$O exchange of 28</td>
</tr>
<tr>
<td>26.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28</td>
</tr>
<tr>
<td>27.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 5.8 - 7.8 δ..............................................</td>
</tr>
<tr>
<td>28.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 6.6 - 6.9 δ..............................................</td>
</tr>
<tr>
<td>29.</td>
<td>300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 5.95 - 6.05 δ....................................</td>
</tr>
<tr>
<td>30.</td>
<td>300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 28</td>
</tr>
<tr>
<td>31.</td>
<td>300 MHz $^{13}$C NMR (CDCl$_3$) of 28</td>
</tr>
<tr>
<td>32.</td>
<td>HSQC correlation spectrum of 28</td>
</tr>
<tr>
<td>33.</td>
<td>Expanded HSQC correlation spectrum of 28</td>
</tr>
</tbody>
</table>
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reaction conditions towards the production of 26</td>
<td>23</td>
</tr>
<tr>
<td>2. Reaction conditions towards the production of 28</td>
<td>29</td>
</tr>
</tbody>
</table>
ACKNOWLEDGMENTS

I would like to give a special thanks to my advisor, and also a friend, Dr. William Feld for giving me the opportunity to work in his group. His guidance and teaching inspired me to be a better student, researcher, and Powerpoint presenter. I would not be the chemist I am today without all that he taught me and for that I am truly grateful.

I would also like to acknowledge the faculty, staff, and graduate students of the Wright State Chemistry Department for all I have learned from them and experienced with them as a student over the past four years.
DEDICATION

I would like to dedicate this work in memory of my wife of thirty years, Chris. Despite a six year battle with non Hodgkin’s lymphoma, never once did she ever lose hope, rarely complained, but forever displayed optimism. Her friendship, love, faith, and support has given me the strength and drive to achieve my goals. She was my biggest cheerleader and my hero. “I (we) can do all things through Christ who strengthens me (us)”, Phil 4:13.
INTRODUCTION

The genus Haplophyllum, belonging to the rutaceae family, or "citrus type plants," is well represented\(^1\) by approximately seventy different plant species that are found across most of the European continent.\(^2\) Haploomyrtin \(1\), was first reported isolated from the perennial Turkish herb, *Haplophyllum myrtifolium* in 1985. The synthetic challenge to produce Haploomyrtin was first addressed by Gilmore\(^3\) in 1996 and by various other researchers\(^4,5,6,7\) over the next sixteen years. Low product purity, low yields, and poor intermediate stability have plagued these synthetic attempts. A lithium-halogen exchange reaction involving benzyl ether \(2\) is hampered by the benzyl methylene acidity that has been clearly identified by D\(_2\)O quenching studies. This suggests that the preparation of \(3^8\) may circumvent these problems.

The objectives of this research were to 1) use \(3\) to prepare the TIPS analog of \(2\), i.e. \(3\) and 2) determine the reactivity of \(3\) in the crucial lithium-halogen exchange reaction.
HISTORICAL

The discovery that certain plant hormones exhibit anticancer properties has generated considerable interest in a possible synthetic route to their production. The chemical diversity of alkaloids present in the rutaceae family correlate well with the various biosynthetic pathways of the aromatic amino acid precursors found in the human body, i.e. tyrosine, tryptophan, histidine, and anthranilic acid. The interest in these rutaceous, polyheterocyclic alkaloids’ use as potential anticancer agents relies on their unique abilities to interact with and disrupt DNA replication through the binding at specific covalent adduction sites on the nucleic acid chains. Many such targeted plant compounds, or lignans, exist naturally in low part per million amounts, necessitating alternative, more practical, means to their production. Seven of the most widely used chemotherapeutic drugs today are still derived from plant origin, i.e., Etoposide and Teniposide (from the American Mayapple *Podophyllum peltatum*), Taxol (from the Pacific Yew bark, *Taxus brevifolia*), Vinblastine and Vincristine (from periwinkle leaves, *Vinca rosea* Linn.), Topotecan and Irinotec (from the Chinese Happy Tree bark, *Camptotheca acuminata*).

The plant arylnapthalene phenol “Haplomyrtin” was first isolated, structurally identified, and reported through the efforts of Gözler in 1985 from a dried, finely divided sample of *Haplophylum myrtifolium*. A crushed, herbal, EtOH extract was acidified, extracted with CHCl₃, fractionalized by way of a silica gel column, dried, and one alkaloid (of several reported), Haplomyrtin, was obtained in the form of a white
amorphous powder. The combined efforts of Ege University, College of Pharmacy in Izmir, Turkey and Penn State University, Department of Chemistry, confirmed the structure was that of Haplomyrtin via $^1$H NMR, UV, IR, and mass spectral data.

Haplomyrtin 1 is only one of hundreds of reported naturally occurring arylnaphtalene lignans that can be found in a number of species of the Turkish perennial herb genus, *Haplophyllum*. Haplomyrtin 1 has also been isolated from certain varieties of the *Phyllanthus* genus of which there are over 600 reported species distributed throughout South America, Asia, and Africa. The arylnaphtalene scaffolding central to haplomyrtin’s structure has readily been synthesized in several commonly used drug intermediates, i.e. Justicin B 4, Taiwanin C 5 and Diphyllin 6, of which there are well over 200 derivatives. The primary differences and overall challenge faced with the synthetic route to Haplomyrtin vs. one of the more common structures, as has been shown, stems from the difficulty of introducing and protecting hydroxyl groups at the C4 and C7 positions of Haplomyrtin’s naphthalene nucleus.
Gilmore Synthesis

The synthesis of the plant-phenol, Haplomyrtin 1, was first attempted at WSU by Gilmore in 1996. Through a combination of both literature search and ingenuity, he proposed a synthetic route utilizing the readily available ingredients, vanillin 7 and piperonal 12a as starting materials. In twelve separate steps, he did manage to produce a crude, non-isolatable product, that via $^1$H NMR, resembled Haplomytin 1. All subsequent research and refinements into the synthesis of this compound were based on Gilmore’s initial efforts.

In order to build the arylnapthalene nucleus of 1, Gilmore chose to begin with the “A” ring portion of which vanillin is used as the starting point. Bromination of vanillin at the desired 6 position of the aromatic ring is strategically accomplished through ring deactivation of vanillin’s ortho directing hydroxyl group by the addition of the acetyl group followed by bromination in acetic acid in order to produce acetylated 6-bromovanillin 9.

Prior to the ensuing lithium halogen exchange step used to insert the pendent “C” ring on to the 6 position of 6-bromovanillin “A”-ring nucleus, double protection of the hydroxyl and aldehyde functions of 6-bromovanillin is needed. The 4-hydroxyl group protection of 10 is accomplished through capping via the benzyl ether formation reaction with benzyl chloride. Protection of the aldehyde 11 is via conversion to the dimethyl acetal through
reaction with trimethyl orthoformate. The newly protected precursor, 2-bromo-4-benzyloxy-5-methoxybenzaldehyde dimethylacetal 12, may now undergo a lithium-bromine exchange. Utilizing butyl lithium to generate a lithiated carbanion product intermediate of 12, the newly formed nucleophile can attack the piperonal aldehyde
generating the target alcohol 13. Acid-catalyzed hydrolysis of the dimethyl acetal to the alcohol 13 allows for an intramolecular condensation followed by cyclization, thereby generating an intermediate isobenzofuran 13a. The Diels-Alder product of the reaction of the intermediate diene 13a with the dienophile, dimethyl acetylenedicarboxylate (DMAD), generates the targeted “A-B-C” ring napthol precursor 14. Prior to the final two steps in forming the terminal butyrolactone ring of the target product, the benzyl, protecting group at C7 must first be removed through catalytic hydrogenation, leaving the diol product, napthol 15. In order to complete butyrolactone ring formation in the final step, the ortho ester function on C3 of 15 is selectively reduced to the primary alcohol intermediate 15a utilizing NaBH₄ prior to acid catalyzed, intramolecular condensation that in turn produces 1.

**Schaaf Refinements**

Refinements to the Gilmore procedures were first reported in 1998 by Schaaf.⁴ Although Schaaf did not succeed in producing 1, his research efforts focused towards the added synthetic burdens created through the required vanillin 7 protection steps. First, Schaaf demonstrated the use of a more “compact” cyclic acetal (in 16) protective group
at the C1 aldehyde in place of Gilmore’s more sterically demanding dimethoxy function (in 12). Second, Schaaf demonstrated the issue of proton lability of the C4 benzylic protecting group of 7 through BuLi metatalation, followed by D$_2$O workup, thus producing the conjugate deuterated acid product. Third, he demonstrated that a possible alternative “Grignard route” to the desired alcohol intermediate 13 was not effective and was not a viable alternative to lithium halogen exchange.

**Chirisa Refinements**

Further refinements to the Gilmore procedure were demonstrated by Chirisa in 2006. First, Chirisa substantially improved the yield of 6-bromovanillin 10 through alternate procedural chemistry. Second, she demonstrated through $^1$H NMR studies that the ideal stoichiometric ratio of butyl lithium to protected precursor 12 during halogen exchange step is 1:1. Third, she reiterates the reactivity issue associated with the benzyl protective group and it’s problematic involvement during the lithium-halogen exchange step. An isolated end product 1 in low yield was obtained.

**Hunter Refinements**

In 2008, Nora Hunter's research at WSU on total Haplomyrtin synthesis again focused on the lithiation reaction difficulties associated with the benzyl ether protection at C4 of the bromovanillin acetal nucleus. In an effort to decrease the susceptibility of the
protective group benzyl protons on C4, Hunter introduced the p-methoxybenzyl (PMB) protection group 16a in an effort to increase the benzylic pKa. The PMB protection, however, soon proved to be problematic. Second, her modification of the acid catalyzed DMAD Diels-Alder cycloaddition step utilizing catalytic amounts of pTSA in place of acetic improved yields of the targeted arylnapthalene diester product 14 over previous researchers. An isolated end product was not produced.

Coen de Oude Refinements

Most recently, in 2012, de Oude\(^7\) researched a variant synthetic route to Haplomyrtin that paralleled the patented “Cleistantin A” procedure.\(^{12}\) Cleistantin A, also an arylnapthalene lignin is structurely similar to Haplomyrtin’s arylnapthalene nucleus but with key differences being the C7 substituents. Cleistantin A contains the stable methyl ether group whereas Haplomyrtin has the problematic hydroxyl function. Key synthetic changes include 1) longer lithium halogen reaction times by a factor of 5 and at a higher temperature, 2) an ammonium chloride solution quench of 17, 3) the DMAD cycloaddition step carried out in sealed tube conditions and 4) LAH reduction of dicarboxylate intermediate 15 in place of NaBH\(_4\). A crude, non-isolatable product was obtained in low yield.
Silyl Protecting Groups

The silyl ethers, $R_3SiOR'$ 19, are one of the most frequently used groups for the protection of the hydroxyl function. They are commonly synthesized by the reaction of an alcohol or a phenol $R'$ with a trialkylsilyl chloride 18 in the presence of an organic base catalyst. Bases generally employed include $R_3N$, imidazole, 2,6-lutidine, DMAP, and DBU.\(^\text{13}\)

Their popularity also stems from the fact that they are readily introduced and removed under mild conditions.\(^\text{13}\) The ability to regulate both steric and electronic effects on the silicon atom through the selective use of attached substituents makes silyl ethers a valuable, multifunctional tools. Silyl ethers can be easily cleavable through select use of compact steric attachments as in the trimethylsilyl (TMS) 21 or made relatively inert to
the harshest conditions as in TBDPS 24. These steric effects can also be advantageous in regiospecific alcohol protection. The large, more sterically demanding TIPS, TBDMS, and TBDPS groups will selectively bind to primary alcohols in the presence of hindered secondary and tertiary OH groups. The compact TMS can be used to cap the most hindered tertiary alcohols. The cleavability of silyl ethers is also dependent upon constituent electronic effects. Electron withdrawing groups on the silicon atom increase susceptibility toward base hydrolysis but decrease sensitivity towards acid. The stability toward acid hydrolysis of the silyl ethers (relative rates) shown earlier increases in the following order: TMS (1) < TES (64) < TBDMS (20,000) < TIPS (700,000) < TBDPS (5,000,000), and stability towards base increases in the following order: TMS (1) < TES (10-100) < TBDMS~TBDPS (20,000) < TIPS (100,000). The TIPS group is easily introduced, is inert under many conditions, is easily removed by specific reagents thus rendering TIPS one of the foremost permanent protecting groups for OH. The bulkiness of TIPS seems to be the correct magnitude as to exhibit a good compromise between useful steric effects on the one hand and ease of removal on the other.

**2-Bromo-5-methoxy-4-triisopropylsilyloxybenzaldehyde**

The synthesis of 2-bromo-5-methoxy-4-triisopropylsilyloxybenzaldehyde 24 was reported in 2004. Aldehyde 10 was reacted with triisopropylsilyl chloride in DMF
using imidazole as a catalyst to produce the TIPS protected aldehyde 24. Subsequent reduction of 24 with sodium borohydride produced an intermediate alcohol that could be converted to the bromide 25 by reaction with phosphorus tribromide. The bromide 25 was used to produce a substituted tetrahydroisoquinoline for rearrangement studies.

![Chemical structure diagram](image)

**Lithium/Halogen Exchange Reactions**

One crucial step in the assembly of the Haplomyrtin nucleus is the lithium/halogen exchange reaction. The organo-lithiums, due to the highly polar nature of the electron deficient lithium atom, can only exist in a hydrocarbon solution through stabilized aggregates of hexamers, tetramers, and dimers.\(^\text{16}\) This particular aggregate state will depend upon the steric nature of the individual organolithium and the stabilizing solvent system. In an alkane hydrocarbon the highly branched alkyl or benzyl lithiurns may only exist as the dimer whereas the straight chain \(n\)-butyl lithium as the hexamer. The use of an electron donating solvent system, such as an ether or amine base, may function as a coordinating ligand allowing the organolithium to shift to a lower degree of aggregation.\(^\text{17,18,19}\) In general, organolithium reactivity, i.e., metallation strength, rises with the Lewis basicity of the solvent system. The reactivity of organolithiums can therefore, in part, be modulated by choice of solvent system. The highly polar amine HMPA is very activating, THF and TMEDA are moderately activating, with diethyl ether the least. However, the de-aggregation effect of the solvent system alone doesn’t always explain the reactivity differences between the various solvents. The solvent properties
may have more to do with stabilization of the reactant transition state or product than solely de-aggregating effects, but it is unclear how. All of the coordinating solvents used with the organolithiums, however, will eventually react with the organolithium, itself, over time. The attention to reaction time, maintaining very low temperature, and a quick workup are all necessary steps to avoid possible solvent decomposition products.

The mechanism of lithium halogen exchange is still unclear but the evidence suggests 3 possible routes. Apparent in lithium halogen exchange is an equilibrium reaction favoring formation of the weaker, more stable organolithium conjugate base. The transition state involved in this process may be either 1) single electron-transfer (radical process), 2) nucleophilic (formation of halogen “ate” complex), or 3) four-centered complex model.

**Figure 2.** Single electron transfer (SET) radical process.

**Figure 3.** Nucleophilic attack on halogen “ate” complex.

**Figure 4.** Four centered complex transition state.
Project Objectives

A synthetic route to Haplomyrtin has been a decade-long-plus subject of graduate research at Wright State University’s (WSU) Feld Group. The synthetic difficulties encountered en route to this compound can be traced back to the necessary, but often problematic, protection and deprotection reaction steps. The following research focuses on the crucial naphthalenediol segment of Haplomyrtin 1. A new silyl ether protection in place of a previously used benzylic ether protection is proposed as shown in Figure 5.

Figure 5. Haplomyrtin Synthetic Scheme via a TIPS protective group.
Experimental

Instrumentation and Chemicals

Melting points were obtained with a DigiMelt MPA-160 or Electrothermal MP Apparatus. Nuclear magnetic resonance (NMR) $^1$H and $^{13}$C spectra were obtained using a Bruker Avance 300 MHz NMR Spectrometer. Solvents for NMR were CDCl$_3$ and DMSO-d$_6$. Infrared (IR) spectra were recorded as thin films (NaCl) with a Nicolet 6700 FT-IR spectrometer. Elemental analyses were obtained through Midwest Microlab, LLC, Indianapolis, IN. A 35 mL Q-Tube™ (pressure tube reactor) was purchased from Sigma-Aldrich Labware. Chemicals were purchased from Aldrich and used as received.

4-Acetoxymethoxybenzaldehyde 8

Vanillin 7 (60 g, 0.38 mol) was suspended in methylene chloride (300 mL). Acetic anhydride (45 mL, 0.48 mol) and pyridine (38 mL, 0.47 mol) were added. The solution was stirred for 18 h at rt. Water (100 mL) was added cautiously and the solution was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, washed with 1N HCl (2 x 100 mL), saturated NaHCO$_3$ (2 x 100 mL), saturated brine (2 x 100 mL) and dried over Na$_2$SO$_4$. The drying agent was filtered and the solution was concentrated under reduced pressure to yield 8 (68 g, 0.35 mol, 91%): mp 76° (lit 77-79°); IR(cm$^{-1}$) 2966 (CH$_3$), 2846 (CH$_3$), 1753 (ester C=O), 1722 (ald C=O), 1219 (C-O), 1200 (C-O); NMR (CDCl$_3$) $\delta$ 2.34 (3H, s, CH$_3$), 3.90 (3H, s, CH$_3$COO); 7.22 (1H, d (J = 7.80 Hz), Ar-6H), 7.48 (1H, d, (J = 7.86 Hz), Ar-5H), 7.50 (1H, s, Ar-2H), 9.94 (1H, s, -CHO).
5-Bromo-4-formyl-2-methoxyphenylacetate 9

Glacial acetic acid (190 mL) and acetylvanillin 8 (68 g, 0.35 mol) were introduced into a 100 mL round-bottomed-flask equipped with stir bar and pressure equalizing dropping funnel. A bromine solution, (43.7 g, 0.27 mol, 14 mL in 40 mL glacial acetic acid) was added dropwise. When addition was complete, acetic acid (140 mL) was added followed by dropwise addition of 30% H$_2$O$_2$ (20.5 g, 0.60 mol). After 20 h the reaction was quenched by the addition of water (5 x 300 mL), cooled to 0° with ice, and the resultant precipitate was filtered and dried to give 9 (64 g, 0.24 mol, 67%): $^1$H NMR (CDCl$_3$) $\delta$ 2.35 (3H, s, C$_3$H$_3$), 3.89 (3H, s, C$_3$H$_2$COO), 7.38 (1H, s, Ar-5H), 7.52 (1H, s, Ar-2H), 10.28, 1H, s, -CHO).

2-Bromo-4-hydroxy-5-methoxybenzaldehyde (6-bromovanillin) 10

Into a 500 mL round-bottomed flask equipped with a condenser was added HCl (250 mL, 6N) and compound 9 (11 g, 0.04 mol). The mixture was refluxed at 90° for 4 h, cooled and the solids were filtered and recrystallized from EtOH to give 10 (2 g, 0.009 mol, 22%): mp 176° (lit mp 178-180°); IR (cm$^{-1}$) 3295 (O-H), 1660 (C=O), 1210 (C-O), 694 (Ar-OH), 637 (Ar-Br); $^1$H NMR (CDCl$_3$) $\delta$ 3.84 (3H, s, C$_3$H$_3$), 7.09 (1H, s, Ar-5H), 7.32 (1H, s, Ar-2H), 10.00 (1H, s, –CHO), 10.77 (1H, s, Ar-OH).

2-Bromo-5-methoxy-4-(triisopropylsilyloxy)benzaldehyde 24

Imidazole (3.872 g, 56.8 mmol) and TIPSCI (3.096 g, 16.2 mmol) were added to a stirred solution of 2-bromo-4-hydroxy-5-methoxybenzaldehyde (BV) 10 (3.750 g, 16.2 mmol) in dry DMF (50 mL). The reaction mixture was stirred for 15 min at room temperature and poured into water (150 mL). The product was extracted with hexane (3 x 100 mL). The extracts were combined and washed with brine (100 mL) and dried over
The solution was filtered and the solvent was removed in vacuo to afford the title compound 24 as an amber oil (1.5 g, 3.8 mmol, 23.4%): IR (cm$^{-1}$) 2944 (CH$_3$), 2892 ((CH$_3$)$_2$C-H), 2867 (CH$_3$), 1686 (C=O), 1387, 1322, 1153 ((CH$_3$)$_2$C-H), 1213, 1042 (C-O-C), 636 (Ar-Br); $^1$H NMR (CDCl$_3$) $\delta$ 1.11 (18H, d (J = 6.99 Hz), (CH$_3$)$_2$CH-), 1.28 (3H, m (J = 6.60 Hz), (CH$_3$)$_2$C-H), 3.86 (3H, s, -OC$_2$H$_3$), 7.09 (1H, s, Ar-6H), 7.42 (1H, s, Ar-3H), 10.19 (1H, s, -CHO); $^{13}$C NMR ppm 12.93, 17.73 (iPr$_3$Si), 55.56 (-OC$_2$H$_3$), 111.23 (Ar-2C-Br), 119.44 (Ar-6C-H), 124.58 (Ar-3C-H), 126.98 (Ar-1C-CHO), 150.85 (Ar-4C-OSi), 152.11 (Ar-5C-OCH$_3$), 190.90 (-CHO).

2-(2-Bromo-4-triisopropysiloxy-5-methoxyphenyl)-1,3-dioxolane 26

The aldehyde 24 (1.00 g, 2.6 mmol) and ethylene glycol (1.5 mL), pTSA (0.03 g) and benzene (90 mL) were introduced into a 100 mL round-bottomed flask equipped with a Dean-Stark trap (DST) and the solution was refluxed for 24 h. The water/benzene azeotrope was removed (3 x 10 mL) from the DST during reflux. The reaction was cooled and the solution was washed with saturated NaHCO$_3$ solution (3 x 20 mL). The organic layer was dried overnight over Na$_2$SO$_4$, filtered, and the solvent removed in vacuo. The yellow oil was passed through a short silica gel column using ethyl acetate/hexane (1:5) to afford the title compound 26 (0.249 g, 0.58 mmol, 22%): IR (cm$^{-1}$) 2945 (CH$_3$), 2892 ((CH$_3$)$_2$C-H), 2867 (CH$_3$), 1387 ((CH$_3$)$_2$C-H), 1208 (ArOCH$_3$), 1168 (OCH$_2$CH$_2$O), 1087 (CHOCH$_2$), 614 (Ar-Br); $^1$H NMR (CDCl$_3$) $\delta$ 1.00 (18H, d (J = 7 Hz), (CH$_3$)$_2$CH-), 1.16 (3H, m (J = 6.8 Hz), (CH$_3$)$_2$C-H-), 3.73 (3H, s, -OCH$_3$), 4.12 (4H m, -OCH$_2$CH$_2$O-), 5.90 (1H, s, -OCHO-), 6.96 (1H, s, Ar-6H), 7.19 (1H, s, Ar-3H); $^{13}$C NMR (CDCl$_3$) ppm 12.75 (-CH-Si), 17.73(CH$_3$)$_2$CH-Si), 55.57 (-OCH$_3$), 65.42 (-OCH$_2$CH$_2$O-), 102.65 (-OCHO-), 110.90 (Ar-2C-Br), 112.76 (Ar-6C-H), 124.20 (Ar-
IC-CH), 128.72 (Ar-3C-H), 147.07 (Ar-4C-OSi), 150.26 (Ar-5C-OCH3); Analytical

1,3-benzodioxol-5-yl-[5-triisopropylsilyloxy-2-(1,3-dioxolane-2-yl)-4-
methoxyphenyl]methanol 27

In a flame-dried, sealed and purged, 15 mL, round-bottomed flask, piperonal
(0.61 g, 4.1 mmol) was dissolved in dry THF (10 mL). In another dried, sealed, and
purged 50 mL round-bottomed flask 26 (1.76 g, 4.1 mmol) was dissolved in anhydrous
THF (25 mL). The 26 solution was transferred to a flame-dried, sealed, two-necked, 50
mL round-bottomed flask equipped with a 10 mL pressure-equalizing dropping funnel,
nitrogen inlet and outlet and the system was cooled to -78°. To the stirred, cooled
solution was added dropwise, n-butyllithium (3 mL, 4.8 mmol, 1.6M). After addition of
n-BuLi to the 26 mixture was complete, it was stirred for 0.5 h. The piperonal solution
was transferred to the 10 mL dropping funnel and added dropwise to the reaction
mixture. After stirring for 1 h at -78°, the reaction was allowed to warm to room
temperature and stirred for an additional 5 h. The reaction was quenched with saturated
NH₄Cl (20 mL), extracted with ethyl acetate (3 x 20 mL) and the extracts were dried over
NaSO₃, filtered, and concentrated to give the intermediate alcohol 27 as a viscous amber
oil that was used in the next step without further purification: IR(cm⁻¹) 34634(OH);¹H
NMR (CDCl₃) δ 7.28 (1H, s, Ar-6H), 7.08 (1H, d, Ar-6’H), 6.88 (1H, s, Ar-3H), 6.79
(1H, s, Ar-2’H), 6.68 (1H, d, Ar-5’H), 5.96 (1H, s, -OCH₂O-), 5.95 (1H, s, -OCH₂O-),
5.92 (1H, s, -OCHO-), 5.91 (1H, s, -CHOH), 4.18 (2H, m, -OCH₂CH₂O-), 4.05 (2H, m, -
OCH₂CH₂O-), 3.83 (3H, s, Ar-OCH₃), 2.04 (1H, s, -CHOH).
**Dimethyl 1-(1,3-benzodioxol-5-yl)-4-hydroxy-6-methoxy-7-triisopropylsiloxynapthalene-2,3-dicarboxylate 28**

To a 35 mL sealed Q-tube was added the 1.94 g of crude 27, 0.39 mL (3.07 mmol) of DMAD, 1.5 mL DCM, 0.89 mL (0.87 mmol) glacial acetic. The mixture was heated at 140° for 84 h. The reaction mixture was cooled, diluted with 30 mL of DCM, washed with NaHCO₃ (3 x 10 mL), dried with NaSO₃, filtered, and concentrated to give 28 as a viscous oil that partially crystallized on standing: mp 141°; ¹H NMR (CDCl₃) δ 0.98 (18H, d, (J = 6.78 Hz), (CH₃)₂CH-), 1.10 (3H, m, J = 6-7.4 Hz), (CH₃)₂C-H, 3.61 (3H, s, -OCH₃), 3.93 (3H, s, -OCOC₂H₅), 3.97 (3H, s, -OCOCH₃), 5.98 (1H, d, -OCH₂O-, J = 1.38 Hz), 6.3 (1H, d, -OCH₂O-, J = 1.38 Hz), 6.73 (1H, dd, Ar-6'H, J = 7.8, 1.65 Hz), 6.756 (1H, d, Ar-4'H, J = 1.44 Hz), 6.813 (1H, s, Ar-5H), 6.81 (1H, d, Ar-7'H), 7.7 (1H, s, Ar-8H), 12.31 (1H, s, Ar-OH); ¹³C NMR (CDCl₃) ppm (12.63, (-CH(CH₃)₂), 17.71, ((CH₃)₂CH-), 51.92, (-OCOC₂H₅), 52.71, (-OCOCH₃), 55.70, (-OCH₃), 100.85, (-OCH₂O-), 103.3*, (Ar-C₅), 107.94, (Ar-7'C), 111.29, (Ar-4'C), 115.29*, (Ar-8C), 120.34, (Ar-C), 124.12, (Ar-6'C), 127.57*, (Ar-5'C), 127.92*, (Ar-3C), 130.77* Ar-C, 132.31*, Ar-C, 147.04*, Ar-C, 147.25*, Ar-C, 149.50*, Ar-C, 151.96*, Ar-C, 159.73*, Ar-4C, 169.42, -C=O, 170.68, -C=O.
RESULTS AND DISCUSSION

In order to construct Haplomyrtin 1 from the starting materials 3-methoxy-4-hydroxybenzaldehyde (vanillin) 7, 1,2-benzodioxole-5-carboxaldehyde (i.e., piperonal) and dimethyl acetylenedicarboxylate (i.e., DMAD), several synthetic challenges must be overcome. These steps include 1) attachment of a 1,3-benzodioxole “C” ring to the C6 position of vanillin, 2) a Diels-Alder cycloaddition to create a naphthalene “B” ring and 3) the formation of a butyrolactone ring through reduction and cyclization of a “B” ring ortho ester, as shown in **Figure 6**.

![General retrosynthetic scheme for the construction of Haplomyrtin 1](image)

**Figure 6.** General retrosynthetic scheme for the construction of Haplomyrtin 1.

The first step in creating the naphthalene nucleus of 1 involves intentional deactivation of the trisubstituted ring of vanillin 7 via acetylation, followed by bromination (Step 2), and then deacylation (Step 3).
The first procedure followed to arrive at the targeted 6-bromovanillin 10 was that originally outlined by Gilmore. This procedure, however, soon proved to be problematic with only miniscule yields of final product. An alternative bromination reaction was, therefore carried out using a modified procedure of Ratton, et. al.\(^1\). The \(^1\)H NMR spectrum (Figure 7) of 9 shows a comparison between the two reaction results. The aldehyde singlet proton absorption of starting material 8 is at 9.95 \(\delta\) while the aldehyde singlet proton absorption of 9 is further downfield at 10.28 \(\delta\). The \(^1\)H NMR spectra (Figure 7) showed that the product from the Gilmore procedure (top spectra) contains as much unreacted 8 as 9 while the product of the Ratton, et. al. procedure (bottom spectra) showed a marked increase in the targeted 9. The differences between the modified Ratton procedure and the original are 1) use of 30% hydrogen peroxide which regenerated bromine from the bromide by product and 2) longer reaction times (20 h). The yield of the intermediate product 5-bromo-4-formyl-2-methoxyphenylacetate 9 was improved to 67\%, however the overall yield of 10 after deacylation of 9 and final recrystallization was only 22\%. The IR spectrum (Figure 8) of 8 indicates the loss of vanillin hydroxyl stretching adsorption in the 3500 cm\(^{-1}\) region and the appearance of a strong acetyl carbonyl stretching absorption at 1753 cm\(^{-1}\). The \(^1\)H NMR (Figure 9) of 8 shows the
acetyl methyl adsorption at 3.88 δ along with loss of the hydroxyl adsorption at 10.77 δ for vanillin. The \(^1\)H NMR (Figure 10) of 9 resulting from the bromination of 8 shows a shift of the aldehyde proton adsorption to 10.28 δ (from 9.90 δ) and two singlet aromatic \textit{para} proton adsorptions at 7.37 δ and 7.52 δ. Deacylation of 9 to the phenol 10 is evident in the IR spectrum (Figure 11) which shows a broad hydroxyl stretching absorption at 3295 cm\(^{-1}\), aromatic aldehyde adsorption shift to 1660 cm\(^{-1}\), and a strong carbon-bromine stretch at 636 cm\(^{-1}\). The \(^1\)H NMR (Figure 12) of 10 shows the reappearance of the hydroxyl singlet absorption at 10.77 δ along with the loss of the acetyl methyl singlet at 2.34 δ.

The protection of the hydroxyl group in 10 utilized triisopropylsilyl chloride and imidazole and yielded the target compound 24 quickly at room temperature following the procedure of Blank, et. al.\(^\text{16}\) The IR spectrum (Figure 13) of 24 lacks the characteristic broad hydroxyl absorption in the 3300 cm\(^{-1}\) region and is replaced with a strong aliphatic carbon hydrogen absorption resulting from the TIPS protection group and an aromatic aldehyde adsorption shift to 1686 cm\(^{-1}\). The \(^1\)H NMR of 24 (Figure 14) contains upfield adsorptions characteristic of the new TIPS group consisting of an 18 proton methyl doublet absorption at 1.11 δ and a 3 proton septet absorption at 1.28 δ. The hydroxyl proton singlet absorption at 10.77 δ is absent. The \(^{13}\)C NMR spectrum of 24 (Figure 15) displays the expected 13 unique carbon absorptions characterizing this compound; isopropyl methyl at 17.73, isopropyl tertiary CH at 12.93, methoxy methyl at 55.56, the six aromatics with Ar-2C-Br at 111.23, Ar-6C-H at 119.44, Ar-3C-H at 124.58, Ar-1C-CHO at 126.98, Ar-4C-OSi at 150.85, Ar-5C-OCH\(_3\) at 152.11, and –CHO at 190.90.
The final protection of 24 involved acetal formation of the susceptible aldehyde function utilizing an acid catalyzed dehydration procedure with ethylene glycol to generate the diprotected 26. Since dehydration is a reversible reaction, the water by-product must be constantly removed in order to maintain equilibrium toward the product. This was accomplished through an azeotropic separation technique utilizing a Dean Stark apparatus along with diligent removal of the trapped water. The initial experimental procedure followed (Anson, et. al.\textsuperscript{23}) called for stoichiometric amounts of pTSA catalyst which soon proved to be problematic. The target product 26 was plagued by the presence of almost equivalent amounts of unreacted 24 following workup and purification. A higher boiling solvent (i.e., toluene 120° vs. benzene 90°) was tried assuming the increased reaction temperature might lead to more complete water removal but with similar results. A decrease in pTSA by almost a factor of 10 to catalytic amounts was finally tried along with increased reaction times (i.e. 20-24 h vs. 6 h). This resulted in an improved yield (i.e., over 90%) of the pure 26 vs the 26/24 (i.e., 50:50) mixtures previously obtained. The $^1$H NMR spectrum (Figure 19) displays the outcome of the various reaction methods employed. The reaction conditions leading to 26 have been summarized in (Table 1).

The final product purification was done by silica gel column chromatography utilizing a hexane/ethyl acetate (5:1) mobile phase followed by concentration under reduced pressure to yield a reasonably pure 26, suitable for the ensuing BuLi step.
Table 1. Reaction conditions towards the production of 26.

<table>
<thead>
<tr>
<th>H NMR Spectra (bottom to top)</th>
<th>26 (mmol)</th>
<th>HOCH₂CH₂OH (mmol)</th>
<th>pTSA (mmol)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.1</td>
<td>31.6</td>
<td>2.3</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>2.9</td>
<td>13.7</td>
<td>2.4</td>
<td>22.5</td>
</tr>
<tr>
<td>3</td>
<td>1.37</td>
<td>6.50</td>
<td>0.47</td>
<td>6.6</td>
</tr>
<tr>
<td>4</td>
<td>1.55</td>
<td>8.77</td>
<td>0.44</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>2.58</td>
<td>26.30</td>
<td>0.15</td>
<td>24</td>
</tr>
</tbody>
</table>

The primary IR (Figure 16) spectral evidence for conversion of 24 to 26 is the appearance of a 1,3-dioxolane-2-yl tertiary carbon hydrogen stretch adsorption at 2892 cm⁻¹ and a 1,3-dioxolane asymmetric aliphatic ether stretching absorption at 1087 cm⁻¹. The carbonyl stretch absorption at 1686 cm⁻¹ is absent. The ¹H NMR spectrum (Figure 17) of 26 shows a 1,3-dioxolane-2-yl one proton singlet at 5.90 δ, a 1,3-dioxolane methylene four proton multiplet at 4.12 δ, a methoxy methyl three proton at 3.82 δ, a triisopropyl tertiary three proton septet at 1.24 δ and a six methyl eighteen proton doublet at 1.09 δ. The aldehyde one proton singlet absorption is absent at 10.19 δ. The ¹³C NMR spectrum (Figure 18) of 26 shows the expected eleven unique carbon adsorptions; isopropyl methyl at 17.88, isopropyl tertiary CH at 12.91, methoxy methyl at 55.59, the 1,3-dioxolane methylenes at 65.35, the dioxolane methine at 102.74 ppm, and the six aromatics with Ar-1C at 110.99, Ar-2C at 128.72, Ar-3C at 112.88, Ar-6C at 124.28, Ar-5C at 147.10, and Ar-4C at 150.42. The DEPT135 (Figure 20) spectrum shows isopropyl
CH at 12.94, isopropyl CH$_3$ at 17.92, methoxy CH$_3$ at 55.63, 1,3-dioxolane CH$_2$ at 65.40, 1,3-dioxolane CH at 102.77, Ar-3 CH at 110.97, and Ar-6 CH at 124.34.

The diprotected 26 was then subjected to the lithium-halogen exchange procedure followed by piperonal addition and workup to yield the intermediate chiral alcohol 27. In an effort to minimize complications from the unstable intermediate, the crude 27 was taken directly to the next step without further purification. The IR (Figure 21) spectrum of the crude 27 reaction product clearly indicates the formation of the alcohol. The IR of 27 shows the appearance of a broad absorption at 3474 cm$^{-1}$ resulting from hydroxyl stretching. The $^1$H NMR (Figure 22), although impure, shows a one-proton absorption at 2.04 $\delta$ that is characteristic for a dibenzylic methanol hydroxyl proton but could possibly be acetone interference. The 5.85 – 6.00 $\delta$ (Figure 23) region shows the four singlet
proton absorptions that can correspond to the methylene protons of the new 1,3-benzodioxole group, the single tertiary methanol proton, and the single tertiary 1,3-dioxolane proton. There are five proton absorptions in the region 6.6 - 7.4 δ (Figure 24) that can be attributed to the five protons on the two aromatic rings. The original two singlet absorptions from the para protons of the starting material 26 have shifted from 7.19 δ (Ar-3H), 6.96 δ (Ar-6H) to 6.89 δ and 6.79 δ, respectively. The 1,3-benzodioxol pendant group shows two ortho protons (Ar’-6H, 7H) as doublet absorptions 7.08 δ and 6.68 δ, respectively and (Ar’-4H) singlet absorption at 6.79 δ. It is also interesting to note from 1H NMR (Figure 22) both the acetal (4.12 δ) and the TIPS (1.1-1.3 δ) protecting groups are still very much intact following the harsh lithium/halogen exchange environment.

The synthetic steps involved in the formation of the crucial intermediate 27 are suspect in a number of unwanted side reactions. The problems associated with the synthesis of intermediate 27 have been addressed repeatedly by previous researchers. The ability to synthesize 27 without producing major byproducts is one primary objective of this research.

All research to date involved in the synthesis of intermediate alcohol 27 has relied upon the benzyl protecting group for the C4 hydroxyl of 16 prior to the lithium/halogen exchange step. The use of the benzyl protection, as was demonstrated by Schaff, introduces additional metallation susceptible protons. Replacement of the benzyl group
with the TIPS protecting group could potentially eliminate this one extraneous metallation source. One advantage of having a TIPS protecting group at the C4 position of 26 is that it may introduce steric protection from α-lithiation (i.e., lithium hydrogen exchange) at C5. The C5 proton of 26 is susceptible to ortho-lithiation through the increased acidity induced by the adjacent bromine atom and also because of the lithium ion ability to coordinate with the C4 oxygen. Even though the lithium halogen exchange product at C6 of 26 is the favored outcome, the formation of an α-lithium product at C5 or the benzyne intermediate are all possible outcomes.

16, \( R = \text{Bn} \)  
26, \( R = \text{TIPS} \)

The molar ratios of butyllithium and piperonal used in the synthesis of 27 must be controlled as this can affect the product yields. Excess piperonal or butyllithium will lead to contaminant producing side reactions that will later prove difficult to remove from the desired product. In order to minimize the deleterious basic and nucleophilic effects of
butyllithium, the molar ratios of 26 to BuLi to piperonal must be maintained close to 1:1:1. This requires a pure, dry, fresh 26, fresh BuLi, anhydrous THF, and a sealed inert atmosphere.

The impure alcohol 27 was taken directly to the next cycloaddition step in order to generate the diester product 28, following a quick workup. The cycloaddition reaction procedure that was followed relied on a modified version of the Cleistanthin A patented process\textsuperscript{12} that was first used during the research work of Oude. This procedure required the use of the Q-Tube apparatus into which the alcohol 27, dimethyl acetylene-dicarboxylate (DMAD), glacial acetic, and methylene chloride were introduced and then heated to 140° for one hour. The reactants were required at the molar ratios of 1:1:3.6 for 27, DMAD, and HOAc, respectively. The molar quantity of 27 that was used as a starting material was not quantified since the crude product was not subjected to final purification but was estimated based upon the number of moles of starting material 26.

The reaction product was then worked up as per the published procedure and finally concentrated under a reduced pressure to yield the crude 28. The \textsuperscript{1}H NMR spectra (Figure 25, spectra 1) of crude 28 shows a strong singlet proton absorption at 3.83 δ from unreacted DMAD, a singlet proton absorption at 12.32 δ corresponding to the new naphthalene C4 hydroxyl proton, and singlet proton absorptions of equal intensities at 10.18 δ and 9.83 δ which are indicative of possible aldehyde byproducts. Absent is the methylene four proton multiplet at 4.06 δ from the 1,3-dioxolane protecting group of 27. The cycloaddition procedure was repeated five more times varying both the molar quantities of 27 with DMAD and also the reaction times (Table 2).
Table 2. Reaction conditions towards the production of 28.

<table>
<thead>
<tr>
<th>H NMR Spectra (bottom to top)</th>
<th>26 (mmol)</th>
<th>27 (mmol crude)</th>
<th>DMAD (mmol)</th>
<th>HOAc (mmol)</th>
<th>Reaction time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.00</td>
<td>1.70</td>
<td>2.37</td>
<td>12.90</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.30</td>
<td>1.06</td>
<td>0.86</td>
<td>4.20</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3.00</td>
<td>2.75</td>
<td>1.58</td>
<td>15.20</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Spectra 3 w/ D&lt;sub&gt;2&lt;/sub&gt;O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.37</td>
<td>2.00</td>
<td>1.00</td>
<td>6.80</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>4.87</td>
<td>4.40</td>
<td>3.07</td>
<td>15.26</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>4.10</td>
<td>3.86</td>
<td>3.07</td>
<td>15.26</td>
<td>84</td>
</tr>
</tbody>
</table>

The six H NMR spectra (Figure 25) single proton absorptions at 12.32 \( \delta \) as a result of the hydroxyl group appearance on the Ar-C4 of 28, were used to judge the overall reaction progress towards the targeted 28 diester product. The appearance of the proton absorption at 12.32 \( \delta \) in the spectrum indicated the presence of 28. The confirmation that this absorption was due to the single aromatic hydroxyl proton is shown in Figure 25, spectra #4 following a D<sub>2</sub>O exchange of 28. The H NMR Figure 25 spectra #4 can be seen showing the two singlet proton absorptions at 9.83 \( \delta \) and 10.18 \( \delta \), but absent is the single proton absorption at 12.32 \( \delta \) owing to a deuterated product of 28.

The Diels-Alder cycloaddition reaction steps necessary to produce the diester 28 from the chiral alcohol 27 are shown on page 28. In order to create the benzofuran intermediate from the protected alcohol 27, acetic acid is first used to catalyze the conversion of the acetal-protecting group back to the original aldehyde. The new aldehyde electrophile can now undergo an intramolecular condensation reaction leading to the benzofuran. The diene intermediate must be formed in order to complete the reaction cycloaddition sequence with the dienophile, DMAD to produce 28. Incomplete formation of 28 due to the \( \alpha \)-lithiation product of 26 or unreacted 27 would ultimately leave aldehyde contaminants in the end product.
The \textsuperscript{1}H NMR spectra shown in \textbf{Figure 25} indicated that all of the six reaction attempts had, indeed yielded measurable amounts of both 28 along with undesired byproducts. The \textsuperscript{1}H NMR spectra of the first and subsequent reaction attempts can be seen in \textbf{Figure 25, spectra # 1} up through and including the latest attempt in \textbf{spectra # 7}. The \textsuperscript{1}H NMR spectra of the most recent reaction also indicated a noticeable increase in the 28 hydroxyl proton absorbance at $\delta$ 12.32, absence of the byproduct proton absorbance at $\delta$ 10.18, and a much reduced byproduct proton absorbance at $\delta$ 9.83 when compared to all previous five reaction \textsuperscript{1}H NMR spectra. A noticeable improvement in the ratio of product 28 to the byproduct was seen in this most recent reaction and would later prove to be significant. The attempt to isolate 28 from the co-eluting contaminant byproducts, however, soon proved difficult utilizing the limited laboratory separation resources that were available. Variations in both column chromatography and acid-base extraction techniques were attempted but neither method yielded the desired product purity. The sterically demanding, non polar TIPS protecting group in place on the C7-hydroxyl of the targeted compound 28 may have contributed to the compound’s indifference to base extraction separation. The same TIPS group on 28 might also be contributing to the increase in aprotic solvent phase mobility during column chromatography thereby preventing a capable mobile/stationary phase separation. However, after several weeks left standing, undisturbed the final reaction product, i.e. reaction 6, \textbf{spectra # 7}, began yielding isolated patches of crystallization in sufficient yield to be manually separated. The isolated yellow crystals were carefully cleaned with hexane and benzene on filter paper. After drying under vacuum the isolated crystalline
material was later identified through $^1$H NMR confirmation to be the targeted 28, pure enough for the ensuing butyrolactone ring creating reduction step.

The $^1$H NMR spectrum of 28 (Figures 26, 27, 28, 29) shows an isopropylsilyl methyl eighteen proton doublet at δ 0.98, an isopropylsilyl methine three proton septet at δ 1.10, a methoxy methyl three proton singlet at δ 3.61, the dicarboxylate methyl three proton singlets at δ 3.93 and 3.97, the 1,3-benzodioxol methylene, one-proton doubles at δ 5.98 and δ 6.3, the 1,3-benzodioxole-6’H one proton doublet of doubles at δ 6.73, the -4’H one proton doublet at δ 6.76, the -7’H one proton doublet at δ 6.86, the naphthalene 5H and 8H one proton singlets at δ 6.81 and δ 7.70, respectively, and the naphthalene C4-hydroxy, one proton singlet at δ12.31. The $^{13}$C NMR spectrum of 28 (Figure 30) shows the expected twenty four unique carbon absorptions for this compound. The $^{13}$C DEPT135 spectrum of 28 (Figure 31) shows the expected ten unique methyl/methine absorptions and the one unique methylene absorption. The HSQC spectrum (Figure 32, 33) provides even further structural identification through the combined correlation of both the $^1$H NMR and the $^{13}$C NMR spectra. Through a combined comparison of the $^{13}$C NMR, $^{13}$C DEPT135, and the HSQC spectra the unique methyl, methylene, methine, and most quaternary carbon assignments can be made with a high degree of certainty. The $^{13}$C NMR (ppm) spectrum of 28 shows isopropylsilyl methine absorption at 12.63, isopropylsilyl methyl absorption at 17.71, carboxylate methyl absorptions at 51.92 and 52.71, methoxy methyl absorption at 55.70, 1,3-benzodioxol methylene absorption at 100.85, naphthalene C5 absorption at 103.3*, 1,3-benzodioxolane C7’ absorption at 107.94, 1,3-benzodioxolane C4’ absorption at 111.29, naphthalene C8 absorption at 120.34*, Ar-C absorption at 120.34*, 1,3-benzodioxolane C6’ absorption at 124.12, 1,3-
benzodioxolane C5 absorption at 127.57*, naphthalene C3 absorption at 127.92*, Ar-C absorptions at 132.31*, 147.04*, 147.25*, 149.50*, 151.96*, 159.73*, naphthalene C4 absorption at 159.73, carboxylate carbonyl absorptions at 169.42 and at 170.68

CONCLUSIONS.

A synthetic route towards the total synthesis of Haplomyrtin is achievable through the selective protection and deprotection of the reactant vulnerable sites on the starting material, vanillin. The durability of the TIPS group for hydroxyl protection and the cyclic acetal for aldehyde protection has exceeded our expectations. Both have proven their remarkable resistance to chemical attack under the harshest of reaction environments.

The overall lower than expected yield of the targeted compound 1 is still at issue which could be due to the very nature of the synthetic process. Similar synthetic experimental attempts towards arylnapthalene production do not always produce the yields that we have come to expect. Overall yields of less than twenty percent (20%) for lithium-halogen exchange, nucleophilic substitution reactions, in general, are more the norm than the exception. At issue, with our synthetic yield, may not be just the lithium-halogen exchange portion producing the alcohol 27 intermediate but more than likely the Diels-Alder cycloaddition sequence of reactions necessary to give the dicarboxylate 28. The cycloaddition events, or lack thereof, appear to still produce a good deal of the aldehyde contaminants in the Diels-Alder step. These contaminants might be from the remaining, deprotected, and unreacted 27 or they may be the carryover byproducts from the butyllithium sequence as was previously addressed by researchers Gilmore and Schaff. There might be several other causes for the failure of 27 not yielding 28. The condensation step of 27 will not occur with the α-lithiation product of 26. There might
also be just one enantiomer of the chiral 27 capable of the intramolecular condensation step.

Improvements to the overall yield of Haplomyrtin 1 might be achieved through several changes. Reverse the order of the lithium-halogen exchange step by producing the protected piperonal carbanion and then reacting with the C4 protected vanillin. The use of cupric ion in the lithium-halogen reaction has been found to increase yields substantially in certain cases. Experimentation with varying types and amounts of the acid catalysts used in the cycloaddition step might yield more of the desired 28. Lastly, better separation methods and instrumentation tools should be made available in order to hasten isolation of the targeted product.
Figure 7. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 9 (BAV). Top Gilmore Rx. Bottom Ratton Rx.

Figure 8. IR Spectrum (NaCl) of 8 (AV).
Figure 9. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 8 (AV).

Figure 10. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 9 (BAV).
Figure 11. IR Spectrum (NaCl) of 10 (BV).

Figure 12. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 10 (BV).
Figure 13. IR Spectrum (NaCl) of 24 (TBV).

Figure 14. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 24 (TBV).
Figure 15. 300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 24 (TBV).

Figure 16. IR Spectrum (NaCl) of 26 (TBVA).
Figure 17. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 26 (TBVA).

Figure 18. 300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 26 (TBVA).
Figure 19. 300 MHz $^1$H NMR spectral comparison of compound 26 reaction attempts (bottom to top is the reaction order).
Figure 20. 300 MHz $^{13}$C DEPT135 NMR Spectrum (CDCl$_3$) of 26 (TBVA).

Figure 21. IR Spectrum (NaCl) of 27 (ROH).
Figure 22. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27 (ROH).

Figure 23. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27; expanded region 5.85 - 6.00 δ.
Figure 24. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 27; expanded region 6.6 - 7.4 $\delta$.

Figure 25. 300 MHz $^1$H NMR Spectra (CDCl$_3$) of the six 28 reaction attempts. Spectra 4 is D$_2$O exchange of 28.
Figure 26. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28.

Figure 27. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 5.8 - 7.8 $\delta$. 
Figure 28. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 6.6 - 6.9 δ.

Figure 29. 300 MHz $^1$H NMR Spectrum (CDCl$_3$) of 28; region 5.95 - 6.05 δ.
Figure 30. 300 MHz $^{13}$C NMR Spectrum (CDCl$_3$) of 28.

Figure 31. 300 MHz $^{13}$C NMR (CDCl$_3$) of 28.
Figure 32. HSQC correlation spectrum of 28.

Figure 33. Expanded HSQC correlation spectrum of 28.
REFERENCES


VITAE

William S. Barrow graduated from Wright State University with a Bachelor of Science degree in Chemistry and Biology in 1979. He has been the President and General Manager of a local environmental consulting and remediation company for thirty years. He and his wife Chris have three sons, one daughter and nine grandkids. He expects to receive his Master of Science degree in Chemistry in August 2013. You can teach an old dog some new tricks.