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Synthesis of defucogilvocarcin V analogs

Mannino, Anthony, Ph.D.
The Ohio State University, 1993
SYNTHESIS OF DEFUCOGILVOCARCIN V ANALOGS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of the Ohio State University

By

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The Ohio State University

1993

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Approved by
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To Michael, "Emily" and My Wife
ACKNOWLEDGEMENTS

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This author owes special thanks to Dr. Swenton for use of the electrochemical equipment and for always having time. Gratitude is owed to Mr. Carl Engleman and Charles Cottrell for NMR spectra and Mr. David Chan for mass spectrometry.
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TABLE OF CONTENTS

DEDICATION.............................................................................................................. ii
ACKNOWLEDGEMENTS........................................................................................ iii
VITA............................................................................................................................. iv
LIST OF FIGURES..................................................................................................... vi
LIST OF SCHEMES.................................................................................................. vii
LIST OF TABLES...................................................................................................... viii

CHAPTER PAGE

I  An Introduction to the Gilvocarcin Family of C-Aryl Glycosides.......................................................... 1
A. Introductions: Statement of Problem................................................................. 1
B. Structural Elucidation and Biosynthesis of the Gilvocarcins.......................... 3
C. Biological Properties and Mode of Action....................................................... 9
D. Selection of Synthetic Targets........................................................................ 21
E. Previous Syntheses of Defucogilvocarcins....................................................... 23
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURES</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Gilvocarcin Family of Natural Products</td>
</tr>
<tr>
<td>2</td>
<td>The Synthetic Target</td>
</tr>
<tr>
<td>3</td>
<td>Mitomycin C and Doxorubicin</td>
</tr>
<tr>
<td>4</td>
<td>Gilvocarcin A</td>
</tr>
<tr>
<td>5</td>
<td>GV (1)-Thymidine Adduct</td>
</tr>
<tr>
<td>6</td>
<td>Psoralens</td>
</tr>
<tr>
<td>7</td>
<td>Selection of the Synthetic Targets</td>
</tr>
<tr>
<td>8</td>
<td>Nuclear Overhauser Enhancement Studies of 77 and 78</td>
</tr>
<tr>
<td>9</td>
<td>Nuclear Overhauser Enhancement Studies of 80 and 81</td>
</tr>
<tr>
<td>10</td>
<td>Nuclear Overhauser Enhancement Studies of 100 and 101</td>
</tr>
<tr>
<td>11</td>
<td>Example of Selectivity Reversal</td>
</tr>
<tr>
<td>12</td>
<td>Chemical Shift Comparison of 111 and 118</td>
</tr>
<tr>
<td>13</td>
<td>Nuclear Overhauser Enhancement Studies of 119</td>
</tr>
<tr>
<td>14</td>
<td>nOe Experiments of 128 and Projected nOe of 129</td>
</tr>
<tr>
<td>15</td>
<td>COLOC of 128 and Projected COLOC of 129</td>
</tr>
<tr>
<td>Page</td>
<td>Section Title</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>16</td>
<td>Percent Growth as Defined by NCI</td>
</tr>
<tr>
<td>17</td>
<td>Biological data of 89</td>
</tr>
<tr>
<td>18</td>
<td>Biological data of 11</td>
</tr>
<tr>
<td>19</td>
<td>Biological data of 108</td>
</tr>
<tr>
<td>20</td>
<td>Biological data of 138</td>
</tr>
<tr>
<td>21</td>
<td>Biological data of 109</td>
</tr>
<tr>
<td>22</td>
<td>Biological data of 12</td>
</tr>
<tr>
<td>23</td>
<td>O-Aryl Glycosides of 11, 12 and 13</td>
</tr>
</tbody>
</table>
# LIST OF SCHEMES

<table>
<thead>
<tr>
<th>SCHEMES</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 13C Labelling Experiments</td>
<td>6</td>
</tr>
<tr>
<td>II Biosynthesis of the Gilvocarcins</td>
<td>8</td>
</tr>
<tr>
<td>III Mechanism of Action of the Gilvocarcins</td>
<td>20</td>
</tr>
<tr>
<td>IV Martin's Synthesis of Defucogilvocarcin Aglycones</td>
<td>24</td>
</tr>
<tr>
<td>V Parker's Chromium Carbene Methodology</td>
<td>26</td>
</tr>
<tr>
<td>VI Suzuki's Synthesis of (+) Gilvocarcin M (53)</td>
<td>28</td>
</tr>
<tr>
<td>VII MAD-Mediated Methodology</td>
<td>29</td>
</tr>
<tr>
<td>VIII Synthesis of Monoketal 54.</td>
<td>30</td>
</tr>
<tr>
<td>IX Rapoport's Protocol</td>
<td>31</td>
</tr>
<tr>
<td>X Synthesis of Naphthol 60 Via Rapoport's Protocol</td>
<td>32</td>
</tr>
<tr>
<td>XI Retrosynthetic Analysis of 11</td>
<td>33</td>
</tr>
<tr>
<td>XII Coupling Reaction of Iodovanillin 68</td>
<td>36</td>
</tr>
<tr>
<td>XIII Synthesis of Oxazoline 67</td>
<td>37</td>
</tr>
<tr>
<td>XIV MAD-Mediated Reaction of 54 and 67.</td>
<td>39</td>
</tr>
<tr>
<td>XV Diethylamide (68) Analog of 67</td>
<td>46</td>
</tr>
<tr>
<td>XVI Proposed Selective Synthesis of 6-Lithiooxazoline</td>
<td>47</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>XVII</td>
<td>MAD-Mediated Conjugate Addition of 67 and 54</td>
</tr>
<tr>
<td>XVIII</td>
<td>Conversion of 77 to 11</td>
</tr>
<tr>
<td>XIX</td>
<td>Retrosynthetic Analysis of 12</td>
</tr>
<tr>
<td>XX</td>
<td>Attempted Iodination of 92</td>
</tr>
<tr>
<td>XXI</td>
<td>Synthesis of 95 by Mercury Route</td>
</tr>
<tr>
<td>XXII</td>
<td>Low Temperature Iodination of 92</td>
</tr>
<tr>
<td>XXIII</td>
<td>Synthesis of Oxazoline 99</td>
</tr>
<tr>
<td>XXIV</td>
<td>Amide Analogs of 98</td>
</tr>
<tr>
<td>XXV</td>
<td>Conjugate Addition of 102 and 54</td>
</tr>
<tr>
<td>XXVI</td>
<td>Conversion of 107 to 12</td>
</tr>
<tr>
<td>XXVII</td>
<td>Retrosynthetic Analysis of 13</td>
</tr>
<tr>
<td>XXVIII</td>
<td>Synthesis and Lithiation Study of 111</td>
</tr>
<tr>
<td>XXIX</td>
<td>Synthesis and Lithiation Study of 118</td>
</tr>
<tr>
<td>XXX</td>
<td>Conjugate Addition of 117 and 54</td>
</tr>
<tr>
<td>XXXI</td>
<td>Attempted Synthesis of 122</td>
</tr>
<tr>
<td>XXXII</td>
<td>Conjugate Addition of 122 and 54</td>
</tr>
<tr>
<td>XXXIII</td>
<td>Conversion of 132 to 134</td>
</tr>
<tr>
<td>XXIV</td>
<td>Projected Synthesis of 13</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Description</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antibiotic Activity of GV (1) and GM (3)</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Antibiotic Activity of GV (1) and DGV (7)</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>GV (1) Against Meth. 1 Fibrosarcoma</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>GV (1) Against MH 134</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Ehrlich Carcinoma Treated with 1 and Mitomycin C (26)</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Conjugate Addition Reactions of 67 and 54</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Lithiation Studies of Oxazoline 67</td>
<td>45</td>
</tr>
</tbody>
</table>
Chapter I

AN INTRODUCTION TO THE GILVOCARCIN FAMILY OF C-ARYL GLYCOSIDES.

A. Introduction: Statement of Problem.

The gilvocarcin family of natural products (Figure 1) have been isolated from *streptomyces* found in soil samples from various parts of the world. Members of this family have in common a benzonaphthopyranone nucleus which varies in substitution at C-4 and C-8. For example, the best known member of this family, gilvocarcin V (1), has a furanofucose substitutent at C-4 and a vinyl group at C-8. Chrysomycin A (4) and ravidomycin (6) have the same aglycone as gilvocarcin V (1), but have different carbohydrates, uncommon hexoses in each case, appended to C-4. Even defucogilvocarcin V (7), which has no carbohydrate at C-4, has been isolated. Although defucogilvocarcin M (8) has not been isolated from natural sources, it serves as the aglycone for gilvocarcin M (3) and chrysomycin B (5). It also serves as the aglycone for BE-12406A (9) and BE-12406B (10), O-glycosides recently isolated from *streptomyces rutgersensis*. These compounds do not formally belong to the gilvocarcin family, as they are O-glycosides rather than C-glycosides. The structural relationship is nonetheless clear. Finally, gilvocarcin E (2) has also been reported.
Figure 1. The Gilvocarcin Family of Natural Products.
The gilvocarcins have generated a great deal of attention because they possess antibiotic and antitumor activity with low mammalian toxicity. For example, while gilvocarcin V (1) shows both antibiotic and antitumor activity, its LD50 in mice is 300 mg/kg when administered intravenously, and it was found not to be toxic at a dose of 1000 mg/kg when administered orally or intraperitoneally.\textsuperscript{11} This thesis deals with the synthesis of defucogilvocarcin V analogs 11-13 (Figure 2). The synthesis of analogs 11-13 was undertaken so they could be tested for antitumor activity and used to carry out structure activity relationship studies into the mode of action of the gilvocarcins. The selection of the synthetic targets (11-13) will be discussed within this chapter. To provide background for the readers, the structure elucidation, biosynthesis, biological properties, and mode of activity of the gilvocarcins will be described. Previous syntheses of the defucogilvocarcins will also be briefly reviewed within this chapter.

B. Structure Elucidation, and Biosynthesis of the Gilvocarcins.

The structures of the gilvocarcins (1-7) have been established by a combination of chemical, spectral, and X-ray analyses.\textsuperscript{1,2} For example, the structure of ravidomycin (6) was assigned by Findlay on the basis of spectral data and chemical degradation studies.\textsuperscript{1d} Gilvocarcin V (1) was characterized, independently by a number of researchers. Hatano and coworkers isolated an antibiotic from \textit{streptomyces collinus}, which they called toromycin.\textsuperscript{19} This compound later became known as gilvocarcin V (1). They were able to characterize the benzonaphthopyranone nucleus and its substitution pattern by chemical degradation studies and spectral analysis.
Hatano identified the C-aryl glycosidic nature of the compound, but did not elucidate the structure of the sugar.

Tomita and coworkers, independently, isolated gilvocarcin V (1) and gilvocarcin M (3) from *streptomyces gilvotanareus* and characterized the benzonaphthopyranone nucleus and established, by proton decoupling experiments, the gross structure of the furanose at C-4.\(^{2a}\) Hirayama and coworkers obtained a crystal structure of gilvocarcin M (3), establishing the relative stereochemistry of the sugar at C-4.\(^{2b}\) Recently Suzuki reported a
synthesis of the enantiomer of gilvocarcin M (3), thus establishing the absolute configuration of gilvocarcin M (3).\textsuperscript{2c} Chrysomycin A (4) and chrysomycin B (5) were isolated in 1955 by Strelitz, but were characterized in 1982 by Weiss. Weiss and coworkers recognized the similarities between the chrysomycins (4 and 5) and the gilvocarcins (1 and 3). By comparison of spectral data with 1 and 3, they established the structures of 4 and 5.

Because defucogilvocarcin V (7) and gilvocarcin E (2)\textsuperscript{1i} have been isolated from fermentation broths, it has been suggested that the biosynthesis of the aglycone proceeds coupling of the sugar to the aromatic system. The biosynthesis of the aglycones is believed to involve the acetate pathway.\textsuperscript{3} Tomita and Takahashi examined the biosynthesis of gilvocarcins by labelling experiments in which they fed \textit{streptomyces gilotanarous} \textsuperscript{13C} labelled sodium acetate and sodium propionate.\textsuperscript{3a} Mixtures of gilvocarcin V (1) and gilvocarcin M (3) were isolated and analyzed for \textsuperscript{13C} enrichment (Scheme I). The feeding studies using sodium [1-\textsuperscript{13C}]acetate enriched the \textsuperscript{13C} content of the aromatic carbons, but \textsuperscript{13C} was not substantially incorporated in the sugar carbons (Scheme I). The \textsuperscript{13C} NMR spectra of 3 and 1 showed enrichment at C-1, C-3, C-4a, C-6a, C-8, C-10, C-10b, and C-12. Feeding studies using sodium [2-\textsuperscript{13C}]acetate caused an enrichment of the aromatic carbons and the C-8 side chain carbons (Scheme I). The \textsuperscript{13C} NMR spectra showed enrichment at C-2, C-4, C-4b, C-6, C-7, C-9, C-10a, C-11, C-12, 12a, both carbons of the vinyl group of gilvocarcin V (1) and the methyl group of gilvocarcin M (3). Studies using sodium [3-\textsuperscript{13C}]propionate only enhanced
Scheme I. $^{13}$C Labelling Experiments.

**CH$_3$CO$_2$Na**

1. $R = \text{CH}=\text{CH}_2$
2. $R = \text{CH}_3$

**$^{13}$CH$_3$CO$_2$Na**

1. $R = ^{13}\text{CH}=\text{CH}_2$
2. $R = ^{13}\text{CH}_3$

**CH$_3$CH$_2$CO$_2$Na**

1. $R = \text{CH}=\text{CH}_2$

**$^{13}$CH$_3$CH$_2$CO$_2$Na**

1. $R = ^{13}\text{CH}=\text{CH}_2$
the β-carbon of the vinyl group of gilvocarcin V (1) while sodium [2-13C]propionate enhanced only the α-carbon of gilvocarcin V (1). Based on these data, Tomika and Takahashi proposed the biosynthetic pathway shown in Scheme II. Their proposal begins with a number of acetate condensation-dehydrations which lead to polyketide 14. Further condensation-dehydration processes afford quinone 15. They proposed that the methyl and vinyl substituents at C-8 are introduced by addition of acetate or propionate to the carbonyl of 15 affording quinone 16, which undergoes decarboxylation-dehydration to give quinone 17. Oxidation of 17 followed by C-C bond rotation and deoxygenation of the C-3 hydroxyl leads to carboxylic acid 18 which cyclizes to lactone 19. In principle, compound 19 can serve as an intermediate in the biosynthesis of all the gilvocarcins. This pathway is consistent with all the 13C data obtained by Tomita and Takahashi except for experiments in which sodium [2-13C]acetate was used. Sodium [2-13C]acetate leads to the enhancement of both carbons of the vinyl group at C-8. This is not predicted by the biosynthetic pathway proposed in Scheme II. Tomita and Takahashi believe that two biosynthetic processes are responsible for this scrambling: (1) the recycling of acetate through the TCA cycle and (2) the synthesis of propionate from acetate through succinate and methylmalonate. They offer no evidence in support of this suggestion.

C. Biological Properties and Mode of Action.

Many studies investigating the biological properties of the gilvocarcins have been published.1,4,5 The gilvocarcins which possess both antitumor
Scheme II. Biosynthesis of the Gilvocarcins.
and antibiotic activity are gilvocarcin V (1),4 ravidomycin (6),5 chrysomycin A (4) and chrysomycin B (5).1b The related glycosides 9 and 10 also show antibiotic and antitumor activity.11 Gilvocarcin V (1) and gilvocarcin M (3), which will be abbreviated GV (1) and GM (3) respectively, also possess antibiotic activity (Table 1).1i These two compounds are most potent against gram-positive organisms, and GV (1) is one order of magnitude more active than GM (3). Defucogilvocarcin V (7), which will be abbreviated DGV (7), has antibiotic activity comparable to that of GV (1) (Table 2) against gram-positive organisms, but is inactive against gram-negative organisms.1k DGV (7), however, is active against mutant gram-negative organisms with permeable membranes. This indicates that with non-mutant gram-negative organisms, DGV (7) is inactive because it cannot enter the cell. Furthermore, it implies that the aglycone may be sufficient for biological activity.

The antitumor activity of the gilvocarcins is the more interesting biological property. Tomita and coworkers have evaluated the antitumor activity of GV (1) in mice.4 A variety of human cancer cell lines were examined in their studies, and some results are summarized in Tables 3-6.4 Mice were inoculated intraperitoneally with cancer cells and then treated with GV (1) or Mitomycin C (20) (Figure 3) for comparison. The increased lifespan percent \[ \text{ILS} \% = \left( \frac{T}{C} - 1 \right) \times 100 \] where T = tumor bearing treated animals and C = tumor bearing animal non-treated animals] was then measured as an indicator of activity. For example, an ILS % of 100 means that the treated animals lived twice as long as non-treated animals.
Table 1. Antibiotic Activity of GV (1) and GM (3).\textsuperscript{1i}

<table>
<thead>
<tr>
<th>Test Organism</th>
<th>MIC (µg/mL)</th>
<th>GV (1)</th>
<th>GM (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ATCC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus*</td>
<td>0.05</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>(6538P)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacillus Subtilis*</td>
<td>0.78</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>(10707)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia Coli**</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>(26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella Sonnei**</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>(9290)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* gram-positive
** gram-negative
Table 2. Antibiotic Activity of GV (1) and DGV (7).

<table>
<thead>
<tr>
<th>Test Organism</th>
<th>MIC (µg/mL)</th>
<th>GV (1)</th>
<th>DGV (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ATCC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus* (6538P0)</td>
<td>0.125</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>Micrococcus Luteus* (9341)</td>
<td>0.008</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Bacillus Subtilis* (10707)</td>
<td>0.008</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Escherichia Coli** (26)</td>
<td>4</td>
<td>&gt;250</td>
<td></td>
</tr>
<tr>
<td>Candida Albicans** (10231)</td>
<td>4</td>
<td>&gt;250</td>
<td></td>
</tr>
</tbody>
</table>

* gram-positive
** gram-negative
GV (1) was active against a number of the cancers tested. Ehrlich carcinoma (Table 5) and MH134 (Table 4) were two cancer cell lines that responded well to GV (1). For Ehrlich carcinoma, GV (1) gave an ILS % of 200 and four of five mice were sixty day survivors. For comparison, mitomycin C (20) gave an ILS % of 173, but there were no sixty day survivors. In general Tomita found that gilvocarcin V (1) was most affective against ascitic tumors and less affective against solid tumors. This observation will be relevant when the mechanism of action is discussed. GM (3) does not possess antitumor activity and there are no reports on the antitumor activity of defucogilvocarcins (7 or 8). Another property which makes the gilvocarcins potentially attractive as medicinal agents is their lack of acute toxicity. GV (1) has an LD₅₀ of 300 mg/kg when administered intravenously and is non toxic when administered orally.¹ In comparison, drugs such as mitomycin C (20)⁶ᵃ and doxorubicin (21)⁶ᵇ (Figure 3) possess LD₅₀ values of 5 mg/kg and 21 mg/kg respectively. It is hoped that, the lack of acute toxicity of the gilvocarcins can be exploited therapeutically.

\[ \text{Figure 3. Mitomycin C and Doxorubicin.} \]
Table 3. GV (1) Against Meth 1 Fibrosarcoma.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/Kg)</th>
<th>Schedule*</th>
<th>ILS (%)</th>
<th>Survivors (60 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GV</td>
<td>25</td>
<td>Day 1</td>
<td>42</td>
<td>0/5</td>
</tr>
<tr>
<td>GV</td>
<td>50</td>
<td>Day 1</td>
<td>95</td>
<td>0/5</td>
</tr>
<tr>
<td>GV</td>
<td>100</td>
<td>Day 1</td>
<td>136</td>
<td>0/5</td>
</tr>
<tr>
<td>GV</td>
<td>200</td>
<td>Day 1</td>
<td>180</td>
<td>1/5</td>
</tr>
<tr>
<td>GV</td>
<td>400</td>
<td>Day 1</td>
<td>153</td>
<td>4/5</td>
</tr>
<tr>
<td>Mytomycin C</td>
<td>4.2</td>
<td>Day 1</td>
<td>109</td>
<td>0/5</td>
</tr>
<tr>
<td>Mytomycin C</td>
<td>5.6</td>
<td>Day 1</td>
<td>115</td>
<td>1/5</td>
</tr>
</tbody>
</table>

* one dose
Table 4. GV (1) Against MH 134.4

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/Kg)</th>
<th>Survival (days)</th>
<th>ILS (%)</th>
<th>Survivors (60 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>_</td>
<td>17</td>
<td>_</td>
<td>0/6</td>
</tr>
<tr>
<td>GV</td>
<td>25</td>
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Table 5. Ehrlich Carcinoma Treated with 1 and Mitomycic C (20).⁴

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*Animals were treated with only one dose. **Animals were treated five consecutive days.
Although the mechanism of action of gilvocarcins containing a C-8 methyl group is uncertain, a fair amount is known about the biochemistry of the gilvocarcins containing a C-8 vinyl group [GV (1), ravidomycin (6), and chrysomycin A (4)]. Tomita, Takahashi, and Tamaoki studied the mode of action of GV (1), GM (3), and gilvocarcin A (22) (Figure 4), a synthetic analog of GV (1). Their study examined the effect of these compounds on the synthesis of DNA, RNA, and protein by *bacillus subtilis* by measuring the incorporation of [methyl-\(^{3}\)H]thymidine, [2-\(^{14}\)C]uracil, or [4,5-\(^{3}\)H]-L-leucine into the aforementioned biomolecules. GV (1) showed a slight inhibition of bacterial growth at a concentration of 0.1 \(\mu\)g/mL and caused lysis of cells, demonstrating an antibiotic effect at 0.5 \(\mu\)g/mL. GM (3) demonstrated comparable activity while gilvocarcin A (22) showed little antibiotic activity even at 100 \(\mu\)g/mL. GV (1) slightly inhibited protein synthesis 20 min after addition at a concentration of 0.25 \(\mu\)g/mL. RNA synthesis was inhibited to a greater extent than protein synthesis after only 5 to 10 min. However, DNA synthesis was completely blocked by GV (1) after 5 min even at a concentration of 0.1 \(\mu\)g/mL. Tomita and coworkers also studied the interaction of 1, 3 and 22 with DNA. GV (1) affected the electrophoretic mobility of DNA and caused DNA cleavage. GM (3) only affected mobility, while gilvocarcin A (22) had neither effect.
Elespuru and coworkers tested GV (1) in a biological induction assay (BIA).\(^8\) This assay detects DNA damaging (lesions, strand breaks, inhibition of synthesis) agents by colorimetrically measuring the increased production of β-galactosidase. Elespuru found that both GV (1) and DGV (7) produce a BIA response only when accompanied by irradiation with low energy light (313-516 nm)\(^9\). In addition, the profile generated by GV (1) in the BIA was similar to its absorbance spectrum with a maximum at 400 nm. In accord with Elespuru's results, McGee showed that both GV (1) and DGV (7) introduce single-strand scission into plasmid DNA, but only in the presence of low energy light (360 nm)\(^10\). In the absence of light 1 and 7 only decreased the linking number of the DNA in a fashion similar to that of intercalating agents such as ethidium bromide. McGee also investigated the photoreaction of 1 and 7 with oligonucleotides. The reaction of 1 with oligo(dT)\(_{20}\) hybrid retarded the electrophoretic mobility of the nucleotide, while the electrophoretic mobility of an oligo(dA)\(_{20}\) was not affected. No effect was
nucleotide when the nucleotides were single stranded. Similar retardation by 1 was observed with heterogeneous self-complementary oligonucleotides containing one and two thymidine residues. Gilvocarcin V (1) also reacted, probably at a cytosine residue, with dCCCGGG but to a lesser degree than with the oligonucleotides containing thymidine. Aglycone 7 fails to react with the oligonucleotides under these conditions. McGee's results showed that double stranded DNA is needed for the covalent binding of GV (1) and that reactions were more prevalent in thymidine rich regions. In short, the results of Tomita, Elespuru, and McGee suggest that DNA is the biological target of the gilvocarcins and that intercalation into DNA and photochemistry may play an important role in the biological activity.

Based in part on the aforementioned studies, the sequence of events shown in Scheme III has been suggested for the mechanism of action of the gilvocarcins.9,10 First, a gilvocarcin molecule, for example DGV (7), intercalates into DNA to form a non-covalent complex. If light is present, then a [2+2] cycloaddition occurs between the vinyl group and a thymidine residue to afford 23. Although the details are not clear, formation of covalent adduct 23 leads to DNA cleavage and cell death. In support of this theory, McGee has isolated the [2+2] adduct of GV (1) and thymidine.11 Specifically, McGee mixed gilvocarcin V (1) and DNA from calf-thymus, irradiated the sample at > 300 nm, digested the DNA, and isolated four [2+2] adducts (in a ratio of 73:6:11:11). These four products are believed to result from rearrangement of the C-4 furanose during the DNA digestion. The major component, which has a rearranged sugar at C-4, was 24 (Figure 5). The syn-syn geometry of the cyclobutane in 24 suggested that the [2+2] cycloaddition occurred while the
GV (1) was intercalated. In light of the proposal presented above, a question arises. If light is necessary for biological activity then how did the gilvocarcins show antitumor activity in the body cavity of mice? Elespuru has suggested that ambient light may sufficiently penetrate the body cavity in small animals such as mice. Tomita's observation that GV (1) is less active with solid tumors may be a result of the diminished ability of ambient light to penetrate such tumors. However, careful studies of the antitumor activity of GV (1) in the absence of light have not been reported.

Figure 5. GV (1)-Thymidine Adduct.
Scheme III. The Mechanism of Action of the Gilvocarcins.

Intercalation : DNA

GILVOCARCIN-DNA
NON COVALENT ADDUCT

hv

DNA BACKBONE
D. Selection of Synthetic Targets.

The psoralens are a family of natural products that exhibit photoactivated biological properties. Two medicinally important members of this family are 8-methoxypsoralen (25) and trimethylpsoralen (26), abbreviated as 8-MOP and TMP, respectively (Figure 6). These compounds are used in the treatment of skin disorders like psoriasis, and vitigolo.

Recently 8-MOP (25) has been used in the treatment of cutaneous T-cell lymphoma. The biological activity of the psoralens involves light-activation in a fashion similar to that of the gilvocarcins. Psoralens intercalate into DNA and then, under the influence of light (320-400 nm) undergo sequential [2+2] cycloaddition reactions at the furan double bond and the lactone double bond, which crosslinks the DNA. Monoadducts from reactions at the furan or the lactone are also produced, but the furan double bond is more reactive. These photochemical events cause DNA cleavage and cell death. The similarities between the gilvocarcins and psoralens led to a side-by-side
comparison by Elespuru in the BIA. Elespuru found that GV (1) could be detected in the BIA at concentration $10^{-3} \text{M}$ to $10^{-5} \text{M}$ lower than 8-MOP (25) and TMP (26), respectively, implying that GV (1) is more active.

![Chemical Structures]

**Figure 7. Selection of Synthetic Targets.**
The relationship between the gilvocarcins and the psoralens generated the selection of compound 11 and 12 as targets for synthesis. These compounds are clearly structural hybrids of DGV (7) and 8-MOP (25) (Figure 7). In the gilvocarcins the vinyl group at C-8 can undergo free rotation and therefore, two extreme conformations are possible in which the aryl and vinyl groups are conjugated. The benzofuran double bond of 11, which serves as a mimic of the vinyl group of 7, is locked in an anti-relationship to the lactone carbonyl, while in 12 a syn-relationship exists. It was thought that structure-activity relationships using 11 and 12 would provide information about the importance of double bond geometry. Finally, azide 13 was selected as a target to see if a photogenerated nitrene (27) could support activity.

E. Previous Syntheses of Defucogilvocarcins.

Many syntheses of defucogilvocarcin V (7) and defucogilvocarcin M (8) have been reported. These have been reviewed by Merriman,\textsuperscript{16} McKinney,\textsuperscript{17} and Young,\textsuperscript{18} and thus will not be covered in detail. Most syntheses revolve around construction of the C(10a)-C(10b) bond. Findlay\textsuperscript{19} and Danishefsky\textsuperscript{20} used Meyer's biaryl coupling methodology in their syntheses of DGV (7). Jung's synthesis of defucogilvocarcin M (8) used a Suzuki biaryl synthesis to construct the same bond.\textsuperscript{21} McKenzie used a
Scheme IV. Martin's Synthesis of Defucogilvocarcin Aglycones.

(a) Ti(OCOCF₃)₃, CF₃CO₂H (b) KI, H₂O, Δ (c) NaOH, H₂O (d) H₃O⁺
(e) Zn, Ac₂O, pyridine-CHCl₃, Δ (80%) (f) MeI, K₂CO₃, acetone, Δ (96%)
(g) KOH, MeOH (60%) (h) DCC, DMAP, CH₂Cl₂
Meerwein coupling reaction in his approach to defucogilvocarcin M (8). A Pechmann condensation was used by McGee and Confalone in their synthesis of defucogilvocarcin V (7). Martin prepared defucogilvocarcin M (8) and defucogilvocarcin E, constructing C(10a)-(10b) bond with a palladium mediated coupling reaction (Scheme IV). In his convergent synthesis, iodides 30 and 31 were coupled with hydroquinone 33 to afford iodoesters 34 and 35. Intramolecular coupling of 34 and 35 afforded 36 and 37 which were converted to 8 and defucogilvocarcin E.

A different approach to the gilvocarcins was reported by Parker as shown in Scheme V. In Parker's approach, the B ring was prepared by a chromium carbene annulation reaction. Acetylene 42 was prepared from vanillin in six steps. Vanillin (38a) was first carboxylated, using a Kolbe-Schmidt reaction, and the resulting carboxylic acid (38b) was esterified with methanolic sulfuric acid to afford 38c. Treatment of 38c with triflic anhydride gave 38d. Triflate 38d was coupled with trimethylsilylacetylene using a palladium mediated process to give 40. Peterson olefination of 40 completed the synthesis of 42. Chromium carbene 43 was prepared from 2-bromoanisole (39) according to a literature procedure. The reaction of acetylene 42 with chromium carbene 43 gave naphthalene 44, which was cyclized to 1-O-methyldefucogilvocarcin V (45).
Scheme V. Parker's Chromium Carbene Methodology.

(a) K₂CO₃, CO₂, 175 °C, 1500 psi, 60% (b) MeOH, H₂SO₄, 96%
(c) Ti₂O, Pyridine, CHCl₃, 79% (d) Pd (II), trimethylsilylacetylene, 94%
(e) LiCH₂SiMe₃ (l) KH, 18-crown-6 (g) MeOH, 61% (h) n-BuLi, Et₂O (i) Cr(CO)₆
(j) MeOBF₄
Although a number of approaches to C(4)-glycosylated aglycones have been described the first synthesis of a gilvocarcin M (3) was only recently reported by Suzuki and coworkers (Scheme VI). This brilliant synthesis used the Martin-Deshpande strategy to assemble the aglycone (50 → 52).

In our laboratory the synthesis of defucogilvocarcin M (8) has been accomplished using a MAD-mediated conjugate addition of an aryl lithium to a naphthoquinone monoketal (54) to construct the C(10a)-C(10b) bond. Thus, bis-(2,6-di-t-butyl-4-methylphenoxide)methylaluminum (MAD) was complexed to 54 to afford naphthoquinone-MAD complex 55. To complex 55 was added aryl lithium 56 to give 57. Conjugate adduct 57 was then cyclized with aqueous hydrochloric acid to afford aglycone 58. Compound 58 was methylated and debenzylated affording defucogilvocarcin M (8). The chemistry described in Scheme VII is the fundamental chemistry that was used to prepare targets 11 and 12. These efforts will be the topic of the next chapter.
Scheme VI. Suzuki's Synthesis of (+) Gilvocarcin M (53).

(a) Cp₂HfCl₂, AgClO₄, 4 Å sieves, CH₂Cl₂, -78 °C → -20 °C
(b) Ti₃O, iPr₂NEt, CH₂Cl₂, -78 °C
(c) 51, iPr₂NEt, cat. DMAP-THF
(d) (Ph₃P)₂PdCl₂, NaOAc, DMA, 125 °C
(e) H₂, Raney Ni-EtOH
Scheme VII. MAD-Mediated Methodology.

\[ \text{MAD} = \text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{acetone, } \Delta \]

(a) \text{H}_2, \text{Pd (C)}
Chapter II
SYNTHESIS OF DEFUCOGILVOCARCIN V ANALOGS

A. Synthesis of Naphthoquinone Monoketal 54.

It was our intention to synthesize analogs 11-13 using the MAD-mediated methodology previously used to prepare defucogilvocarcin M (8). Application of this method requires the A and B rings of the targets to come from naphthoquinone monoketal 54.\textsuperscript{28d,e} Compound 54 had previously been prepared from 5-hydroxynaphthoquinone (59), commonly known as juglone, as shown in Scheme VIII. Although this was an efficient synthesis,

Scheme VIII. Synthesis of Monoketal 54.

\[ \text{59} \xrightarrow{a,b,c} \text{60 (64\%)} \]

(a) BnBr, Ag\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}
(b) Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4}
(c) Me\textsubscript{2}SO\textsubscript{4}, K\textsubscript{2}CO\textsubscript{3}
(d) anodic oxidation, MeOH 2% LiClO\textsubscript{4}

\[ \text{54 (88\%)} \]
the throughput of 54 was limited by the lack of availability of juglone. Juglone is commercially available, but it is expensive ($20 per gram), and literature preparations of juglone typically give low yields and are cumbersome. Therefore it was thought that an alternative pathway to 54, which avoided the use of juglone, would be desirable. The work of Rapoport suggested an alternative route to naphthol 60, the precursor of monoketal 54 (Scheme IX). Rapoport was able to selectively demethylate 62 to 63 using boron

Scheme IX. Rapoport's Protocol.

\[
\begin{align*}
61 & \xrightarrow{\text{a}} 62 & \quad 63 \ (82\%) \\
\xrightarrow{\text{c, d}} & \\
& \quad 64 \ (77\%)
\end{align*}
\]

(a) POCl₃-DMF
(b) BBr₃, CH₂Cl₂
(c) MCPBA, CH₂Cl₂
(d) KOH, MeOH-THF
tribromide, and also reported the oxidation of 62 to naphthol 64. Thus, naphthol 63 was prepared and converted to 60 as shown in Scheme X. Compound 63 was benzylated using benzyl bromide and potassium carbonate to afford 65 in a 99% yield. Compound 65 was oxidized with MCPBA to the formate ester, which was hydrolyzed with methanolic potassium hydroxide to afford a 73% yield of 60. This route to 60 is superior to the sequence described in Scheme VIII and can be conducted on a large scale beginning with 1,5-dimethoxynaphthalene, an inexpensive starting material.

Scheme X. Synthesis of Naphthol 60 Via Rapoport's Protocol.

(a) BnBr, K₂CO₃
(b) MCPBA, CH₂Cl₂
(c) KOH, MeOH-THF
B. Synthesis of Defucogilvocarcin V Analog (11).

A retrosynthetic analysis of analog 11, using the MAD methodology, requires naphthoquinone monoketal 54 and aryl lithium 66 as coupling partners (Scheme XI). It was projected that 66 would be prepared by the deprotonation of 67 (Scheme XI). Compound 67 was to be prepared by coupling an aryl halide of type 68 with trimethylsilylacetylene 69 (equation 1).

Scheme XI. Retrosynthetic Analysis of 11
The coupling of 2-halophenols with copper acetylides to afford benzofurans is known as the Castro-Stephens reaction. For the synthesis of 67, this methodology would require the use of cuprous trimethylsilylacetylide. Logue and coworkers, however, have reported that cuprous trimethylsilylacetylide is too unstable to undergo the Castro-Stephens reaction, and thus this method was not attempted. Another method that was considered and ultimately used to couple 68 and 69 was a palladium-mediated process. Villemin and coworkers have reported the coupling of 2-bromophenol with phenylacetylene using a bis(triphenylphosphine)-palladium (II) chloride-cuprous iodide (Pd-Cu) in triethylamine at room temperature to afford 2-phenylbenzofuran. Thus, it was hoped that bromovanillin and trimethylsilylacetylene could be coupled under Villemin's conditions to give a precursor of compound 67. Therefore, vanillin was brominated according to a literature procedure to afford a 79% yield of 3-bromovanillin (68), but this aryl halide failed to react with acetylene 69.
under the conditions prescribed by Villemin (equation 2). Since it is well established that aromatic iodides are more reactive than bromides in palladium coupling processes, it was decided to use 3-iodovanillin in place of 3-bromovanillin. Iodovanillin (68) was prepared in good yields according to two literature methods, using either chloramine-t and sodium iodide\textsuperscript{35} or tert-butyl hypochlorite and sodium iodide\textsuperscript{36} (Scheme XI). Unfortunately, the coupling of 3-iodovanillin (68) and trimethylsilylacetylene (69) with the Pd-Cu system in triethylamine gave only a 3% yield of alkyne 71 (Scheme XI). However, it quickly became apparent that the low yield of alkyne 71 was due to the low solubility of 3-iodovanillin (68) in triethylamine, and the yield was increased to 54% when dichloromethane was used as a cosolvent (Scheme XII). Treatment of alkyne 71 with catalytic cuprous iodide in dimethylformamide at reflux gave benzofurans 72 and 73, in 71% and 6% yields, respectively (equation 3). Although the desired benzofuran (72) was prepared, it was hoped that 3-iodovanillin (68) could be converted directly to 72 in a one pot process. This was achieved by performing the reaction at reflux in acetonitrile-triethylamine (Scheme XIII), directly affording benzofurans 72 and 73 in 69% and 8% yields, respectively. The synthesis of
Scheme XII. Coupling Reaction of Iodovanillin 68.

67 was completed in a straightforward manner (Scheme XIII). Thus, aldehyde 72 was oxidized under Jones conditions to afford carboxylic acid 74 in an 81% yield. The acid was sequentially treated with thionyl chloride, 2-amino-2-methylpropanol and thionyl chloride to give an 83% yield of oxazoline 67. Compound 67 was prepared in an overall yield of 46% from 68.
Scheme XIII. Synthesis of Oxazoline 67.

68 \xrightarrow{(\text{Ph}_3\text{P})_2\text{PdCl}_2, \text{CuI}} \xrightarrow{\text{Et}_3\text{N}-\text{CH}_3\text{CN (1:3)}} \xrightarrow{\Delta} 72 (69\%) + 73 (8\%)

67 (83\%)

(a) Jones (b) SOCl\textsubscript{2}, PhH, \Delta
(c) NH\textsubscript{2}(\text{CH}_3)\textsubscript{2}CH\textsubscript{2}OH, CH\textsubscript{2}Cl\textsubscript{2}
(d) SOCl\textsubscript{2}
With oxazoline 67 in hand, the MAD-mediated conjugate addition between 67 and 54 was examined (Scheme XIV). Oxazoline 67 (2 equivalents) was lithiated using n-butyllithium at -45 °C in THF and the resulting aryl lithium was added to the MAD complex of 54 (1 equivalent) to afford conjugate adducts 75 and 76, which were not characterized but were carried on to the next step. Treatment of 75 and 76 with aqueous hydrochloric acid afforded lactones 77 (19%) and 78 (9%). The formation of both 77 and 78 indicated that in addition to lithiation at C-6, 67 was unexpectedly undergoing lithiation at C-4 to afford 79 (equation 4). The lithiation properties of 67 will be discussed later in the chapter, but first we will concentrate on the structure proofs of 77 and 78.

The structures of isomeric lactones 77 and 78, and by inference the isomeric conjugate adducts, were assigned on the basis of nOe experiments (Figure 8). In 77, irradiation of the trimethylsilyl protons produced a 6% enhancement of H_b, irradiation of H_b caused a 5% enhancement of H_a, and irradiation of both the methoxy protons and H_D caused 7% and 4% enhancements, respectively, at H_c. In 78, irradiation of the trimethylsilyl protons and H_D caused enhancement of H_c, by 30% and 2%, respectively. Having proved the structures of 77 and 78 we turn our attention back to the MAD conjugate addition and the lithiation properties of 67.
Scheme XIV. MAD-Mediated Reaction of 54 and 67.

1. MAD, toluene -78 °C
2. n-butyllithium, THF, -45 °C

54

1. MAD, toluene -78 °C
2. n-butyllithium, THF, -45 °C

67

75 (19%)

76

77 (19%)

78 (9%)
Figure 8. Nuclear Overhauser Enhancement Studies of 77 and 78.

The arrow begins at the irradiated proton and ends at the enhanced proton.
The yields of three conjugate additions between 67 and 54 are shown in Table 6. For the sake of comparison, the yield for the conjugate addition between 54 and 56 in the synthesis of DGM (8) was 72% (Scheme VII), while under the same conditions (entry 1) the addition of 67 to 54 afforded about a 30% yield of conjugate adducts. The yield increased to 56% when three equivalents of 67 were used (entry 3), but still the yield was 16% lower than in the reaction of 56 with 54. It was reasoned that the low yield of conjugate adducts might have been due to an incomplete deprotonation of 67. To understand the lithiation behavior of oxazoline 67, the studies described in Table 7 were carried out. The aims of these studies were to establish the degree of lithiation and improve selectivity in the deprotonation of 67. The studies were conducted by metallating 67 under a variety of conditions,
Table 6. Conjugate Addition Reactions of 67 and 54.

![Chemical structures](image)

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<tr>
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<td>36</td>
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<tr>
<td>3</td>
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<td>38</td>
<td>18</td>
<td>56</td>
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</table>
quenching the aryl lithium species with methyl iodide, and analyzing the ratio of products. In this limited study we did not examine all possible variables, but did investigate the affects of temperature, alkyl lithium, tetramethyl-ethylendiamine (TMEDA) as an additive, reaction time, and a tertiary amide as a substitute for the oxazoline. The structures of the methylated products were confirmed by NOe experiments (Figure 9). For example, irradiation of the trimethylsilyl protons of 80 caused a 6% enhancement of H3, and irradiation of H3 caused a 5% enhancement at H4. There was no NOe observed between the aryl methyl group and the methoxy protons of 80. This was not surprising due to the steric congestion that would be caused by proximity between these groups. In oxazoline 81, irradiation of H3 caused a 9% enhancement of aryl methyl group, and irradiation of the methoxy group produced a 20% enhancement at H6.

Figure 9. Nuclear Overhauser Enhancement Studies of 80 and 81.

The arrow begins at the irradiated proton and ends at the enhanced proton.
The degree of lithiation of oxazoline 67 with n-BuLi at -45 °C and -78 °C (entries 1 and 2) was 18% and 33%, respectively. The selectivity between lithiation at C-6 and C-4 was 3:1 in each case. When tetramethyl-ethylenediamine was used as an additive, metallation using n-butyllithium at -45 °C and -78 °C produced 95% and 86% of methylation products, respectively (entries 3 and 4). The selectivity between C-6 and C-4 (80:81) was 2:1 in each case. Reaction time slightly affected the regioselectivity (entries 5 and 6). A reaction time of 10 min showed the lowest selectivity (1.6:1) while at a reaction time of 1.5 h the ratio of (80:81) improved to 2:1.

The degree of lithiation under the conditions used in the MAD-mediated conjugate addition of 67 (entry 1) was small (Scheme XIII). Thus, less then one equivalent of aryl lithium was present under these conditions even though two equivalents of 67 were used. This was undoubtedly responsible for the low yields of conjugate adduct. An analog of 67, amide 82, was considered in an attempt to improve the selectivity of deprotonation, as Beak had established conditions for the lithiation of diethyamides. Thus, amide 82 was prepared from 74 in a 96% yield as shown in Scheme XV. The lithiation of 82 under the conditions prescribed by Beak, however, afforded a disappointing 1:1:1 ratio of 82:83:84 (Scheme XV).
Table 7. Lithiation Studies of Oxazoline 67

\[
\begin{align*}
\text{Entry} & \quad \text{RLi} & \quad \text{Temperature} & \quad \text{Reaction}^* & \quad \text{Ratio (67:80:81)} \\
& \quad \text{(additive)} & \quad ^\circ C & \quad \text{Time (hours)} & \\
1 & \text{n-BuLi} & -45 & 1.5 & 6.5:1:0.4 \\
2 & \text{n-BuLi} & -78 & 1.5 & 8:3:1 \\
3 & \text{n-BuLi} & -45 & 1.5 & 1:12:6 \\
 & & \text{(TMEDA)} & & \\
4 & \text{n-BuLi} & -78 & 1.5 & 1:4:2 \\
 & & \text{(TMEDA)} & & \\
5 & \text{n-BuLi} & -45 & 0.16 & 1:8:5 \\
 & & \text{(TMEDA)} & & \\
6 & \text{s-BuLi} & -78 & 1.5 & 1:1:4 \\
7 & \text{t-BuLi} & -78 & 1.5 & 8:1:4 \\
\end{align*}
\]

* All reactions in THF at 0.8 to 0.1
Scheme XV. Diethylamide (82) Analog of 67.

We felt that the degree of lithiation and the selectivity achieved in entries 2 and 3 were sufficient for our synthetic goals. However, if at later date a selective preparation of 77 is needed, the C-4 position of oxazoline 67 might be blocked as shown in Scheme XVI. Deprotonation of 67 with s-butyllithium, using the conditions of entry 6 in Table 7, followed by the quenching of the resulting anions with trimethylsilylchloride would be expected to afford 86. This compound has only one position for deprotonation and this compound could be used, in principle, to prepare 77.

The optimal conditions for the coupling of 67 and 54 were those outlined in entry 4 of Table 7. Thus, anion generation, MAD-mediated addition to 54 and cyclization of the conjugate adducts afforded lactones 77.
Scheme XVI. Proposed Selective Synthesis of 6-Lithiooxazoline.

and 78, in 51% and 20% yields, respectively (Scheme XVII). The conversion of 77 to 11 was then carried out in a straightforward fashion (Scheme XVIII). Compound 77 was methylated with dimethyl sulfate and potassium carbonate to afford a 97% yield of 88 which was debenzylated by hydrogenolysis over Pd on C, affording a 90% yield of 89. Compound 89 was converted to 11 by removal of trimethylsilyl group with tetra-n-butylammonium fluoride (TBAF) to afford an 88% yield of 11. Overall the conversion of 77 to 11 was accomplished in a 75% yield.
Scheme XVII. MAD-Mediated Conjugate Addition of 67 and 54.

1. MAD, toluene -78 °C
2. 3 eq. n-butyllithium-TMEDA,
   THF, -78 °C
3 eq. 67

75
76
77
78

51% from 54
20% from 54
Scheme XVIII. Conversion of 77 to 11.

77 → 88 (97%)

77 (a) (CH₃O)₂SO₂, K₂CO₃, CH₂Cl₂, 6 days, Δ
    H₂ (50 psi), Pd(C), EtOH
(c) TBAF, AcOH, THF-CH₂Cl₂ (1:3)

11 (88%)
75% from 77

88 → 89 (90%)

89 → 88 (b)
C. Synthesis of Analog 12.

It was anticipated that DGV (7) analog 12 could be synthesized by a procedure similar to 11 (Scheme XIX). It was hoped that conjugate addition of 90 to 54, followed by cyclization, would afford the carbon skeleton of 12. The benzofuran ring system of 90 was to be prepared by the coupling 3-iodo-2-hydroxy-5-methoxybenzaldehyde (91) with trimethylsilylacetylene (69).

Scheme XIX. Retrosynthetic Analysis of 12.
The preparation of aryl iodide 91 was initially addressed as shown in Scheme XX. Treatment of 92 with t-butyl hypochlorite and sodium iodide gave no reaction (Scheme XX). The reaction of 92 with chloramine-t and sodium iodide afforded a 43% yield of dimer 93 and only a 3% yield of 91 (Scheme XX).

**Scheme XX. Attempted iodination of 92.**

![Scheme XX](image)

Other iodinating protocols, such as thallation-iodination methods and iodine monochloride, were attempted but gave no reaction or unsatisfactory ratios of 93 to 91. Tetraethylammonium diacetoxyiodate had been used by Doleschall and Toth to bis-iodinate p-hydroxybenzaldehyde in an 89%
yield. When 92 was treated with this reagent, however, a low yield of a mixture of 93 and 91 was obtained with 93 being the major component.

Mercuration-iodination procedures were investigated next because electrophilic substitution of 92 using mercuric acetate had been reported. Thus, treatment of 92 with mercuric (II) acetate, followed by iodination of the

Scheme XXI. Synthesis of 95 by Mercury Route.
aryl mercuric chloride 94 gave aryl iodide 91 in 31% yield from 92 (Scheme XXI). Although, the yield of 91 had increased ten fold it was still low for the first step of a synthetic sequence. Furthermore, when aryl iodide 91 obtained from this route was coupled with trimethylsilylacetylene using Pd-Cu only a 31% yield of benzofuran 95 was obtained. Thus, because of the toxicity of mercury, low yield of the coupling reaction and practical considerations prohibited the production of large quantities of 95 by this route.

Based on the lack of success with the synthesis of benzofuran 95 bromide 97 was considered as a replacement of aryl iodide 91. This seemed reasonable because it was well established that the more electron deficient an aromatic system, the easier the palladium coupling process becomes. It was hoped that the electron-withdrawing effect of the acetyl group would increase the reactivity of the aromatic ring making the bromide sufficiently

![Chemical structure](image)

reactive to couple with trimethylsilylacetylene. Thus, phenol 92 was brominate according to a literature procedure (Br₂, AcOH, AcONa, 10 °C)⁴⁰ and
the resulting bromide 96 was reacted with acetic anhydride-pyridine to afforded a 93% yield of 97. Unfortunately, the coupling of 97 with trimethylsilylacetylene, using Pd-Cu under a variety of conditions, gave only the hydrolysis product 96.

Looking for a solution to our problems in the preparation of iodide 91 led us to re-examine the source of dimer 93 (Scheme XX). It was felt that if the production of dimer 93 could be minimized, maybe the yield of 91 would increase. An oxidative coupling process may be responsible for the production of dimer 93. Two factors were investigated in an attempt to

**Scheme XXII. Low Temperature Iodination of 92**

```
\[ \text{Chloramine-t, Nal} \]
\[ \text{DMF, -15 °C, 2 days} \]
\[ \text{Et}_4\text{Ni(OAc)}_2 \cdot \text{CH}_2\text{Cl}_2 \]
\[ -15 °C, 1 \text{ day} \]
\[ \text{Et}_4\text{Ni(OAc)}_2 \cdot \text{CH}_2\text{Cl}_2 \]
```

92 → 91 (28%) + 93 (14%)
minimize this process: (1) deoxygenation of reaction solvents and (2) reaction temperature. The degassing of the reaction solvents had no affect on the amount of dimer produced. Conducting the reaction at a lower temperature, however, had a dramatic affect on the product distribution. The reaction of 92 with chloramine-t and sodium iodide at -15 °C gave only 91 in a 28% yield (Scheme XXII). Although the yield had increased, this still did not produce large amounts of 91. The problem was solved, however, when it was found that the treatment of 92 with tetraethylammonium diacetoxyiodate at -15 °C for 24 h gave a 54% yield of 91 and only 14% of dimer 93 (Scheme XXII). Moreover, this reaction was easily scaled up, and thus large amounts of 91 were available.

The synthesis of 12 proceeded as shown in Scheme XXIII. Treatment of 91 and trimethylsilylacetylene (69) with Pd-Cu while heating at reflux in acetonitrile-triethylamine afforded benzofuran 95 in a 71% yield. Aldehyde 95 was oxidized to carboxylic acid 98 in a 73% yield using Jones reagent. Sequentially treatment of 98 with thionyl chloride, 2-amino-2-methylpropanol, and thionyl chloride gave oxazoline 99 in a 78% yield. In summary, oxazoline 99 was prepared in an overall yield of 40% from aryl iodide 91.

In light of the lithiation problems encountered with oxazoline 67, we felt that lithiation studies of 99 were necessary. Much to our dismay, oxazoline 99 was reluctant to ortho lithiate under a variety of conditions. Attempted lithiation of 99 gave either no reaction or complex mixtures. For example, treatment of 99 with s-butylithium-TMEDA at -78 °C, followed by methyl
Scheme XXIII. Synthesis Oxazoline 99.

\[ \text{H} \quad \text{TMS} \]

91 \[ \xrightarrow{(\text{Ph}_3\text{P})_2\text{PdCl}_2, \text{Cul}} \]

\[ \text{Et}_3\text{N-CH}_3\text{CN (1:3)} \]

\[ \Delta \]

\[ \text{H} \quad \text{TMS} \]

95 (71%)

\[ \text{a} \]

\[ \text{TMS} \]

98 (73%)

\[ \text{b, c, d} \]

90 \[ \xrightarrow{?} \]

99 (78%)

(a) Jones  
(b) SOCl\(_2\), PhH, \(\Delta\)  
(c) NH\(_2\)C(CH\(_3\))\(_2\)CH\(_2\)OH  
(d) SOCl\(_2\), rt,
iodide, afforded a complex mixture in which 100 and 101 (1:1) were the major components (equation 6). Compound 100 was derived from the methylation of the desired anion 90, and 101 resulted from the addition of s-butyllithium to 99 followed by methylation of the resulting anion. The addition of alkyllithiums to aryl oxazolines has been previously reported by Meyers. The structures of compounds 100 and 101 were supported by nOe experiments (Figure 10). For compound 100 irradiation of the trimethylsilyl
protons caused a 5% enhancement of H₃, irradiation of H₃ caused a 4% enhancement of H₄, and irradiation of H₄ caused an 11% enhancement of the methoxy group. For 101, irradiation of the trimethylsilyl protons caused a 4% enhancement of H₃, irradiation of H₃ caused a 4% enhancement of H₄, irradiation of H₄ caused a 9% enhancement of the methoxy group, and irradiation of the methoxy group caused 24% enhancement of H₄. There was no nOe observed between the aryl methyl group and the methoxy of compound 100, as was the case with 80 (Figure 9).

Figure 10. Nuclear Overhauser Enhancement Studies of 100 and 101.

The arrow begins at the irradiated proton and ends at the enhanced proton.
Failure to cleanly generate 90 led us to consider two alternatives for compound 98, diethylamide 102 and methylamide 103. The cyclization of the conjugate adduct resulting from the addition of 102 was of concern, because of the tertiary amide. The cyclization of the conjugate adduct resulting from 103 should be less problematic since it is only a secondary amide.

Scheme XXIV. Amide Analogs of 98.
amide. However, because of the intramolecular nature of the cyclizations we hoped that both of the adducts derived form 102 and 103 would cyclize. Compounds 102 and 103 were prepared from carboxylic acid 98. Carboxylic acid 98 was treated with thionyl chloride and the crude acid chloride was reacted with diethylamine or methylamine to afford amide 102 and 103 in a 96% and a 44% yield, respectively (Scheme XXIV). The lithiation properties of 102 and 103 were examined as shown in Scheme XXIV. Treatment of 103 with n-butyllithium (2 equivalents) followed by a methyl iodide quench afforded only N-alkylation product 105. The treatment of 102 with s-butyllithium-TMEDA followed by methyl iodide, however, afforded a 66% conversion of 101 to 104 by NMR (Scheme XXIV).

Having established that diethylamide 102 could be cleanly ortholithiated and trapped by an electrophile, the synthesis of 12 proceeded as shown in Scheme XXV. Addition of the aryl lithium generated from 102 (s-butyllithium-TMEDA at -78 °C) to a MAD complex of 54 afforded conjugate adduct 106. This intermediate was then treated with aqueous THF-HCl to afford a 55% yield of lactone 107.

The synthesis of 12 was completed as shown in Scheme XXVI. Naphthol 106 was methylated with dimethyl sulfate and potassium carbonate to afford 107 in an 88% yield. The debenzylolation of 107 was accomplished by catalytic hydrogenation (Pd on C) affording an 83% yield of naphthol 108 which was treated with TBAF to afford a 91% yield of 12. Naphthol 106 was converted to 12 with an overall yield of 69%.
Scheme XXV. Conjugate Addition of 102 to 54.

(a) MAD, -78 °C, PhCH$_3$
(b) 102, s-BuLi, TMEDA, THF, - 78 °C
(c) HCl (aq), THF, 24 h

55% from 54
D. Progress Toward the Synthesis of 13.

It was projected that the synthesis of analog 13 could be accomplished according to the retrosynthetic analysis shown in Scheme XXVII. The conjugate addition of lithiated bis-oxazoline 110 followed by cyclization
Scheme XXVII. Retrosynthetic Analysis of 13.

would lead to a compound with an oxazoline at C-8. Hydrolysis of the oxazoline to the carboxylic acid and degradation of the acid to the aryl amine followed by diazonium chemistry would afford azide 13. The key to this plan was the selective deprotonation of 111 since deprotonation could occur both at C-2 and C-6. Although at first glance the C-2 seems the likely site of deprotonation, because it is ortho to both oxazolines. Most examples of 1,3-diaactivated benzenes do lithiate at C-2 preferentially to C-6, but there are a few examples in which this is not the case. For example, the deprotonation of
112\textsuperscript{42} occurs predominatly at C-2, but under identical conditions its dimethylamino analog (113)\textsuperscript{43} lithiates at predominatly at C-6 (Figure 11). The hope of lithiating 111 at C-6 instead of C-2 was supported by a report of Boekelheide and coworkers.\textsuperscript{44}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure11.png}
\end{center}

Figure 11. Example of Selectivity Reversal.

They were interested in deprotonating oxazoline 114 at C-2 with alkylolithiums, but found that instead, alkylolithiums added to 114 to afford

\begin{center}
\includegraphics[width=0.5\textwidth]{figure11.png}
\end{center}

115
compounds of type 115. The addition to the aromatic ring occurred exclusively at C-6. It was hoped that oxazoline 111 would not undergo addition because the electron-donating methoxy group decreases the electrophilicity of the aromatic ring and provides an additional activating group for lithiation.

Oxazoline 111 was prepared as shown in Scheme XXVIII. Oxidation of 3,5-dimethylanisole according to a literature procedure provided bis-acid 116

Scheme XXVIII. Synthesis and Lithiation Study of 111.

(a) SOCl₂ (b) NH₂C(CH₃)₂CH₂OH
(c) SOCl₂ (d) n-BuLi, THF, -78 °C (e) CH₃I

116

117 (13%)
in 19% yield. Sequential treatment of 116 with thionyl chloride, 2-amino-2-methylpropanol, and thionyl chloride afforded bis-oxazoline 111 in 43% yield. It was disappointing that lithiation experiments with 111 under a variety of conditions resulted only in a product of addition. For example, with n-butyllithium a 13% yield of 117 was obtained (Scheme XXVIII).

Based on our earlier success with the diethylamide group, an obvious substitute for 111 would be bis-amide 118 (Scheme XXIX). Amides are less electron-withdrawing than the oxazolines since appropriate signals in the NMR spectra of the amides were always further upfield than in the oxazolines.

Scheme XXIX. Synthesis and Lithiation Study of 118.
For example, the three aromatic protons of bis-amide 118 are found at 6.9 ppm while the protons of bis-oxazoline 111 are found at 7.5 and 8.0 ppm (Figure 12). Thus, it was hope that alkyllithiums would not add to 118. However, the same selectivity question had to be answered for 118. Bis-amide 118 was prepared in 89% yield from bis-acid 116 by treating 116 with thionyl chloride and adding diethylamine to the crude bis-acid chloride

affording 118 (Scheme XXIX). Fortunately, amide 118 could be lithiated at C-6 using s-butyllithium-TMEDA as shown in Scheme XXIX. The lithiation of 118, followed by a benzaldehyde quench and cyclization of the resulting alcohol with p-toluenesulfonic acid afforded a 30% yield of lactone 119 (Scheme XXIX). The structure of 119 was supported by a nOe experiment

Figure 12. Chemical Shift Comparison of 111 and 118.
(Figure 13). Irradiation of the methoxy group gave a 25% enhancement of the signal due to $H_b$ and no enhancement of the signal due to $H_a$.

![Figure 13. Nuclear Overhauser Enhancement Studies of 119. The arrow begins at the irradiated proton and ends at the enhanced proton.](image)

Although the results shown in Scheme XXIX suggested that metallation of 117 at C-6 might not be a high yield process, the coupling of 118 with 54 was attempted as shown in Scheme XXX. Treatment of the aryl lithium species generated by reacting 118 with s-butyllithium-TMEDA at -78 °C, with a MAD complex of 54 afforded conjugate adduct 120 (Scheme XXX). The separation of conjugate adduct 120 from excess bis-amide 118 was not possible, therefore the mixture of 120 and 118 was heated at reflux in aqueous hydrochloric acid-THF for 24 h to afford a 25% yield of lactone 121. The low yield of 121 and the difficult isolation procedure caused us to abandon the use of compound 118 in the synthesis of 13.
Scheme XXX. Conjugate Addition of 117 and 54.

We next returned to the idea of using aryl lithium 110 in the conjugate addition process. Aryl lithium 110, as mentioned above, could not be generated directly from 111 (Scheme XXVIII). So we turned to a metal-halogen exchange of a halo-bis-oxazoline of type 122 as an alternate source of 110 (equation 8).
The synthesis of bromo-(bis)-oxazoline 122 is shown in Scheme XXXI. Rearrangement of 4-bromo-3,5-dimethylphenol (123) to 2-bromo-3,5-dimethylphenol (124) was accomplished using hydrogen bromide in chloroform as reported by Balsley and coworkers. Methylation of 124 with dimethyl sulfate and potassium carbonate afforded 125 in a 95% yield. Potassium permanganate oxidation of 125 gave bis-acid 126 in a 52% yield. The conversion of bis-acid 126 to bromo-(bis)-oxazoline 122 was attempted as before. Carboxylic acid 126 was sequentially treated with thionyl chloride, 2-amino-2-methylpropanol, and thionyl chloride at room temperature. Unfortunately, these conditions afforded 128 (52%) as the major product and 122 (20%) as a minor product (Scheme XXXI). This synthetic problem will be addressed later in this chapter, but first we will address the structure proof of 128.
Scheme XXXI. Attempted Synthesis of 122.

123 \[ \xrightarrow{a} \] 124 (45\%)

124 \[ \xrightarrow{b} \] 125 (95\%)

125 \[ \xrightarrow{c} \] 126 (52\%)

126 \[ \xrightarrow{d, e} \] 127

128 (52\%)

122 (20\%)

(a) HBr, CHCl₃ (b) Me₂SO₄, K₂CO₃
(c) KMnO₄ (d) PhCH₃, SOCl₂, Δ
(e) NH₂C(CH₃)₂CH₂OH, CH₂Cl₂
(f) SOCl₂, rt
The structure of 128 was supported by nOe and COLOC experiments as shown in Figures 13 and 14. The nOe experiments of 128 gave the following results. Irradiation of the amide proton caused a 7% enhancement of $H_A$ and irradiation of $H_A$ caused a 4% enhancement of the amide proton. Irradiation of the methoxy group also caused a 25% enhancement of $H_B$. Although, this nOe experiment supported the structure of 127 the same results may have been obtained with the isomeric amide (129) (Figure 14). Compound 129

![Structures](image)

Figure 14. nOe Experiments of 128 and Projected nOe of 129.

would provide the same nOe as 127 and depending on its conformation it may or may not show an nOe between $H_B$ and the amide proton. Since, a sample of 129 was not available the assignment could not be certain and
thus, it was necessary to obtain additional data to support the nOe results. This complimentary data was provided by a COLOC experiment (Figure 14). For compound 127 the amide proton and H_A both showed a correlation with the sp² carbon of the amide, and H_B and H_A both showed a correlation to the sp² carbon of the oxazoline (Figure 15). These results would not be expected for isomer 129 (Figure 15). The correlation of H_A and the amide proton with the amide sp² would also be expected for 129 but the correlation of H_B and H_A with the oxazoline sp² carbon would not be expected for 129. The combination of nOe and COLOC experiments established the structure of 128.

Figure 14. COLOC of 128 and Projected COLOC of 129.
The formation of chloroamides of type 128 has been reported to occur by the ring opening of the oxazoline hydrochloride salt. This ring opening is less prevalent when the reactions are carried out at lower temperatures. Thus, we were pleased that cyclization of 127 at -5 to 0°C gave a 75% yield of 122 (equation 9).

\[
\begin{array}{c}
\text{127} \\
\text{122 (75\%)}
\end{array}
\]

(a) SOCl$_2$, -5°C to 0°C, 3 hr

Studies were then conducted to establish metal-halogen exchange conditions for 122 (equation 10). Thus, treatmetnt of 122 with an alkyl lithium was followed by a methyl iodide quench. In addition to the expected methylated bis-oxazoline 130, reduction product 111 was also observed. Experiments to elucidate the source of the proton which leads to 111 were inconclusive. However, some general comments about the metal-halogen exchange reaction can be made. First, the exchange is not complete at -78°C with either n-butyllithium or t-butyllithium. The exchange is complete in 15 min at -100°C with t-butyllithium. The yield of methylated compound 130
was increased when TMEDA was added prior to the addition of methyl iodide, but after the exchange. The best conditions for metal-halogen exchange and methylation of 122 are shown in equation 11. These conditions afforded 130 and 111 in 80% and 20% yields respectively (equation 11).

(a) t-BuLi, -100 °C, THF, 15 min; -100 °C → -78 °C; TMEDA, 5 min
(b) CH₃I, 45 min  (c) H₂O

The conditions established in equation 11 encouraged us to proceed with the conjugate addition of 122 and 54 (Scheme XXXII). The addition of 122 was then carried out as shown in Scheme XXXII to afford a 47% yield of
adduct 131. Conjugate adduct 131 was cyclized by heating to reflux in aqueous hydrochloric acid-tetrahydrofuran to give a 72% yield of 132.

Scheme XXXII. Conjugate Addition of 122 and 54.

54 \[\xrightarrow{a,b} \] 131 (47%)

132 (72%)

(a) MAD, PhCH$_3$, -78°C (b) 2 eq. 122, 4 eq. t-BuLi, -100°C, THF, 15 min; -100°C → -78°C; TMEDA, 5 min (c) HCl (aq), THF, 1hr
The next task en route to 13 involved the degradation of the C-8 oxazoline of 132 to an aryl amine. Treatment of 132 with dimethyl sulfate and potassium carbonate methylated the phenolic hydroxyl group and converted the oxazoline to the methyl ester 133 (Scheme XXXIII). Methyl ester 133 was hydrolyzed with methanolic potassium hydroxide in the absence of oxygen, affording presumably the bis-carboxylic

**Scheme XXXIII. Conversion of 132 to 134.**

(a) (CH₃O)₂SO₂, K₂CO₃, acetone, Δ
(b) KOH, MeOH-THF, Δ (c) recrystallization
acid which cyclized during recrystallization to give a 68% yield of carboxylic acid 134 (Scheme XXXIII). One attempt to convert 134 to 135 using diphenylphosphoryl azide and benzyl alcohol, however, met with failure. The conversion of 134 to an aryl amine and the subsequent preparation of 13 is continuing in other hands.

In summary, syntheses of 11 and 12 have been achieved and substantial progress has been made toward azide 13. The syntheses of 11 and 12 are convergent with nine steps in the longest linear sequence in each case. Each sequence proceeds in 38% overall yield from the point of convergence. Although, compound 13 was not prepared, a viable precursor (134) as been prepared. We hope that conversion of 134 to 13 will be accomplished as shown in Scheme XXXIV.

The biological and spectral properties of 11 and 12 and intermediates prepared en route to these targets will be the topic of the next chapter.
Scheme XXXIV. Projected Conversion of 134 to 13.
Chapter III

UV and BIOLOGICAL DATA of Gilvocarcin Analogs

Since the absorbance of light may play an important role in the biological activity of the gilvocarcins, the UV spectra of 11 and 12 were recorded for comparison. These data, as well as spectra of gilvocarcin V (1)\textsuperscript{2a} and gilvocarcin M (3)\textsuperscript{2a} are shown in Figure 15. The UV spectra of 11 and 12 were obtained in dichloromethane while the spectra for 1 and 3 were recorded in methanol. The similarities between the UV spectra of these compounds, however, are nonetheless obvious. Gilvocarcin V (1) has its highest absorbance at 398 nm with an extinction coefficient of 16,982. Gilvocarcin M (3) as its highest absorbance at 387 nm with an extinction coefficient of 10,000. The UV spectrum of 11 is more similar to gilvocarcin M (3), while the spectrum of 12 is more similar to gilvocarcin V (1). The spectrum of 11 shows the highest absorbance at 384 nm with extinction coefficient of 13,182. The spectrum of 12 shows the highest absorbance at 394 nm with an extinction coefficient of 7,762.
Figure 15. UV Data of 11, 12, GV(1) and GM (3).
As we have seen, GV(1) and GM (3) both possess antibiotic activity, but only GV (3) possesses antitumor activity. A direct correlation between UV absorbance and antitumor activity between GV (1) and GM (3) cannot be made because they have different groups at C-8. However, analogs 11 and 12 both have a double bond available for photochemistry. Since the UV spectrum of 12 is more like GV (3), which has antitumor activity, it might be expected that 12 would show activity instead of 11 without taking into account pharmokinetics of the compounds.

Biological testing was done through the National Cancer Institute's preclinical antitumor drug discovery screen. Sixty human tumor cell lines from seven cancer types were tested: lung, colon, melanoma, renal, ovarian, brain and leukemia. The activity of a particular compound was measured by calculating percent growth (PG). The percent growth is calculated as shown in Figure 16. The population of cells is measured by using sulforhodamine B (SRB) as a staining agent and then using a colorimeter to measure optical densities. Sulforhodamine is an anionic pink dye which binds electrostatically to basic amino acids.

The compounds tested were 11, 89, 12, 108, 109 and 138. Compound 138 was prepared from 108 as shown in equation 12. PG was plotted against the log10 of the concentration dose in the dose-response curves shown in Figure 17-22. As their dose-response curves show
compounds 89 (Figure 17), 11 (Figure 18), 109 (Figure 21), and 12 (Figure 22) possess no activity against the cancers tested. Compound 138 (Figure 20) shows slight activity at a concentration of $10^{-4}$. The greatest activity by 138 was demonstrated against renal cancers where PG values of 23, and -10 were observed for two of the renal cancer cell lines. Much to our delight, compound 108 (Figure 19) showed good activity with a variety of cancer cell lines at $10^{-4}$. This compound showed percent growths of less than zero for some of the cancer cell lines in all the different cancers expect for colon. The best activity was shown against central nervous system cancers where all the PG values were negative. With other cancers such as melanoma (line, UACC-62), renal (CAKI-1), and non-small cell lung cancer (HOP-62) 108 showed percent growths of -65, -68, and -40, respectively.

The only compound that showed activity was a precursor of 12. The analogous structure of compound 1 has not been prepared or tested to date. Since only a small number of compounds have been tested, no definite structure activity relationships can be recognized. However, the only compound with activity (108) was a precursor of 12 which absorbs light more
like gilvocarcin V (1). Whether this is the cause for the activity of 108 or its pharmokinetic properties is not known.

Although, the results of compound 138 were exciting the activity it showed was at a high concentration. The pharmokinetics of the compounds prepared thus far are certainly not optimal. For example, the water solubilities of these compound are certainly very low. It would be desirable to synthesize

\[
\text{Percent Growth (PG)}
\]

\[
\text{Mean } OD_{t\text{zero}} = \text{The average of the optical density measurements of SRB-derived color just before exposure of cells to test compounds.}
\]

\[
\text{Mean } OD_{t\text{test}} = \text{The average of optical density measurements of SRB-derived color after 48 hours exposure of cells to the test compounds.}
\]

\[
\text{Mean } OD_{t\text{ctrl}} = \text{The average of optical density measurements of SRB-derived color after 48 hours with no exposure of cells to the test compound.}
\]

If \((\text{Mean } OD_{t\text{test}} - \text{Mean } OD_{t\text{zero}}) \geq 0\) then

\[
PG = 100 \times \frac{\text{Mean } OD_{t\text{test}} - \text{Mean } OD_{t\text{zero}}}{\text{Mean } OD_{t\text{zero}}}
\]

If \((\text{Mean } OD_{t\text{test}} - \text{Mean } OD_{t\text{zero}}) < 0\), then

\[
PG = 100 \times \frac{\text{Mean } OD_{t\text{test}} - \text{Mean } OD_{t\text{zero}}}{\text{Mean } OD_{t\text{zero}}}
\]

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Percent Growth as Defined by NCI.}
\end{figure}
Figure 17. Biological Evaluation of 89.
Figure 18. Biological Evaluation of 11.
Figure 19. Biological Evaluation of 108.
Figure 20. Biological Evaluation of 138.
Figure 21. Biological Evaluation of 109.
Figure 22. Biological Evaluation of 12.
analogs of DGV (7) with improved water solubility. Since BE-12406 A (9) and Be-12406 B (10) (Figure 1) recently have been isolated and possess antitumor activity, a second generation of compounds should be synthesized (Figure 23). These compounds should be more water soluble due to the rhamnose residue at O-12. It is hoped that this increase in water solubility will manifest itself in an increase in activity. The synthesis of 139, 140, 141 is currently being pursued.

Figure 23. O-Aryl Glycosides of 11, 12 and 13
Chapter IV
Experimental

All melting points were taken with a Thomas-Hoover capillary melting point apparatus or a Fisher-Johns melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker AM-250, AC-300, AC-200, AM-500, or MSL 300 spectrometers. The $^1$H NMR spectra are reported as follows: chemical shift [ multiplicity ( s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet ), coupling constants in hertz, integration, interpretation ]. $^{13}$C NMR data were obtained with a Bruker AM-250 and are reported as follows: chemical shift (multiplicity). Infrared spectra were taken with Perkin-Elmer 457 or 1600 instruments. UV data were recorded on a HP8452A diode array spectrophotometer. Mass spectra were obtained on Kratos MS-30 or Kratos VG70-250s instruments at an ionization energy of 70 ev. Compounds for which an exact mass is reported exhibited no significant peaks at $m/z$ ratios greater than that of the parent peak. A GC-MS-IR instrument consisting a 5890 Series II Hewlett Packard gas chromatograph (65% phenyl, 35% methyl silicone column), HP5965A IR, and HP5970 mass spectrometer was used for analysis of inseparable mixtures. Conditions for GC data are reported as follows: [tr (retention time); initial temperature (initial time)-(heating rate)-final temperature (final time)]. Combustion analysis were performed by Micro-Analysis, Inc., Wilmington, DE or Atlantic Microlab, Inc., Atlanta, GA.
Solvents and reagents were dried and purified prior to use where indicated: tetrahydrofuran, diethyl ether, toluene and benzene were distilled from sodium metal. Acetonitrile was dried over 4 Å molecular sieves for 12 hr and then sequentially distilled from calcium hydride and phosphorus pentoxide. Solvents were degassed by bubbling argon or nitrogen through them. All Grignard reagents and organolithiums were titrated prior to use with menthol using 1,10-phenanthroline as the indicator. Reactions requiring an inert atmosphere were carried out under argon. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica 60F-254 plates. Preparatory thin-layer chromatography was performed with EM laboratory 2 mm thick precoated silica 60F-254. Column chromatography was performed over EM laboratory silica gel (70-230 mesh) or Brockman activity-I basic alumina (60-235 mesh). All electrochemical oxidations were carried out with a solid platinum cathode (1 cm²) and a cylindrical platinum gauze anode (5.0 x 2.5 cm) using a Kepco Inc. Model JQE 0-36 V, 0-3 A power supply.

\[ \text{1,5-Dimethoxynaphthalene (61)} \] To a mechanically stirred mixture of 60 g (375 mmol) of 1,5-dihydroxynaphthalene, 192 g (144 mL, 1.52
mol) of dimethyl sulfate and 900 mL of methanol was added at 0 °C 180 g (4.5 mol) of sodium hydroxide in 192 mL of water over 2.5 h. After the addition was complete, the cold bath was removed. The reaction was stirred for 1 h, and then heated at reflux for 0.5 h. This mixture was diluted with 2.4 L of water, and the resulting solid was collected, rinsed with two 200-mL portions of water, and dried to yield 55 g (78%) of 61 as a brown solid: mp 172-173 °C; 1H NMR (CDCl₃) δ 4.00 (s, 6H, (ArOCH₃)₂), 6.83 (d, J = 8.8 Hz, 2H, C₂H and C₆H), 7.38 (t, J = 8.8 Hz, 2H, C₃H and C₇H), 7.81 (d, J = 8.8 Hz, 2H, C₄H and C₈H).

\[
\begin{align*}
\text{OCH}_3 \\
\text{CH}_3 \text{O} & \text{CHO} \\
\end{align*}
\]

4,8-Dimethoxynaphthalene-1-carboxaldehyde (62).²⁹ A slurry of 49 g (261 mmol) of 61, 30 mL (383 mmol) of dimethylformamide and 48 mL of dry toluene was cooled with an ice bath and 29 mL (310 mmol) of phosphorus oxychloride was added in one portion. The reaction was stirred at 0 °C for 0.5 h and then heated at reflux for 2.5 h. The mixture was cooled to room temperature and poured into a mixture of 350 mL of 10% aqueous sodium hydroxide and 350 mL of ice. This mixture was extracted with four 700-mL portions of benzene. The combined organic phases were sequentially washed with two 1000-mL portions of 5% aqueous hydrochloric
acid, two 700-mL portions of water, and 700 mL of brine. The organic phase was dried (MgSO₄) and concentrated in vacuo to afford 46 g (88%) of 62 as a tan solid: mp 124-125°C (lit²⁹ 125-126°C); ¹H NMR (CDCl₃) δ 4.02 (s, 3H, ArOCH₃), 4.06 (s, 3H, ArOCH₃), 6.91 (d, J = 8.2 Hz, 1H, C₇H), 7.01 (dd, J = 7.7, 0.7, 1H, ArH), 7.45 (dd, J = 8.2, 7.7 Hz, 1H, C₆H), 7.96 (dd, J = 7.7, 1 Hz, 1H, ArH), 8.08 (d, J = 8.2 Hz, 1H, C₂H), 11.05 (s, 1H, CHO).

![Structure of 63]

1-Formyl-8-hydroxy-4-methoxynaphthalene (63).²⁹ To a solution of 25.7 g (118 mmol) of 62 in 600 mL of dichloromethane was added at -78°C under argon 25 g (9.43 mL, 101 mmol) of boron tribromide. After the addition was complete, the cold bath was removed and the reaction was stirred for 2 h at room temperature. The reaction was poured into 2.4 L of saturated sodium bicarbonate and stirred for 2 h. The layers were separated and the aqueous phase was extracted with three 400-mL portions of dichloromethane. The combined organic phases were sequentially washed with two 900-mL portions of saturated aqueous sodium bicarbonate and two 900-mL portions of water and brine. The organic phase was dried (MgSO₄) and concentrated in vacuo to afford an orange solid. This material was dissolved in a minimal amount of dichloromethane and filtered through 60 g
of silica gel (eluted with 800 mL of dichloromethane). The filtrate was concentrated in vacuo to afford 22 g (92%) of 63 as tan solid: mp 87-88 °C (lit52 91-93 °C); 1H NMR (CDCl3) δ 4.10 (s, 3H, ArOCH3), 6.85 (d, J = 8 Hz, 1H, ArH), 7.15 (dd, J = 7.3, 1.3 Hz, 1H, ArH), 7.48 (t, J = 7.3 Hz, 1H, ArH), 7.85 (dd, J = 8, 1.3 Hz, 1H, ArH), 7.99 (d, J = 8 Hz, 1H, ArH), 9.60 (s, 1H, CHO), 12.17 (s, 1H, ArOH).

8-(Benzylxoy)-1-formyl-4-methoxynaphthalene (65). A heterogeneous mixture of 16.89 g (83.20 mmol) of 63, 18.69 g (13 mL, 109 mmol) of benzyl bromide, 54 g (391 mmol) of potassium carbonate and 330 mL of acetone was heated at reflux for 48 h. The reaction was filtered, and the potassium carbonate was rinsed with acetone. The filtrate was concentrated in vacuo and the excess benzyl bromide was removed by Kugelrohr distillation (80 °C, 0.5 mmHg) to afford 24 g (99%) of 65 as a yellow solid: mp 127-128 °C; IR (CH2Cl2 ) 1670 cm−1; 1H NMR (CDCl3) δ 4.05 (s, 3H, ArOCH3), 5.28 (s, 2H, CH2O), 6.89 (d, J = 8.2 1H, ArH), 7.10 (d, J = 7.7, 1H, ArH), 7.41 (m, 6H, ArH), 7.97 (d, J = 7.4, 1H, ArH), 8.08 (d, J = 8.3, 1H, ArH), 11.05 (s, 1H, CHO); 13C NMR (CDCl3) δ 55.9 (q), 71.1 (t), 103.9 (d), 109.3 (d), 115.7 (d), 124.9 (s), 125.7 (d), 127.2 (s), 127.7 (d), 127.8 (s), 128.2
(d), 128.8 (d), 129.5 (d), 136.1 (s), 155.46 (s), 159.4 (s), 194.3 (d); exact mass calcd. for C_{19}H_{16}O_{3} m/z 292.1099, found m/z 292.1095.

Anal. calcd. for C_{19}H_{16}O_{3}: C, 78.05; H, 5.52. Found: C, 77.97; H, 5.54.

\[ \text{OCH}_3 \]
\[ \text{BnO} \text{ OH} \]

8-(Benzyloxy)-1-hydroxy-4-methoxynaphthalene (60). To a solution of 10.0 g (34.3 mmol) of 65 in 350 mL of dichloromethane was added in one portion 15.5 g (67.6 mmol, 75% by iodometric titration) of m-chloroperoxybenzoic acid. The reaction was stirred for 3 h and 125 mL of 10% aqueous sodium thiosulfate was added. The resulting heterogeneous mixture was stirred for 0.5 h and an additional 350 mL of 10% aqueous sodium thiosulfate was added along with 400 mL of dichloromethane. The mixture was shaken, the layers were separated, and the aqueous layer was extracted with 400 mL of dichloromethane. The combined organic phases were washed with two 700-mL portions of 10% aqueous sodium thiosulfate and 700-mL portion of aqueous saturated sodium bicarbonate. The organic phase was dried (MgSO_{4}) and concentrated in vacuo to afford 9.6 g of a red solid. This material was dissolved in 307 mL of degassed (with argon) THF:MeOH (1:1) and cooled with an ice bath. To the cold solution under argon was added 60 mL of degassed (with argon) ice cold methanolic
potassium hydroxide (1.1 M) via a cannula. The resulting dark mixture was stirred for 0.5 h at 0 °C, acidified to a pH of 1 with 10% aqueous hydrochloric acid, diluted with 900 mL of water, and extracted with two 400-mL portions of dichloromethane. The combined organic phases were washed with 300 mL of water, and 300 mL of brine, dried (MgSO₄), and concentrated in vacuo to afford a red solid. This material was dissolved in a minimal amount of dichloromethane and filtered through 80 g of silica gel, eluted with 800 mL of dichloromethane. The filtrate was concentrated in vacuo to afford 7 g (73%) of 60 as a brown solid: mp 112-114 °C (lit92 108 °C); ¹H NMR (CDCl₃) δ 3.94 (s, 3H, ArOCH₃), 5.26 (s, 2H, CH₂O), 6.77 (s, 2H, ArH), 6.93 (d, J = 7.7 Hz, 1H, ArH), 7.41 (m, 6H, ArH), 7.9 (d, J = 8.57 Hz, 1H, ArH), 8.99 (s, 1H, ArOH).

8-(Benzyloxy)-4,4'-dimethoxynaphthalene-1-one (54). A solution of 3.00 g (10.7 mmol) of 60 and 9.67 g (91 mmol) of lithium perchlorate in 1400 mL of methanol was degassed with nitrogen for 1.5 h. The reaction was cooled with ice water and was electrolyzed at 0.1 amps (3 volts) for 6 h while nitrogen was bubbled through the mixture. The reaction was concentrated to about 500 mL and then poured into 700 mL of aqueous saturated sodium
bicarbonate. The resulting milky mixture was extracted with two 700-mL portions of dichloromethane. The combined organic phases were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a dark oily residue. This material was chromatographed over 120 g of alumina (eluted with petroleum ether-ethyl acetate, 10:1) to afford 2.15 g (65%) of 54 as a yellow solid: mp 103-105 °C (lit$^{17}$ 106-108 °C); $^1$H NMR (CDCl$_3$) δ 3.18 (s, 6H, (OCH$_3$)$_2$), 5.24 (s, 2H, OCH$_2$), 6.54 (d, J = 10.4 Hz, 1H, C$_2$H), 6.74 (d, J = 10.4 Hz, 1H, C$_3$H), 7.06 (d, J = 7.6 Hz, 1H, C$_7$H), 7.35 (m, 5H, ArH), 7.6 (m, 2H, ArH).

4-Hydroxy-5-methoxy-3-(trimethylsilyl)ethynylbenzaldehyde (71). A solution of 0.33 g (1.19 mmol) of 3-iodovanillin (68),$^{35,36}$ 14.6 mg (0.021 mmol) of bis(triphenylphosphine)palladium (II) chloride, 7.7 mg (0.041 mmol) of copper (I) iodide, 10 mL of triethylamine and 30 mL of dichloromethane was stirred under argon for 2 min followed by addition of 198 mg (0.28 mL, 2 mmol) of trimethylsilylacetylene. The solution was stirred at room temperature for 19 h, and the supernatant was decanted and concentrated in vacuo. The residue was dissolved in 100 mL of ethyl acetate, washed with 60 mL of 10% aqueous hydrochloric acid, and the acidic wash was extracted with two 60-mL portions of ethyl acetate. The combined
organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with cyclohexane-ethyl acetate, 5:1) to give a light yellow solid. This material was recrystallized twice from hexane-dichloromethane to give 0.23 g (78%) of acetylene 71 as a tan solid: mp 179-183 °C (dec.); IR (CHCl₃) 3500, 2150, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 0.28 (s, 9H, Si(CH₃)₃), 3.96 (s, 3H, ArOCH₃), 6.50 (s, 1H, ArOH), 7.35 (d, J = 1.7 Hz, 1H, ArH), 7.52 (d, J = 1.7 Hz, 1H, ArH), 9.78 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ -0.12 (q), 56.4 (q), 98.0 (s), 101.5 (s), 108.8 (d), 110.0 (s), 129.3 (s), 130.7 (d), 147.3 (s), 152.6 (s), 190.2 (d); exact mass calcd. for C₁₃H₁₆O₃Si m/z 248.3562, found m/z 248.0926.

7-Methoxy-2-trimethylsilylbenzofuran-5-carboxaldehyde (72) and 7-Methoxybenzofuran-5-carboxaldehyde (73). A solution of 2.0 g (7.19 mmol) of 3-iodovanillin (68), 88 mg (0.12 mmol) of bis(triphenylphosphine)palladium (II) chloride,³²,³³ 48 mg (0.24 mmol) of copper (I) iodide, 42 mL of triethylamine and 164 mL of acetonitrile was stirred under argon for 2 min followed by addition of 1.39 g (2 mL, 2 mmol) of trimethylsilylacetylene. The solution was heated at reflux for 18 h and concentrated in vacuo. The residue was chromatographed over 100 g of
silica gel (eluted with petroleum ether-ethyl acetate, 10:1) to give 1.23 g (69%) of aldehyde 72 as a light brown solid: mp 65-65.5 °C (after recrystallization from methanol-water); IR (CDCl₃) 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 0.38 (s, 9H, Si(CH₃)₃), 4.07 (s, 3H, ArOCH₃), 7.05 (s, 1H, C₃H), 7.34 (d, J = 1.1 Hz, 1H, C₆H), 7.67 (d, J = 1.1 Hz, 1H, C₄H), 9.99 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ -1.8 (q), 56.1 (q), 104.2 (d), 116.9(d), 119.8 (d), 129.8 (s), 132.1 (s), 146.2 (s), 151.3 (s), 166.2 (s), 191.8 (d); exact mass calcd. for C₁₃H₁₆O₃Si m/z 248.3562, found m/z 248.0868.


Continued elution afforded 0.1 g (8%) of aldehyde 73 as a white solid: mp 78-80 °C; IR (CH₂Cl₂) 1613 cm⁻¹; ¹H NMR (CDCl₃) δ 4.04 (s, 3H, ArOCH₃), 6.87 (d, J = 2.2 Hz, 1H, C₃H), 7.35 (d, J = 1.2 Hz, 1H, C₆H), 7.71 (m, 2H, C₂H and C₄H), 9.98 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ 56.1 (q), 104.3 (d), 107.6 (d), 119.7 (d), 129.0(s), 133.55 (s), 146.3 (s), 146.5 (d), 147.9 (s), 191.6 (d); exact mass calcd. for C₁₀H₈O₃ m/z 176.0573, found m/z 176.0502.

Anal. calcd. for C₁₀H₈O₃: C, 68.18; H, 4.58. Found: C, 68.17; H, 4.55.
7-Methoxy-2-trimethylsilylbenzofuran-5-carboxylic acid (74).
To a solution of 1.19 g (4.8 mmol) of aldehyde 72 in 17 mL of acetone cooled in an ice bath was added 6 mL of Jones reagent (16 mmol of 2.65 M stock solution) over 2 min. The cooling bath was removed, the reaction was stirred for 3.5 h, and the mixture was filtered through a plug of celite which was rinsed with acetone. The acetone was removed in vacuo and the resulting heterogeneous mixture was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to give 1.04 g (83%) of carboxylic acid 74 as a cream colored solid: mp 231-232 °C; IR (CDCl₃) 3100-2800, 1720 cm⁻¹; ¹H NMR (CDCl₃) δ 0.38 (s, 9H, Si(CH₃)₃), 4.08 (s, 3H, ArOCH₃), 7.02 (s, 1H, C₃H), 7.53 (d, J = 1.3 Hz, 1H, C₆H), 8.06 (d, J = 1.3 Hz, 1H, C₄H), 12.00 (br s, 1H, CO₂H); ¹³C NMR (CDCl₃) δ -1.81 (q), 56.1 (q), 107.4 (d), 116.9 (d), 117.3 (d), 124.5 (s), 129.6 (s), 145.2 (s), 150.8 (s), 165.8 (s), 172.6 (s); exact mass calcd. for C₁₃H₁₆O₄Si m/z 264.082, found m/z 264.082.

Anal. calcd. for C₁₃H₁₆O₄Si: C, 59.06; H, 6.11. Found: C, 58.40; H, 5.91.
2-Trimethylsilyl-5-(4',4'-dimethyloxazolin-2'-yl)-7-methoxy-benzofuran (67). A heterogeneous mixture of 1.21 g (4.58 mmol) of carboxylic acid 74, 1.63 g (1 mL, 13.92 mmol) of thionyl chloride and 18 mL of benzene was heated at reflux for 2 h. The resulting solution was concentrated in vacuo and the crude acid chloride was dissolved in 12 mL of dichloromethane. This mixture was slowly added to a solution of 1.0 g (12 mmol) of 2-amino-2-methyl-1-propanol in 10 mL of dichloromethane and stirred at room temperature for 2 h. The heterogeneous mixture was diluted with 50 mL of dichloromethane and washed with 40 mL of 10% aqueous citric acid. The acidic wash was extracted with two 30-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was stirred in 7 mL of thionyl chloride at room temperature for 1 h followed by addition of 60 mL of petroleum ether-ethyl ether (2:1). This mixture was stirred for 1 h and the resulting solid was collected and washed with three 20-mL portions of ice-cold ethyl ether. The solid was dissolved in 60 mL of dichloromethane, washed for 5 min with 100 mL of 10% aqueous sodium hydroxide, and the basic phase was extracted with two 30-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to give 1.17 g (81%) of oxazoline 67 as a tan solid: mp 92-93 °C; IR (CDCl₃) 1640 cm⁻¹; ¹H NMR (CDCl₃) δ 0.34 (s, 9H, Si(CH₃)₃), 1.38 (s, 6H, C(CH₃)₂), 4.03 (s, 3H, ArOCH₃), 4.09 (s, 2H, CH₂O), 6.93 (s, 1H, C₃H), 7.40 (d, J = 1.4 Hz, 1H, C₆H), 7.77 (d, J = 1.4 Hz, 1H, C₄H); ¹³C NMR (CDCl₃) δ -1.8 (q), 28.4 (q), 56.1 (q), 67.5 (s), 79.1 (t), 106.2 (d), 114.3 (d), 116.7 (d), 123.3 (s), 129.4 (s),
145.1 (s), 149.3 (s), 162.4 (s), 165.0 (s); exact mass calcd. for C$_{17}$H$_{23}$NO$_3$Si m/z 317.144, found m/z 317.148.

Anal. calcd. for C$_{17}$H$_{23}$NO$_3$Si: C, 64.32; H, 7.31. Found: C, 64.38; H, 7.36.

2-Trimethylsilyl-5-(4',4'-dimethyl-2'-oxazolinyl)-6-methyl-7-methoxybenzofuran (80) and 2-Trimethylsilyl-5-(4',4'-dimethyl-2'-oxazolinyl)-4-methyl-7-methoxybenzofuran (81). The following experiment (Table 7, entry 4) is an example of the procedure followed in the lithiation studies listed in Table 7: To a solution of 60 mg (0.19 mmol) of 67 and 0.036 mL (0.24 mmol) of tetramethylethylenediamine in 3 mL of dry tetrahydrofuran cooled at -78 °C (dry ice-acetone) under argon was added 0.17 mL (0.23 mmol, 1.3 M in hexanes) of n-butyllithium. The resulting orange solution was stirred at -78 °C for 1.5 h. The mixture was quenched with 0.18 mL (3 mmol) of methyl iodide and allowed to warm to room temperature. The reaction was diluted with 25 mL of water and extracted with two 30-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo to afford 58 mg of an oil. The ratio
of 80 and 81 (Table 7, entry 4) was 4:2 as determined by integration of the C3 protons. Residues from the lithiation experiments (Table 7, entries 1-4) were combined and chromatographed on a silica gel rotary plate (2 mm, eluted with petroleum ether-ethyl acetate, 12:1) to afford 80 as an oil: IR (CDCl3) 1650 cm⁻¹; ¹H NMR (CDCl3) δ 0.34 (s, 9H, Si(CH3)3), 1.39 (s, 6H, C(CH3)2), 2.50 (s, 3H, ArCH3), 4.06 (s, 2H, CH2O), 4.12 (s, 3H, ArOCH3), 6.87 (s, 1H, C3H), 7.63 (s, 1H, C4H); ¹³C NMR (CDCl3) δ -1.9 (q), 13.2 (q), 28.4 (q), 60.2 (q), 67.8 (s), 78.6 (t), 116.2 (d), 116.9 (d), 124.1 (s), 125.5 (s), 127.8 (s), 143.0 (s), 150.6 (s), 163.2 (s), 163.7 (s); exact mass calcd. for C18H25NO3Si m/z 331.160, found m/z 331.160.

Continued elution afforded 81 as a white solid: mp 105-105.5 °C; IR (CDCl3) 1644 cm⁻¹; ¹H NMR (CDCl3) δ 0.35 (s, 9H, Si(CH3)3), 1.42 (s, 6H, C(CH3)2), 2.62 (s, 3H, ArCH3), 4.10 (s, 3H, ArOCH3), 4.18 (s, 2H, CH2O), 7.00 (s, 1H, C3H), 7.29 (s, 1H, C6H); ¹³C NMR (CDCl3) δ -1.7 (q), 16.7 (q), 28.5 (q), 56.1 (q), 67.8 (s), 78.6 (t), 108.1 (d), 115.9 (d), 121.7 (s), 124.7 (s), 130.6 (s), 143.0 (s), 148.1 (s), 163.1 (s), 164.1 (s); exact mass calcd. for C18H25NO3Si m/z 331.160, found m/z 331.1604.

5-N,N-Diethyl-7-methoxy-2-trimethylsilylbenzofuran-5-carboxamide (82). A mixture of 0.2 g (0.76 mmol) of 74, 1.63 g (1 mL, 13 mmol) of thionyl chloride and 10 mL of benzene was heated at reflux for 2 h. The resulting solution was concentrated in vacuo and the crude acid chloride was dissolved in 3 mL of dichloromethane. This mixture was slowly added to a solution of 0.29 g (0.41 mL, 4 mmol) of diethylamine in 3 mL of dichloromethane and stirred at room temperature for 2 h. The heterogeneous mixture was diluted with 20 mL of dichloromethane and washed with 20 mL of 10% aqueous hydrochloric acid. The acidic wash was extracted with two 25-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with hexane-ethyl acetate, 1:1) to afford 233 mg of 82 as an oil which solidified on standing: mp 90-91 °C; IR (CDCl₃) 1612 cm⁻¹; ¹H NMR (CDCl₃) δ 0.38 (s, 9H, Si(CH₃)₃), 1.20 (br s, 6H, (CH₃)₂), 3.42 (br s, 4H, (CH₂)₂), 3.98 (s, 3H, ArOCH₃), 6.80 (d, J = 1.2 Hz, 1H, C₃H), 6.94 (s, 1H, C₃H), 7.16 (d, J = 1.2 Hz, 1H, C₄H); ¹³C NMR (CDCl₃) δ 13.5, 39.9, 56.1 (q), 105.4 (d), 111.3 (d), 116.5 (d), 129.4 (s), 132.4 (s), 145.3 (s), 147.8 (s), 165.0 (s), 171.52 (s); exact mass calcd. for C₁₇H₂₅N₁O₃Si m/z 319.1603, found m/z 319.1602. The multiplicities of the ¹³C signals at 13.5, 39.9, and 56.1 were not determined because of broadening.

Anal. calcd. C₁₇H₂₅NO₃Si: C, 63.91; H, 5.70. Found: C, 63.96; H, 5.55.
1-(Benzyloxy)-13-hydroxy-11-methoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (77) and 8-(Benzyloxy)-3,4-dihydro-4,4-dimethoxy-3-[7-methoxy-2-(trimethylsilyl)-4-benzofuranyl]-1(2H)naphthalenone (76). To a solution of 4.5 g (14.2 mmol) of oxazoline 67 and 2.7 mL (18 mmol) of tetramethylethylenediamine in 135 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) was slowly added 11.36 mL (17.04 mmol, 1.5 M in hexanes) of n-butyllithium via a syringe and the solution was stirred for 1.5 h. In a separate flask, a solution of MAD was prepared by dissolving 4.26 g (19.35 mmol) 2,6-di-butyl-4-methylphenol in 150 mL of toluene and slowly adding 4.8 mL (9.69 mmol, 2 M in hexane) of trimethylaluminum at room temperature followed by stirring for 30 min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 1.50 g (4.83 mmol) of naphthoquinone monoketal 54 was added in a solution of 50 mL of toluene. The resulting dark solution was stirred for 15 min followed by addition of the aryl lithium via a cannula. The color of the solution slowly turned light orange during the addition. Upon completion of this addition the reaction was stirred for 15 min followed by addition of 30 mL of water. The cooling bath was removed and the reaction
was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of celite which was rinsed with dichloromethane. The filtrate was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 300 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1, 4:1 and 2:1) to afford 1.48 g of 75 as an off-white foam. Attempts to purify 75 for full characterization caused its decomposition. Therefore, this conjugate adduct was fully characterized after the next step.

Continued elution afforded 0.62 g (21%) of 76 as a light green foam. A sample of this material was recrystallized from petroleum ether to afford a tan solid: mp 163-165 °C; IR (CH$_2$Cl$_2$) 1685 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 0.27 (s, 9H, Si(CH$_3$)$_3$), 1.28 (s, 3H, CCH$_3$), 1.33 (s, 3H, CCH$_3$), 2.77 (s, 3H, OCH$_3$), 2.99 (s, 3H, OCH$_3$), 3.02 (dd, $J = 18$, 8 Hz, 1H, CH$_2$), 3.29 (dd, $J = 18$, 8 Hz, 1H, CH$_2$), 4.01 (s, 3H, ArOCH$_3$), 4.04 (m, 2H, CH$_2$OPh), 4.88 (t, $J = 8.5$ Hz, 1H, CH), 5.25 (s, 2H, OCH$_2$Ph), 6.79 (s, 1H, C$_3$H-furan), 7.01 (s, 1H, ArH), 7.09 (d, $J = 8$ Hz, 1H, C$_7$H), 7.5 (m, 7H, ArH); $^{13}$C NMR (acetone-d$_6$) $\delta$ -1.74 (q), 28.3 (q), 28.4 (q), 43.9 (d), 44.7 (t), 49.7 (q), 50.3 (q), 56.3 (q), 69.0 (s), 71.1 (t), 79.1 (t), 100.8 (s), 108.8 (d), 115.4 (d), 119.2 (d), 119.7 (d), 124.3 (s), 126.0 (s), 127.3 (s), 127.8 (d), 128.4 (d), 129.2 (d), 130.0 (s), 133.5 (d), 138.2 (s), 145.1 (s), 145.6 (s), 149.6 (s), 158.08 (s), 163.1 (s), 163.5 (s), 195.4 (s); exact mass calcd. for C$_{36}$H$_{41}$NO$_7$Si $m/z$ 627.2652, found $m/z$ 627.2641.

Anal. calcd. C$_{36}$H$_{41}$NO$_7$Si: C, 68.87; H, 6.58. Found: C, 68.90; H, 6.77.

A solution of 1.55 g (2.47 mmol) of conjugate adduct 75 in 45 mL of tetrahydrofuran and 6 mL 5 N aqueous HCl was heated to reflux for 3 h.
reaction was diluted with 200 mL of dichloromethane and washed with 200 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 1.26 g (51%) of 77 as an orange solid: mp 222-226 °C (dec.); IR (CH₂Cl₂) 3410, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ 0.42 (s, 9H, Si(CH₃)₃), 4.34 (s, 3H, ArOCH₃), 5.30 (s, 2H, CH₂O), 7.00 (d, J = 7.8 Hz, 1H, C₂H), 7.08 (s, 1H, C₈H), 7.5 (m, 6H, ArH), 8.22 (d, J = 8.5 Hz, 1H, C₄H), 8.43 (s, 1H, C₁₂H), 8.51 (s, 1H, C₇H), 9.20 (s, 1H, ArOH); ¹³C NMR(CDCl₃) δ -1.9 (q), 60.8 (q), 71.9 (t), 107.1 (d), 107.2 (d), 115.1 (s), 115.7 (s), 116.5 (d), 116.6 (d), 118.6 (s), 119.1 (d), 122.0 (s), 126.1 (s), 126.6 (d), 128.0 (d), 128.96 (d), 129.1 (d), 131.0 (s), 135.1 (s), 139.0 (s), 142.5 (s), 150.1 (s), 153.6 (s), 154.8 (s), 161.9 (s), 167.4 (s); exact mass calcd. for C₃₀H₂₆O₆Si m/z 510.150, found m/z 510.152.

![Structural formula of 78](image)

1-(Benzyloxy)-13-hydroxy-8-methoxy-10-(trimethylsilyl)-6H-furo[2,3-f]naphtho[1,2-c][2]benzopyran-6-one (78). A solution of 0.62 g (0.99 mmol) of 76, 45 mL of tetrahydrofuran, and 6 mL 5 N aqueous HCl was heated to reflux for 3 h. The reaction was diluted with 200 mL of
dichloromethane and washed with 200 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 0.51 g (98%) of 78 as an orange solid: 240-244 °C (dec.); IR (CH₂Cl₂) 3300, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ 0.45 (s, 9H, Si(CH₃)₃), 4.11 (s, 3H, ArOCH₃), 5.24 (s, 2H, CH₂O), 6.94 (d, J = 7.8 Hz, 1H, C₂H), 7.46 (m, 6H, ArH), 7.6 (s, 1H, C₁₂H), 7.68 (s, 1H, C₁₁H), 7.78 (s, 1H, C₇H), 8.13 (d, J = 8.6 Hz, 1H, C₄H), 9.25 (s, 1H, ArOH); ¹³C NMR (CDCl₃) δ -1.7 (q), 56.3 (q), 72.0 (t), 104.3 (d), 106.3 (d), 107.4 (d), 114.9 (s), 115.9 (s), 116.3 (d), 116.7 (d), 118.3 (s), 123.9 (s), 125.0 (s), 126.4 (s), 127.0 (d), 128.0 (d), 129.1 (d), 129.1 (d), 134.9 (s), 139.6 (s), 146.5 (s), 150.7 (s), 152.1 (s), 155.0 (s), 161.8 (s), 166.5 (s); exact mass calcd. for C₃₀H₂₆O₆Si m/z 510.149, found m/z 510.150.

1-(Benzyloxy)-11,13-dimethoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (88). To a solution of 100 mg (0.196 mmol) of 77 in 25 mL of dichloromethane was added 235 mg (1.7 mmol) of potassium carbonate and 0.284 mg (0.214 mL, 2.25 mmol) of
dimethyl sulfate. The mixture was heated to reflux under argon for six days. The reaction was diluted with 100 mL of dichloromethane, filtered, and the residual potassium carbonate was rinsed with 50 mL of dichloromethane. The filtrate was washed with 50 mL of 10% aqueous citric acid, and the acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 100 mg (97%) of 87 as a yellow solid: mp 187-188.5 °C; IR (CH₂Cl₂) 1712 cm⁻¹; ¹H NMR (CDCl₃) δ 0.43 (s, 9H, Si(CH₃)₃), 4.04 (s, 3H, ArOCH₃), 4.34 (s, 3H, ArOCH₃), 5.20 (s, 2H, OCH₂), 7.01 (d, 1H, ArH), 7.08 (s, 1H, ArH), 7.40 (m, 4H, ArH), 7.61 (m, 2H, ArH), 8.20 (d, J = 8.5 Hz, 1H, C₇H), 8.48 (m, 2H, C₄H and C₁₂H); ¹³C NMR (CDCl₃) δ -1.9 (q), 56.4 (q), 60.9 (q), 71.4 (t), 103.2 (d), 110.2 (d), 114.1 (s), 115.4 (d), 116.6 (d), 118.0 (s), 118.5 (s), 119.4 (d), 122.3 (s), 126.9 (s), 126.9 (d), 127.1 (d), 127.6 (d), 128.4 (d), 130.8 (s), 137.4 (s), 140.1 (s), 142.0 (s), 153.1 (s), 153.7 (s), 155.6 (s), 161.8 (s), 167.3 (s); exact mass calcd. for C₃₁H₂₈O₆Si m/z 524.165, found m/z 524.165.

Anal. calcd. for C₃₁H₂₈O₆Si: C, 70.97; H, 5.38. Found: C, 70.81; H, 5.42.
1-Hydroxy-11,13-dimethoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (89). To a solution of 200 mg (0.381 mmol) of 88 in 120 mL of ethanol-dichloromethane (6:1) was added 50 mg of 5% palladium on carbon. The solution was hydrogenated at 50 psi for 26 h using a Parr hydrogenation apparatus. The mixture was dissolved by adding dichloromethane and filtered through a plug of celite which was rinsed with dichloromethane. The filtrate was concentrated in vacuo, and the residue was dissolved in chloroform and precipitated with petroleum ether to afford 149 mg (90%) of 89 as a white solid: mp 228-230 °C; IR (CH₂Cl₂) 1712 cm⁻¹; ¹H NMR (CDCl₃) δ 0.44 (s, 9H, Si(CH₃)₃), 4.16 (s, 3H, ArOCH₃), 4.34 (s, 3H, ArOCH₃), 6.98 (dd, J = 7.7, 0.8 Hz, 1H, C₂H), 7.08 (s, 1H, C₆H), 7.44 (t, J = 8 Hz, 1H, C₃H), 8.06 (dd, J = 8.4, 0.8 Hz, 1H, C₄H), 8.46 (s, 1H, C₁₂H), 8.51 (s, 1H, C₇H), 9.34 (s, 1H, ArOH); ¹³C NMR (CDCl₃) δ -1.9 (q), 56.1 (q), 60.9 (q), 100.9 (d), 112.5 (d), 113.4 (s), 113.5 (d), 114.7 (s), 116.6 (d), 118.3 (s), 119.3 (d), 122.0 (s), 126.3 (s), 128.4 (d), 130.9 (s), 141.0 (s), 141.8 (s), 152.0 (s), 153.5 (s), 154.1 (s), 161.6 (s), 167.4 (s); exact mass calcd. for C₂₄H₂₂O₆Si m/z 434.118, found m/z 434.119.
1-Hydroxy-11,13-dimethoxy-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (11). To a solution of 307 mg (0.71 mmol) of 89, and 0.041 mL (0.71 mmol) acetic acid in 80 mL of dichloromethane-tetrahydrofuran (3:1) was added 0.71 mL (1.42 mmol) 1M tetra-n-butylammonium fluoride in tetrahydrofuran. The mixture was stirred for 2 h and diluted with 150 mL of dichloromethane. The mixture was washed with two 100-mL portions of water and the aqueous wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford an off-white solid. This material was recrystallized from nitromethane to afford 226 mg (88%) of 11 as a rosy white solid: mp 249-252 °C (dec.); IR (CH₂Cl₂) 3685, 1716 cm⁻¹; UV_max CH₂Cl₂ (log ε) 258 (4.75), 282 (4.15), 316 (4.10), 366 (4.15), 384 (4.12); 1H NMR (CDCl₃) δ 4.18 (s, 3H, ArOCH₃), 4.34 (s, 3H, ArOCH₃), 6.96 (d, J = 2.2 Hz, 1H, C₈H), 7.01 (dd, J = 7.7, 1.0 Hz, 1H, C₂H), 7.49 (t, J = 7.9 Hz, 1H, C₃H), 7.81 (d, J = 2.2 Hz, 1H, C₉H), 8.08 (dd, J = 8.4, 1.0 Hz, 1H, C₄H), 8.44 (s, 1H, C₁₂H), 8.57 (s, 1H, C₇H), 9.35 (s, 1H, ArOH); 13C NMR (DMSO-d₆ at 335 K) δ 56.1 (q), 60.9 (q), 100.7 (d), 107.4 (d), 112.1 (d), 112.2 (d), 112.9 (s), 114.4 (s), 118.0 (s), 118.8 (d), 121.2 (s), 125.6 (s), 128.4 (d), 130.2 (s),
139.6 (s), 141.7 (s), 148.8 (d), 149.9 (s), 151.8 (s), 153.8 (s), 160.0 (s); exact mass calcd. for C$_{21}$H$_{14}$O$_6$ m/z 362.079, found m/z 362.083.

2-Hydroxy-3-iodo-5-methoxybenzaldehyde (91) and 2,2'-Dihydroxy-5,5'-dimethoxybiphenyl-3,3'-dicarboxaldehyde (93).

**Procedure A:** To a solution of 0.2 g (1.32 mmol) of 2-hydroxy-5-methoxybenzaldehyde (92) in 5 mL of dichloromethane at -15 °C was added 0.6 g (1.58 mmol) of tetraethylammonium diacetoxyiodate. After stirring for 12 h, an additional 0.3 g (0.78 mmol) of tetraethylammonium diacetoxyiodate was added. The reaction was stirred for an additional 10 h and concentrated in vacuo. To the residue was added 30 mL of an acidic hydrosulfite solution (3 g sodium hydrosulfite and 2.5 mL of concentrated hydrochloric acid in 30 mL of water). This mixture was extracted with two 200-mL portions ethyl acetate. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. The residue was loaded onto 2 g of silica gel and chromatographed over 20 g of silica gel (petroleum ether:ethyl acetate, 10:1) to afford 0.2 g (54%) of iodide 91 as a yellow solid: mp 102-104 °C; IR (CH$_2$Cl$_2$) 1667, 1654 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 3.81 (s, 3H, ArOCH$_3$), 7.05 (d, $J = 3$ Hz, 1H, ArH), 7.61 (d, $J = 3$ Hz, 1H, ArH), 9.72 (s, 1H, CHO), 11.32 (s,
1H, ArOH); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.2 (q), 85.6 (s), 116.9 (d), 119.5 (s), 133.4 (d), 153.2 (s), 154.9 (s), 195.5 (d); exact mass calcd. for C$_8$H$_7$IO$_3$ $m/z$ 277.941, found $m/z$ 277.943.

Anal. calcd. for C$_8$H$_7$IO$_3$: C, 34.54; H, 2.54. Found: C, 34.68; H, 2.44.

Continued elution afforded 0.055 g (14%) of 93 as a light orange solid: mp 217-218 °C; IR (CH$_2$Cl$_2$) 1658, 1608 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.84 (s, 6H, ArOCH$_3$), 7.08 (d, $J = 3$ Hz, 2H, ArH), 7.26 (d, $J = 3$ Hz, 2H, ArH), 9.91 (s, 2H, CHO), 10.99 (s, 2H, ArOH); $^{13}$C NMR (CDCl$_3$) $\delta$ 56.0 (q), 115.9 (d), 120.5 (s), 126.0 (s), 126.6 (d), 152.3 (s), 153.5 (s), 196.1 (d); exact mass calcd. for C$_{16}$H$_{14}$O$_6$ $m/z$ 302.079, found $m/z$ 302.078.

Anal. calcd. for C$_{16}$H$_{14}$O$_6$: C, 63.56; H, 4.67. Found: C, 63.59; H, 4.66.

**Procedure B:** To a mixture of 2 g (13.16 mmol) of 92, 68 mL of ethanol-water (1:1), and 1 mL of glacial acetic acid was added in one portion 16.2 g (50.9 mmol) of mercuric (II) acetate. The reaction was heated at reflux for 1 h and the hot mixture was filtered into 200 mL of 3% aqueous sodium hydroxide. The resulting heterogeneous mixture was filtered and the filtrate was acidified to a pH of 1 with 10% aqueous hydrochloric acid. The yellow precipitate was collected, washed with water, air dried for 3 h and then dried under high vacuum (0.1 mmHg) for 12 h. The yellow solid was stirred at room temperature in a solution of 5.5 g (22 mmol) of iodine in 100 mL of chloroform for 4 days. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo to afford 1.13 g (31%) of iodide 91 as orange solid.
2-Acetyl-3-bromo-5-methoxybenzaldehyde (97). A mixture of 1 g (4.33 mmol) of 96 in 10 mL of pyridine and 10 mL of acetic anhydride was stirred for 2.5 h. The mixture was then diluted with 500 mL of dichloromethane and washed with three 250 mL portions of 10% aqueous hydrochloric acid. The organic layer was dried (MgSO₄) and concentrated in vacuo to afford an orange oil which solidified after being placed under high vacuum (0.1 mmHg) for 12 h to afford 1.1 g (93%) of 97. This material was recrystallized from petroleum ether-dichloromethane to afford rosy needles of 97: mp 120-121°C; IR (CDCl₃) 1770, 1669 cm⁻¹;¹H NMR (CDCl₃) δ 2.43 (s, 3H, CH₃C=O), 3.84 (s, 3H, ArOCH₃), 7.30 (d, J = 3 Hz, 1H, ArH), 7.38 (d, J = 3 Hz, 1H, ArH), 9.97 (s, 1H, CHO);¹³C NMR (CDCl₃) δ 20.4 (q), 56.1 (q), 113.3 (d), 118.5 (d), 124.9 (d), 129.9 (s), 143.3 (s), 157.9 (s), 168.7 (s), 187.5 (d); exact mass calcd. for C₁₀H₉BrO₄ m/z 271.9684, found m/z 271.9691.

Anal. calcd. for C₁₀H₉BrO₄: C, 44.12; H, 3.34. Found: C, 44.06; H, 3.35.
7-Formyl-5-methoxy-2-(trimethylsilyl)benzofuran (95). A solution of 5 g (17.98 mmol) of 91, 200 mg (0.253 mmol) of bis-(triphenylphosphine)palladium (II) chloride, 108 mg (0.57 mmol) of copper (I) iodide, 95 mL of triethylamine and 365 mL of acetonitrile was stirred under argon for 2 min followed by addition of 3.47 g (5 mL; 39 mmol) of trimethylsilylacetylene. The solution was heated to reflux for 18 h and concentrated in vacuo. The residue was chromatographed over 120 g of silica gel (eluted with petroleum ether-ethyl acetate, 20:1) to afford 3.16 g (71%) of the benzofuran 95 as a brown oil which solidified on standing. A sample of this solid was recrystallized from methanol-water (charcoal) to afford a white solid: mp 46-47 °C; IR (CDCl₃) 1689 cm⁻¹; ¹H NMR (CDCl₃) δ 0.37 (s, 9H, Si(CH₃)₃), 3.88 (s, 3H, ArOCH₃), 6.95 (s, 1H, C₃H), 7.32 (d, J = 2.6 Hz, 1H, C₄H), 7.37 (d, J = 2.6 Hz, 1H, C₆H), 10.58 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ -1.9 (q), 56.2 (q), 109.6 (d), 111.9 (d), 115.5 (d), 120.5 (s), 130.8 (s), 153.7 (s), 155.7 (s), 166.5 (s), 188.0 (d); exact mass calcd. for C₁₃H₁₆O₃Si m/z 248.0869, found 248.0893.

5-Methoxy-2-trimethylsilylbenzofuran-7-carboxylic acid (98).

To a solution of 3.16 g (12.74 mmol) of 95 in 40 mL of acetone at 0 °C was added 16 mL of Jones reagent (42 mmol, 2.65 M stock solution) dropwise. The ice bath was removed, and the reaction was stirred for 5 h. The reaction was filtered through a plug of celite, which was rinsed with acetone. The filtrate was concentrated in vacuo and the residue was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to give 2.46 g (73%) of carboxylic acid 98 as a white solid: mp 169-170 °C; IR (CH₂Cl₂) 3000, 1691 cm⁻¹; ¹H NMR (CDCl₃) δ 0.40 (s, 9H, Si(CH₃)₃), 3.89 (s, 3H, ArOCH₃), 6.95 (s, 1H, C₃H), 7.31 (d, J = 2.6 Hz, 1H, C₄H), 7.63 (d, J = 2.6 Hz, 1H, C₆H), 11.30 (s, 1H, CO₂H); ¹³C NMR (CDCl₃) δ -1.8 (q), 56.2 (q), 111.0 (d), 113.9 (s), 114.3 (d), 115.7 (d), 130.8 (s), 152.1 (s), 155.2 (s), 166.3 (s), 169.7 (s); exact mass calcd. for C₁₃H₁₆O₄Si m/z 264.082, found m/z 264.080.

Anal. calcd. for C₁₃H₁₆O₄Si: C, 59.06; H, 6.11. Found: C, 58.87; H, 6.05.
2-Trimethylsilyl-7-(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzofuran (99). A heterogeneous mixture of 1.00 g (3.79 mmol) of carboxylic acid 98, 2.66 g (1.67 mL, 23 mmol) of thionyl chloride and 30 mL of benzene was heated to reflux for 2 h. The reaction was concentrated in vacuo and the crude acid chloride was dissolved in 15 mL of dichloromethane. This mixture was slowly added to a solution of 1.0 g (12 mmol) of 2-amino-2-methyl-1-propanol in 10 mL of dichloromethane. The reaction was stirred at room temperature for 2.5 h. The resulting heterogeneous mixture was diluted with 100 mL of dichloromethane and washed with 75 mL of 10% aqueous citric acid. The acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. The residue was stirred in 15 mL of thionyl chloride at room temperature for 1 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in 100 mL of dichloromethane. This was washed for 5 min with 100 mL of 10% aqueous sodium hydroxide. The basic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and
concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate, 7:1) to afford 0.94 g (78%) of oxazoline 99 as tan solid: mp 69-70 °C; IR (CDCl3) 1650, 1588 cm⁻¹; ¹H NMR (CDCl3) δ 0.36 (s, 9H, Si(CH3)3), 1.42 (s, 6H, C(CH3)2), 3.85 (s, 3H, ArOCH3), 4.18 (s, 2H, CH2O), 6.89 (s, 1H, C3H), 7.14 (d, J = 2.6 Hz, 1H, C4H), 7.45 (d, J = 2.6 Hz, 1H, C6H); ¹³C NMR (CDCl3) δ -1.8 (q), 28.3 (q), 56.1 (q), 67.3 (s), 79.1 (t), 107.7 (d), 112.7 (d), 112.7 (s), 115.7 (d), 130.3 (s), 150.8 (s), 155.1 (s), 160.2 (s), 165.4 (s); exact mass calcd. for C17H23NO3Si m/z 317.144, found m/z 317.145.

Anal. calcd. for C17H23NO3Si: C, 64.32; H, 7.31. Found: C, 64.54; H, 7.39.

6-Methyl-2-Trimethylsilyl-7-(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzofuran (100) and 2-[6-sec-Butyl-6,7-dihydro-5-methoxy-7-methyl-2-(trimethylsilyl)-7-benzofuranyl]-4,4-dimethyl-2-oxazoline (101). To a solution of 52 mg (0.164 mmol) of 99 and 27 mg (0.036 mL, 0.24 mmol) of tetramethylethylenediamine in 3 mL of dry tetrahydrofuran at -78 °C under argon was added 0.29 mL (0.197 mmol, 0.68
M in cyclohexane) of s-butyllithium. The resulting green-yellow solution was stirred for 1.5 h and quenched with 0.185 mL (3 mmol) of methyl iodide. The reaction was stirred for 3 minutes at -78 °C, warmed to room temperature, and diluted with 20 mL of water. The aqueous phase was extracted with two 30-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford 52 mg of an oil consisting of a 1:1 mixture of 100 and 101 (by integration of C₃H). The compounds were separated by preparatory TLC (eluted with petroleum ether-ethyl acetate, 10:1) to afford 100 and 101 as oils. Data for 100: ¹H NMR (CDCl₃) δ 0.31 (s, 9H, Si(CH₃)₃), 1.47 (s, 6H, C(CH₃)₂), 2.36 (s, 3H, ArCH₃), 3.85 (s, 3H, ArOCH₃), 4.16 (s, 2H, CH₂O), 6.85 (s, 1H, C₃H), 7.01 (s, 1H, C₄H). Data for 101: ¹H NMR (CDCl₃) δ 0.22 (s, 9H, Si(CH₃)₃), 0.77 (d, J = 6.7 Hz, 3H, CHCH₃), 0.85 (t, J = 9 Hz, 3H, CH₂CH₃), 1.30 (m, 3H, CH and CH₂), 1.32 (s, 3H, CCH₃), 1.34 (s, 3H, CCH₃), 1.45 (s, 3H, CH₃), 2.41 (d, J = 3 Hz, 1H, CH), 3.58 (s, 3H, OCH₃), 3.95 (ab q, J = 9 Hz, 2H, CH₂O), 5.32 (s, 1H, CH), 6.38 (s, 1H, ArH). Compounds 100 and 101 were characterized only by ¹H NMR.

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\text{N,N-Diethyl-5-methoxy-2-trimethylsilylbenzofuran-7-carboxamide (102). A heterogeneous mixture of 3.93 g (14.89 mmol) of}
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![TMS](image-url)
carboxylic acid 98, 14.67 g (9 mL, 124 mmol) of thionyl chloride and 130 mL of benzene was heated to reflux for 2 h. The reaction was concentrated in vacuo and the crude acid chloride was dissolved in 60 mL of dichloromethane. The mixture was added to a solution of 4.13 g (5.9 mL, 56 mmol) of diethylamine in 40 mL of dichloromethane. The mixture was stirred for 2 h, diluted with 200 mL of dichloromethane, and washed with 100 mL of 10% aqueous hydrochloric acid. The acidic wash was extracted with 50 mL of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford a dark orange oil. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate, 4:1) to yield 4.4 g (93%) of 102 as an orange oil: IR (CDCl₃) 1623 cm⁻¹; ¹H NMR (CDCl₃) δ 0.31 (s, 9H, Si(CH₃)₃), 1.06 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.30 (t, J = 7.1, 3H, CH₂CH₃), 3.21 (q, J = 7.1 Hz, 2H, CH₂CH₃), 3.65 (q, J = 7.1, 2H, CH₂CH₃), 3.83 (s, 3H, ArOCH₃), 6.88 (s, 1H, C₃H), 6.90 (d, J = 2.5 Hz, 1H, C₄H), 7.03 (d, J = 2.5 Hz, 1H, C₆H); ¹³C NMR (CDCl₃) δ 1.9 (q), 12.8 (q), 14.1 (q), 39.0 (t), 42.9 (t), 56.1 (q), 104.8 (d), 111.3 (d), 116.0 (d), 121.6 (s), 129.2 (s), 148.5 (s), 155.7 (s), 165.2 (s), 167.0 (s); exact mass calcd. for C₁₇H₂₅NO₃Si m/z 319.161, found m/z 319.161.
N,N-Diethyl-6-methyl-5-methoxy-2-trimethylsilylbenzofuran-7-carboxamide (104). To a solution of 50 mg (0.157 mmol) of 102, 0.030 mL (0.197 mmol) of tetramethylethylenediamine in 3 mL of dry tetrahydrofuran at -78 °C (dry ice-acetone) under argon was added 0.276 mL (0.188 mmol, 0.68 M in cyclohexane) of s-butyl lithium. The resulting red-orange solution was stirred for 1.5 h and was quenched with 0.185 mL (3 mmol) of methyl iodide. The reaction was stirred for 3 minutes at -78 °C and allowed to warm to room temperature. This mixture was diluted with 20 mL of water and extracted with two 30-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 43 mg of an oil consisting of a 2:1 mixture of 104 and 102 (based on the integration of C3H). For the purpose of characterization, the oil was subjected to preparative TLC over silica gel (eluted with hexane-ethyl acetate, 10:1) to afford 104 as an oil: IR (neat) 1632 cm⁻¹, ¹H NMR (CDCl₃) δ 0.26 (s, 9H, Si(CH₃)₃), 0.94 (t, J = 7 Hz, 3H, CH₂CH₃), 1.29 (t, J = 7 Hz, 3H, CH₂CH₃), 2.21 (s, 3H, ArCH₃), 3.08 (q, J = 7 Hz, 2H, CH₂CH₃), 3.65 (m, 2H, CH₂CH₃), 3.81 (s, 3H, ArOCH₃), 6.83 (s, 1H, ArH), 6.91 (s, 1H, ArH); ¹³C NMR (CDCl₃) δ -2.0 (q), 12.7 (q), 12.9 (q), 13.7 (q), 38.6 (t), 42.5 (t), 55.8 (q), 101.2 (d), 115.8 (d), 120.8 (s), 121.4 (s), 126.0 (s), 148.5 (s), 154.1 (s), 163.5 (s), 166.7 (s);
exact mass calcd. for C₁₈H₂₇NO₃Si m/z 333.176, found 333.175. The presence of 104 in the product mixture was based on appearance of the C(3)-H as a singlet at δ 6.83 ppm.

N-Methyl-5-methoxy-2-trimethylsilylbenzofuran-7-carboxamide (103). A mixture of 0.2 g (0.76 mmol) of 98, 3.26 g (2 mL, 27 mmol) of thionyl chloride and 20 mL of benzene was heated to reflux for 2 h. The reaction was concentrated in vacuo and the crude acid chloride was dissolved in 5 mL of tetrahydrofuran. This mixture was slowly added to a solution of 5 mL (66 mmol) of 40% (w/w) aqueous methylamine. The reaction was stirred at room temperature for 2 h and the resulting heterogeneous mixture was partitioned between 20 mL of dichloromethane and 20 mL of 10% aqueous hydrochloric acid. The organic layer was washed with 20 mL of 10% aqueous sodium hydroxide, dried (MgSO₄) and concentrate in vacuo. The residue was chromatographed over 4 g of silica gel (eluted with petroleum ether-ethyl acetate, 4:1) to afford 75 mg (44%) of 103 as a transparent oil: IR (neat) 3444, 1656 cm⁻¹; ¹H NMR (CDCl₃) δ 0.37 (s, 9H, Si(CH₃)₃), 3.10 (s, 1.5H, NCH₃), 3.12 (s, 1.5H, NCH₃), 3.86 (s, 3H, ArOCH₃),
6.95 (s, 1H, C₃H), 7.15 (d, J = 2.7 Hz, 1H, C₄H), 7.56 (br s, 1H, NH), 7.71 (d, J = 2.7 Hz, 1H, C₆H); ¹³C NMR (CDCl₃) δ -1.8 (q), 26.7 (q), 56.2 (q), 108.6 (d), 113.1 (d), 116.5 (d), 117.5 (s), 129.5 (s), 150.0 (s), 164.6 (s), 164.6 (s) (one carbon was not observed); exact mass calcd. for C₁₄H₁₉NO₃Si m/z 277.1134, found m/z 277.1128.

8-(Benzyloxy)-7-hydroxy-5-methoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho[1,2c][2]benzopyran-13-one (107). To a solution of 3.08 g (9.66 mmol) of amide 102, 1.8 mL (12 mmol) of tetramethyl-ethylenediamine in 130 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) was slowly added 10.54 mL (11.59 mmol, 1.1 M in hexanes) of s-butyllithium via a syringe, and the solution was stirred for 2 h. In a separate flask, a solution of MAD was prepared by dissolving 2.84 g (12.90 mmol) 2,6-di-t-butyl-4-methylphenol in 100 mL of dry toluene and slowly adding 3.22 mL (6.45 mmol, 2 M in hexane) of trimethylaluminum at room temperature under argon followed by stirring for 30 min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 1.0 g (3.22 mmol) of naphthoquinone monoketal 54
15 min followed by addition of the aryl lithium via a cannula. The color of the solution slowly turned light orange during the addition. Upon completion of the addition, the reaction was stirred for 15 min followed by addition of 30 mL of water. The cooling bath was removed, and the reaction was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of Celite which was rinsed with dichloromethane. The filtrate was dried (Na₂SO₄), concentrated in vacuo and the residue was chromatographed over 150 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1, 4:1 and 2:1) to afford 1.3 g (64%) of 106 as an brown foam. Attempts to purify conjugate adduct 106 resulted in its decomposition. Therefore, characterization was performed after the next reaction.

A solution of 1.3 g (2.06 mmol) of 106 in 45 mL of tetrahydrofuran and 9 mL of aqueous 5 N HCl was heated at reflux for 24 h under argon. The reaction was diluted with 150 mL of dichloromethane and washed with 100 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane, the combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 1.16 g of an orange solid. This material was recrystallized from chloroform-hexanes to afford 0.9 g (86%) of pentacycle 107 as a yellow solid: mp 206-209 °C; IR (CDCl₃) 1721 cm⁻¹; ¹H NMR (CDCl₃) δ 0.44 (s, 9H, Si(CH₃)₃), 4.08 (s, 3H, ArOCH₃), 5.32 (s, 2H, CH₂O), 7.00 (m, 2H, CgH and C₃H), 7.46 (m, 7H, ArH), 8.22 (d, J = 11.7, 1H, C₁₁H), 8.52 (s, 1H, C₆H), 9.17 (s, 1H, ArOH); ¹³C NMR (CDCl₃) δ -1.7 (q), 56.5 (q), 71.9 (t), 107.3 (d), 107.9 (d), 108.2 (s), 109.4 (d), 115.1 (s), 115.4 (s), 115.5 (d), 116.7 (d), 122.1 (s), 125.9 (s), 126.5 (d), 128.0 (d), 128.9 (d), 129.1 (d), 129.5 (s), 135.1 (s), 139.9 (s) 149.7 (s), 152.0 (s), 153.5 (s),
154.7 (s), 157.9 (s), 167.7 (s); exact mass calcd. for C$_{30}$H$_{26}$O$_{6}$Si $m/z$ 510.150, found $m/z$ 510.150.

8-(Benzyloxy)-5,7-dimethoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho[1,2c][2]benzopyran-13-one (108). A mixture of 0.5 g (0.98 mmol) of 107, 1.17 g (0.88 mL, 9.3 mmol) of dimethyl sulfate, 1.28 g (9.3 mmol) of potassium carbonate, and 16 mL of dichloromethane was heated at reflux for five days. The reaction mixture was filtered and the potassium carbonate was rinsed with dichloromethane. The filtrate was diluted with 100 mL of dichloromethane, washed with 50 mL of 10% aqueous citric acid and the acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo to afford a yellow solid. This material was recrystallized from chloroform-petroleum ether to afford 0.41 g (88%) of 108 as a yellow solid: mp 227-228 °C; IR (CDCl$_3$) 1722 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 0.45 (s, 9H, Si(CH$_3$)$_3$), 3.99 (s, 3H, ArOCH$_3$), 4.08 (s, 3H, ArOCH$_3$), 5.20 (s, 2H, CH$_2$O), 6.98 (s, 1H, C$_3$H), 7.02 (d, $J = 7.4$ Hz, 1H, C$_9$H), 7.50 (m, 7H, ArH), 8.57 (d, $J =...
8.5 Hz, 1H, C_{11}H), 8.51 (s, 1H, C_{6}H); $^{13}$C NMR (CDCl$_3$) $\delta$ - 1.7 (q), 56.4 (q), 56.8 (q), 71.5 (t), 104.2 (d), 108.1 (s), 109.7 (d), 110.4 (d), 113.8 (s), 115.4 (d), 115.6 (d), 118.1 (s), 122.3 (s), 126.7 (s), 126.9 (d), 127.0 (d), 127.5 (d), 128.3 (d), 129.2 (s), 137.5 (s), 141.1 (s), 152.0 (s), 152.6 (s), 153.2 (s), 155.5 (s), 157.9 (s), 167.5 (s); exact mass calcd. for C$_{31}$H$_{28}$O$_6$Si $m/z$ 524.1655, found $m/z$ 524.1660.

Anal. calcd. for C$_{31}$H$_{28}$O$_6$Si: C, 70.97; H, 5.32. Found: C, 70.73; H, 5.42.

8-Hydroxy-5,7-dimethoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho[1,2-c][2]benzopyran-13-one (109). To a solution of 60 mg (0.13 mmol) of 108 in 60 mL ethyl alcohol-dichloromethane (1:1) was added 25 mg of 10% palladium on carbon. This mixture was hydrogenated with a Parr hydrogenator at 50 psi of hydrogen for 14 h. The reaction mixture was dissolved in 100 mL of dichloromethane, filtered through a plug of celite and the filtrate was concentrated in vacuo to afford a yellow solid which was recrystallized from dichloromethane-hexanes to afford 40 mg (82%) of 109 as
recrystallized from dichloromethane-hexanes to afford 40 mg (82%) of 109 as a yellow solid: mp 227-228 °C; IR (CH2Cl2) 1728 cm⁻¹; ¹H NMR (CD2Cl2) δ 0.47 (s, 9H, Si(CH3)3), 4.14 (s, 3H, ArOCH3), 4.18 (s, 3H, ArOCH3), 7.00 (d, J = 7.7 Hz, 1H, C9H), 7.11 (s, 1H, C3H), 7.54 (dd, J = 7.9, 8.2 Hz, 1H, C₁₀H), 7.61 (s, 1H, C4H), 8.07 (d, J = 8.4 Hz, 1H, C₁₁H), 8.61 (s, 1H, C6H), 9.39 (s, 1H, ArOH); ¹³C NMR (CD2Cl2) δ -1.73, 56.50, 57.20, 102.42, 110.23, 112.79, 113.72, 116.12, 126.57, 128.84, 129.95, 152.21, 153.69, 154.75, 168.16. (because of low solubility in variety of deuterated solvents, multiplicities could not be obtained and some signals were not detected); exact mass calcd. for C₂₄H₂₂O₆Si m/z 434.1186, found m/z 434.1176.

8-(Benzyloxy)-5,7-dimethoxy-13-H-furo[3.2-h]naptho-[1,2c][2]benzopyran-13-one (138). To a solution of 0.22 g (0.42 mmol) of 108, 0.024 mL (0.025 g, 0.042 mmol) of acetic acid in 40 mL dichloromethane-tetrahydrofuran (1:1) was added 0.42 mL (0.84 mmol) of 2 M tetra-n-butylammonium fluoride in tetrahydrofuran. The reaction was stirred for 5 h, washed with 50-mL of water and the aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic phases
with ethyl acetate to yield 160 mg (85%) of 138 as a yellow solid: mp 252-255 °C (dec.); IR (CDCl$_3$) 1720 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 4.04 (s, 3H, ArOCH$_3$), 4.15 (s, 3H, ArOCH$_3$), 5.26 (s, 2H, CH$_2$O), 6.89 (s, 1H, C$_4$H), 7.10 (d, $J$ = 2.1 Hz, 1H, C$_3$H), 7.50 (m, 7H, ArH), 7.94 (d, $J$ = 2.1 Hz, 1H, C$_2$H), 8.33 (d, $J$ = 7.6 Hz, 1H, C$_{11}$H), 8.61 (s, 1H, C$_6$H); $^{13}$C NMR (CDCl$_3$) $\delta$ 59.2 (q), 59.7 (q), 74.3 (t), 106.9 (d), 109.2 (d), 111.2 (s), 112.8 (d), 113.3 (d), 116.6 (s), 118.4 (d), 121.0 (s), 125.5 (s), 129.5 (s), 129.8 (d), 130.0 (d), 130.5 (d) 131.3 (d), 140.3 (s), 143.9 (s), 150.7 (d), 151.4 (s), 155.8 (s), 156.4 (s), 158.5 (s), 161.0 (s), 171.9 (s); exact mass calcd. for C$_{28}$H$_{20}$O$_6$ m/z 452.1260, found m/z 452.1261.

[Image]

8-Hydroxy-5,7-dimethoxy-13-H-furo[3.2-h]naphto-[1,2c][2]benzopyran-13-one (12). To a heterogeneous mixture of 0.04 g (0.092 mmol) of 109 and 7 mL dichloromethane-tetrahydrofuran (2.5:1) was added 0.092 mL (0.184 mmol) of 2 M tetra-n-butylammonium fluoride in tetrahydrofuran. The resulting red mixture was stirred for 3 h and diluted with 100 mL of dichloromethane. This mixture was washed with 50 mL of water, and the aqueous phase was extracted with five 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and
concentrated in vacuo to afford a yellow solid. This material was triturated with toluene to afford 30 mg (91%) of 12 as a yellow solid: mp > 350 °C; IR (CD$_2$Cl$_2$) 1722 cm$^{-1}$; $^1$H NMR (CD$_2$Cl$_2$) $\delta$ 4.15 (s, 3H, ArOCH$_3$), 4.18 (s, 3H, ArOCH$_3$), 6.95 (d, $J$ = 2.1 Hz, 1H, C$_3$H), 7.00 (dd, $J$ = 8, 0.8 Hz, 1H, C$_{11}$H), 7.35 (s, 1H, C$_4$H), 7.52 (t, $J$ = 8 Hz, 1H, C$_{10}$H), 7.95 (d, $J$ = 2.1 Hz, 1H, C$_2$H), 8.07 (dd, $J$ = 8, 0.9 Hz, 1H, C$_{11}$H), 8.62 (s, 1H, C$_6$H), 9.40 (s, 1H, ArOH); $^{13}$C NMR (DMSO-d$_6$, at 333 K) $\delta$ 56.1, 56.9, 101.7, 106.6, 111.3, 112.2, 112.9, 114.3, 128.8, 140.9, 148.5, 151.5, 153.1, 153.7; exact mass calcd. for C$_{21}$H$_{14}$O$_6$ m/z 362.0790, found m/z 362.0781. Because of low solubility in variety of deuterated solvents, $^{13}$C multiplicities could not be obtained and some signals were not detected.

1,3-Bis(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzene (111). A heterogeneous mixture of 0.78 g (4.0 mmol) of 5-methoxyisophthalic acid (116), 45.4 g (2.82 mL, 39 mmol) of thionyl chloride and 20 mL of toluene was heated at reflux for 3 h. The resulting homogeneous mixture was concentrated in vacuo, and the crude acid chloride was dissolved in 10 mL of dichloromethane. This solution was added to 1.25 g
dissolved in 10 mL of dichloromethane. This solution was added to 1.25 g (14 mmol) of 2-amino-2-methyl-1-propanol in 8 mL of dichloromethane. The mixture was stirred for 2 h, diluted with 100 mL of dichloromethane, and washed with 50 mL of 10% aqueous citric acid. The acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was stirred in 10 mL of thionyl chloride for 2 h. The reaction mixture was diluted with 100 mL of petroleum ether and stirred for 1 h. The solid was collected, dissolved in 100 mL of dichloromethane, and washed with 100 mL of 20% aqueous sodium hydroxide for 10 minutes. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:1) to afford 0.48 g (43%) of 111 as a white solid: mp 99-100 °C; IR (CDCl₃) 1649 cm⁻¹; ¹H NMR (CDCl₃) δ 1.34 (s, 12H, [C(CH₃)₂]₂), 3.84 (s, 4H, (CH₂O)₂), 4.07 (s, 3H, ArOCH₃), 7.54 (d, J = 1.4 Hz, 2H, C₄H and C₅H), 8.06 (t, J = 1.4 Hz, 1H, C₂H); ¹³C NMR (CDCl₃) δ 28.3 (q), 55.7 (q), 67.7 (s), 79.2 (t), 116.3 (d), 120.6 (d), 129.6 (s), 159.5 (s), 161.3 (s); exact mass calcd. for C₁₇H₂₂N₂O₃ m/z 302.1630, found m/z 302.1689.

Anal. calcd. for C₁₇H₂₂N₂O₃: C, 67.51; H, 7.34. Found: C, 67.39; H, 7.32.
5-n-Butyl-1,3-bis(4',4'-dimethylloxazolin-2'-yl)-5-methoxybenzene (117). To a solution of 0.1 g (0.33 mmol) of 111 in 4 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) under argon was added 0.242 mL (0.363 mmol, 1.5 M in hexane) of n-butyllithium. The resulting brownish-yellow solution was stirred for 2 h and then quenched with 2 mL of deuterium oxide. The reaction was allowed to warm to room temperature, diluted with 25 mL of dichloromethane and washed with 20 mL of water. The aqueous wash was extracted with two 20-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford an oily residue. This material was chromatographed over 3 g of silical gel (eluted with petroleum ether-ethyl acetate, 2:1), to afford 13 mg (11%) of 117 as a clear oil: IR (neat) 1649 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, J = 4.8 Hz, 3H, CH₂CH₃), 1.36 (broad s, 16H, [C(CH₃)₂]₂ and (CH₂)₂), 2.94 (dd, J = 7.2, 8.1 Hz, 2H, CH₂Ph), 3.86 (s, 3H, ArOCH₃), 4.05 (s, 2H, CH₂O), 4.07 (s, 2H, CH₂O), 7.46 (d, J = 1.5 Hz, 1H, C₅H), 7.80 (d, J = 1.6 Hz, 1H, C₂H); ¹³C NMR (CDCl₃) 13.9 (q), 23.0 (t), 26.6 (t), 28.3 (q), 32.1 (t), 55.9 (q), 67.6 (s), 68.0 (s), 78.9 (t), 79.1 (t), 111.4 (d), 122.0 (d), 126.0 (s), 129.3 (s), 135.8 (s), 157.7 (s), 161.7 (s), 162.2 (s); exact mass calcd. for C₂₁H₃₀N₂O₃ m/z 358.2256, found m/z 358.2263.
Bis-(N,N-diethyl-5-methoxybenzene-1,3-dicarboxamide) (118). A slurry of 1 g (5.1 mmol) of 5-methoxyisophthalic acid (116), 5.89 g (3.7 mL, 50 mmol) of thionyl chloride and 28 mL of toluene was heated to reflux for 15 h. The resulting solution was concentrated in vacuo, and the crude acid chloride was dissolved in 20 mL of dichloromethane. This mixture was added to a solution of 3.9 g (5.6 mL, 54 mmol) of diethylamine in 16 mL of dichloromethane. The reaction was stirred for 2 h, diluted with 100 mL of dichloromethane and washed with 50 mL of 10% aqueous hydrochloric acid. The acidic wash was extracted with 25 mL dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to afford 1.06 g (65%) of 118 as a viscous oil: IR (neat) 1632 cm⁻¹; ¹H NMR (CDCl₃) δ 1.17 (m, 12H, [C(CH₃)]₂), 3.45 (m, 8H, (CH₂)₄), 3.82 (s, 3H, ArOCH₃), 6.92 ( broad s, 3H, ArH); ¹³C NMR (CDCl₃) δ 12.8 (q), 14.1 (q), 39.2 (t), 43.2 (t), 55.5 (q), 112.7 (d), 116.1 (d), 138.8 (s), 159.6 (s), 170.1 (s); exact mass calcd. for C₁₇H₂₆N₂O₃ m/z 306.1943, found m/z 306.1949.
6-(Diethylcarboxamide)-4-methoxy-3-phenylphthalide (119). To a solution of 54 mg (0.18 mmol) of 118, 0.033 mL (0.22 mmol) of tetramethylethylenediamine in 3 mL of dry tetrahydrofuran was added, at -45 °C under argon, 0.211 mL (0.211 mmol, 1 M in cyclohexane) of s-butyllithium. The resulting orange solution was stirred for 1 h and quenched with 0.30 mL (3 mmol) of benzaldehyde. The reaction was allowed to warm to room temperature, diluted with 20 mL of dichloromethane and washed with 20 mL of water. The organic layer was dried (MgSO₄), concentrated in vacuo, and the excess benzaldehyde was removed by Kugelrohr distillation (80 °C, 1 mm Hg). The pot residue was heated at reflux for 12 h in 3 mL of benzene in the presence of catalytic ρ-toluenesulfonic acid with removal of water by a Dean Stark trap. The reaction was concentrated in vacuo, the residue was dissolved in 20 mL of ethyl acetate, and washed with 20 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with 20 mL of ethyl acetate, the combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford a solid residue. This material was recrystallized from hexane-ethyl acetate to afford 17 mg (30%) of 119 as a white solid: mp 163-164 °C; IR (CDCl₃) 1622, 1771 cm⁻¹; ¹H NMR (CDCl₃) δ
1.21 (broad s, 6H, (CH$_3$)$_2$), 3.31 (broad s, 2H, CH$_2$), 3.59 (broad s, 2H, CH$_2$), 3.77 (s, 3H, ArOCH$_3$), 6.41 (s, 1H, CH), 7.13 (d, $J$ = 1 Hz, 1H, C$_5$H), 7.45 (m, 5H, ArH), 7.50 (d, $J$ = 1 Hz, 1H, C$_7$H); $^{13}$C NMR (CDCl$_3$) $\delta$ 12.9, 14.2, 39.5, 43.5, 55.9 (q), 81.9 (d), 114.4 (d), 114.5 (d), 127.4 (d), 127.7 (s), 128.6 (d), 129.1 (d), 135.2 (s), 138.0 (s), 140.8 (s), 154.9 (s), 169.4 (s), 169.7 (s); exact mass calcd. for C$_{20}$H$_{21}$NO$_4$ m/z 339.1471, found m/z 339.1478. The multiplicities of the $^{13}$C signals at 12.9, 14.2, 39.5, and 43.5 were not determined because of broadening.

Anal. calcd. for C$_{20}$H$_{21}$NO$_4$: C, 70.77, H, 6.25. Found: C, 70.68, H, 6.25.

**12-Hydroxy-10-methoxy-8-(N,N-diethylamide)-6H-benzo[d]-naphtho[1,2-b]pyran-6-one (121).** To a solution of 2 g (6.58 mmol) of bis(amide) 118 and 1.25 mL (8.29 mmol) of tetramethylethylenediamine in 50 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) under argon was slowly added 4.6 mL (7.9 mmol) of 1.7 M t-butyllithium in pentane via a syringe, and the solution was stirred for 2 h. In a separate flask a solution of
MAD was prepared by dissolving 1.14 g (5.16 mmol) 2,6-di-t-butyl-4-methylphenol in 50 mL of dry toluene and slowly adding 1.29 mL (2.58 mmol) of 2 M trimethylaluminum in hexane at room temperature under argon followed by stirring for 30 min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 0.4 g (1.29 mmol) of naphthoquinone monoketal 54 was added in a solution of 10 mL of dry toluene. The resulting dark solution was stirred for 15 min followed by addition of the aryl lithium via a cannula. Upon completion of this addition the reaction was stirred for 5 min followed by addition of 10 mL of water. The cooling bath was removed and the reaction was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of celite which was rinsed with dichloromethane. The filtrate was dried (Na$_2$SO$_4$), concentrated in vacuo and the residue was chromatographed over 100 g of silica gel (eluted with petroleum ether-ethyl acetate, 2:1) to afford an oil which consisted of bis(amide) 118 and conjugate adduct 120. Separation of these two compounds was not possible at this point, therefore the separation was performed after the next reaction.

The oil containing bis(amide) 118 and conjugate adduct 120 was heated at reflux in 20 mL of tetrahydrofuran and 5 mL of 5 N aqueous hydrochloric acid for 18 h. The reaction was diluted with 100 mL of dichloromethane and washed with 50 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo to afford an oily residue. This was chromatographed over 100 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to
afford 0.29 g of a yellow solid which was recrystallized from ethyl acetate-petroleum ether to afford 160 mg of 121 (25%) as a yellow solid: mp 209-210 °C; IR (CDCl$_3$) 3412, 1720 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.26 (broad s, 6H, (CH$_3$)$_2$), 3.37 (broad s, 2H, CH$_2$), 3.59 (broad s, 2H, CH$_2$), 4.10 (s, 3H, ArOCH$_3$), 5.33 (s, 2H, CH$_2$O), 7.04 (d, $J$ = 7.5 Hz, 1H, C$_2$H), 7.49 (m, 7H, ArH), 8.12 (d, $J$ = 1.6 Hz, 1H, C$_7$H), 8.23 (dd, $J$ = 8.6, 0.6 Hz, 1H, C$_4$H), 8.39 (s, 1H, C$_{11}$H), 9.23 (s, 1H, ArOH); $^{13}$C NMR (CDCl$_3$) $\delta$ 10.7, 12.9, 39.6 (t), 43.6 (t), 56.2 (q), 71.9 (t), 107.6 (d), 107.7 (d), 114.5 (s), 115.2 (d), 115.5 (s), 116.4 (s), 119.8 (d), 123.2 (s), 125.1(s), 125.8 (s), 126.7 (d), 128.0 (d),129.0 (d), 129.1 (d), 135.0 (s), 137.9 (s), 140.0 (s), 150.7 (s), 154.7 (s), 158.0 (s), 160.7 (s), 169.3 (s); exact mass calcd. for C$_{30}$H$_{27}$NO$_6$ m/z 497.1838, found m/z 497.1859. The multiplicity of the signals at 10.7, and 12.9 in the $^{13}$C spectrum, was not attainable because of broadening.

![124](image)

**2-Bromo-3,5-dimethylphenol (124).**$^{46}$ To a solution of 20 g (164 mmol) of 3,5-dimethylphenol (123) in 500 mL of glacial acetic acid was added 10.16 mL (197 mmol) of bromine in one portion. The reaction was stirred for 1 h, diluted with 1 L of water, and the resulting milky mixture was extracted with two 500-mL portions of ethyl ether. The combined organic phases were washed with four 1000-mL portions of water, 500 mL of
saturated aqueous sodium bicarbonate, dried (MgSO₄) and concentrated in vacuo to afford 34.31 g of a cream color solid. This residue was dissolved in 350 mL of chloroform and hydrogen bromide was bubbled into the solution for approximately 1 h. The reaction was allowed to stand for an additional 1 h, and was washed with 1 L of water, 500 mL of saturated aqueous sodium bicarbonate, dried (MgSO₄) and concentrated in vacuo to afford a yellowish oil. This material was distilled by Kugelrohr (70-80 °C, 0.8-1 mm Hg) followed by a second distillation of the distillate at the same temperature and pressure to afford 13.5 g (40%) of 124 as a clear oily solid: mp 49 -51 °C (lit54, 54 °C); ¹H NMR (CDCl₃) 6 2.28 (s, 3H, ArCH₃), 2.38 (s, 3H, ArCH₃), 5.52 (s, 1H, ArOH), 6.62 (s, 1H, C₆H), 6.67 (s, 1H, C₂H).

2-Bromo-3,5-dimethylanisole (125). A heterogeneous mixture of 10.28 g (51.14 mmol) of 124, 23 mL (243 mmol) of dimethyl sulfate, 35 g (269 mmol) of potassium carbonate and 500 mL of acetone was heated at reflux for 36 h. The reaction was filtered and the potassium carbonate was rinsed with acetone. The filtrate was concentrated in vacuo and the residue was dissolved in 500 mL of ethyl ether. This mixture was washed with two 250-mL portions of 10% aqueous sodium hydroxide followed by two 250-mL portions of 10% aqueous citric acid and 200 mL of water. The organic phase was
dried (MgSO₄) and concentrated in vacuo to afford 10.49 g (95%) of 125 as an oil which solidified on standing: mp 38-39.5 °C; ¹H NMR (CDCl₃) δ 2.29 (s, 3H, ArCH₃), 2.37 (s, 3H, ArCH₃), 3.87 (s, 3H, ArOCH₃), 6.56 (d, J = 0.6 Hz, 1H, C₆H), 6.69 (d, J = 0.6 Hz, 1H, C₄H).

4-Bromo-5-methoxyisophthalic acid (126). A mechanically stirred heterogenous mixture of 7.61 g (35.4 mmol) of 125 and 170 mL of water was heated to 110 °C (external temperature). To the hot mixture was added 32.34 g (205 mmol) of potassium permagnanate in 200 mL of hot water over 2 h. The reaction was heated at 110 °C for 4 h, allowed to cool to room temperature and filtered through a plug of celite which was rinsed sequentially with 200 mL of water and 200 mL of ethyl ether. The basic aqueous phase was washed with 300 mL of ethyl ether and acidified to a pH of 1 by addition of concentrated hydrochloric acid. A white precipitate formed and the mixture was extracted with two 300-mL portions of ethyl acetate. The aqueous phase was saturated with sodium chloride, cooled in an ice bath, and extracted with 300 mL of ethyl acetate. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 5.04 g (52%) of 126 as a white solid: mp 320-322 °C; IR (nujol) 1701 cm⁻¹; ¹H
NMR (DMSO-d$_6$) $\delta$ 4.10 (s, 3H, ArOCH$_3$), 7.71 (s, 1H, C$_6$H), 7.98 (s, 1H, C$_2$H), 9.10 (s, 1H, C$_2$H); $^{13}$C NMR (DMSO-d$_6$) $\delta$ 56.8 (q), 113.8 (d), 114.4 (s), 121.8 (d), 131.1 (s), 136.3 (s), 156.2 (s), 166.0 (s), 167.0 (s); exact mass calcd. for C$_{9}$H$_{7}$BrO$_5$ m/z 273.9474, 275.9456, found m/z 273.9481, 275.9462. The acidic protons were not detected.

Anal. calcd. for C$_{9}$H$_{7}$BrO$_5$: C, 39.30; H, 2.57. Found: C, 39.56; H, 2.69.

4-Bromo-1-(4',4'-dimethyloxazolin-2'-yl)-3-[N-3-(1-chloro-3,3-dimethylpropyl)carboxamide]-5-methoxybenzene (128) and 4-Bromo-1,3-bis-(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzene (122). A heterogeneous mixture of 0.41 g (1.5 mmol) of 126, 2 g (3.26 mL, 17 mmol) of thionyl chloride and 9 mL of toluene was heated at reflux for 20 h. The resulting homogeneous mixture was concentrated in vacuo, and the crude acid chloride was dissolved in 6 mL of dichloromethane. This solution was added to 0.55 g (6 mmol) of 2-amino-2-methyl-1-propanol in 4 mL of dichloromethane. The mixture was stirred for 2 h, diluted with 50 mL of dichloromethane, and washed with 50 mL of 10% aqueous citric acid. The acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$), concentrated in vacuo and
the residue was stirred in 7.5 mL of thionyl chloride for 2 h. The reaction mixture was concentrated in vacuo and the residue was partitioned between 30 mL of aqueous 10% sodium hydroxide and 30 mL of dichloromethane. The organic layer was dried (MgSO₄) and concentrate in vacuo to afford an oily residue. This material was chromatographed over 50 g of silica gel (eluted with chloroform-petroleum ether, 10:1) to afford 0.32 g (52%) of 128 as a white solid: mp 109-110.5 °C; IR (CDCl₃) 1653, 1627 cm⁻¹; ¹H NMR (CDCl₃) δ 1.39 (s, 6H, C(CH₃)₂), 1.53 (s, 6H, C(CH₃)₂), 3.93 (s, 2H, CH₂Cl), 3.97 (s, 3H, ArOCH₃), 4.13 (s, 2H, OCH₂), 5.30 (br s, 1H, NH), 7.50 (br s, 1H, ArH), 7.60 (d, J = 2 Hz, 1H, ArH); ¹³C NMR (CDCl₃) δ 24.9 (q), 28.8 (q), 51.0 (t), 55.0 (s), 56.7 (q), 67.8 (s), 79.3 (t), 111.7 (d), 112.5 (s), 120.1 (d), 128.4 (s), 140.3 (s), 156.0 (s), 160.8 (s), 166.7 (s); exact mass calcd. for C₁₇H₂₂BrClN₂O₃ m/z 416.0503, found m/z 416.0484.

Continued elution afforded 144 mg (20%) of 122 as an oil: (Data for this compound is given below. The ¹H NMR of 122 was identical to that obtained from the following experiment).

4-Bromo-1,3-bis(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzene (122). A heterogeneous mixture of 5 g (18.18 mmol) of 2-bromo-
5-methoxyisophthalic acid (126), 40 g (25 mL, 345 mmol) of thionyl chloride and 100 mL of toluene was heated at reflux for 32 h. The reaction was concentrated in vacuo and the crude diacid chloride was dissolved in 100 mL of dichloromethane. This solution was added to a solution of 6.77 g (75 mmol) of 2-amino-2-methyl-1-propanol in 90 mL of dichloromethane. The reaction was stirred for 3 h, diluted with 800 mL of ethyl acetate, and washed with 200 mL of 10% aqueous citric acid. The acidic wash was extracted with 100 mL of ethyl acetate. The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford a white solid. This solid was cooled to -5 to 0 °C (ice/salt water) and 100 mL of cold thionyl chloride was added. The mixture was stirred at -5 to 0 °C for 5 h and concentrated in vacuo. To the residue was added 200 mL of 10% aqueous sodium hydroxide while being cooled at -45 °C (dry ice/acetonitrile). The heterogeneous mixture was diluted with 300 mL of dichloromethane and the two layers were shaken for 5 min. The aqueous phase was extracted with 100 mL of dichloromethane. The combined organic phases were dried (MgSO₄), concentrated in vacuo and the residue was chromatographed over 100 g of silica gel (eluted with chloroform-petroleum ether, 10:1), to afford 5.2 g (75%) of 122 as a viscous oil which slowly solidified; mp 85-87 °C; IR (neat) 1648 cm⁻¹;¹H NMR (CDCl₃) δ 1.35 (s, 6H, C(CH₃)₂), 1.38 (s, 6H, C(CH₃)₂), 3.94 (s, 3H, ArOCH₃), 4.08 (s, 2H, CH₂O), 4.10 (s, 2H, CH₂O), 7.48 (d, J = 1.7 Hz, 1H, C₆H), 7.74 (d, J = 1.8 Hz, 1H, C₂H);¹³C NMR (CDCl₃) δ 28.2 (q), 28.3 (q), 56.8 (q), 67.9 (s), 68.2 (s), 79.3 (t), 79.4 (t), 112.3 (d), 115.2 (s), 122.6 (d), 128.1 (s), 132.3 (s), 156.2 (s), 160.7 (s), 161.2 (s); exact mass calcd. for C₁₇H₂₁BrN₂O₃ m/z 380.0736, found m/z 380.0741.
Anal. calcd. for C\textsubscript{17}H\textsubscript{21}BrN\textsubscript{2}O\textsubscript{3}: C, 53.55; H, 5.55. Found: C, 53.61; H, 5.56.

5-Methyl-1,3-bis(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzene (130) and 1,3-Bis(4',4'-dimethyloxazolin-2'-yl)-5-methoxybenzene (111). To a solution of 73 mg (0.189 mmol) of 122 in 2 mL of dry tetrahydrofuran at -100 °C (liquid nitrogen-toluene) under argon was added 0.32 mL (0.416 mmol) of 1.3 M t-butyllithium in pentane. This mixture was stirred for 15 min and the -100 °C cold bath was replaced with a -78 °C (dry ice-acetone) cold bath. Tetramethylethylenediamine (0.034 mL, 0.227) was added, the mixture was stirred for 5 min and quenched with 0.1 mL (1.6 mmol) of methyl iodide. The reaction was stirred for 30 min at -78 °C and 0.05 mL of D\textsubscript{2}O was added. The mixture was allowed to warm to room temperature, and was partitioned between 20 mL of dichloromethane and 20 mL of water. The organic layer was dried (MgSO\textsubscript{4}) and concentrated in vacuo to afford 54 mg of a yellowish oil. This material consisted of two major components, 130 and 111, in a 4:1 ratio, respectively (by integration of C\textsubscript{2}H in the \textsuperscript{1}H-NMR). These two compounds were found to be inseparable. For
the purpose of characterization the GC-IR-MS instrument was used. The GC trace of the mixture showed two major components. Component 1 (130): $t_r = 14.23$ min (0 min)-(10 °C/min)-200 °C-(30 min): IR (gas) 1654 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.55 (d, $J = 1.4$ Hz, 2H, C$_4$H and C$_6$H), 8.07 (t, $J = 1.4$ Hz, 1H, C$_2$H); mass calcd. for C$_{17}$H$_{22}$N$_2$O$_3$ m/z 302.38, found m/z 302.15. Component 2 (11): $t_r = 15.17$ min (0 min)-(10 °C/min)-200 °C-(30 min): IR (gas) 1655 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.42 (s, 3H, ArCH$_3$), 7.44 (d, $J = 1.3$ Hz, 1H, C$_3$H), 7.82 (d, $J = 1.5$ Hz, 1H, C$_2$H); mass calcd. for C$_{18}$H$_{24}$N$_2$O$_3$ m/z 316.54, found m/z 316.25. The $^1$H NMR data were obtained from the spectrum of the mixture of 130 and 111.

![Chemical Structure](image)

3-[2,4-Bis(4',4'-dimethyl-2-oxazolin-2'-yl)-6-methoxy-4-methylphenyl]-3,4-dihydro-4,4-dimethoxy-8-(phenylmethoxy)-1(2'H)naphthalenone (131). To a solution of 0.62 g (1.61 mmol) of 122 in 16 mL of dry tetrahydrofuran at -100 °C (liquid nitrogen-toluene) was added in one portion 2.72 mL (3.54 mmol) of 1.3 M $t$-butyllithium in pentane via a syringe and the solution was stirred for 15 min. The toluene cold bath
was replaced by a -78 °C (dry ice-acetonitrile) and the reaction was allowed to warm to -78 °C. At this temperature 0.29 mL (1.93 mmol) of tetramethylethylenediamine was added and stirring was continued for 5 min. In a separate flask a solution of MAD was prepared by dissolving 0.71 g (3.22 mmol) 2,6-di-butyl-4-methylphenol in 25 mL of toluene and slowly adding 0.81 mL (1.61 mmol) of 2 M trimethylaluminum in hexane at room temperature under argon followed by stirring for 30 min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 0.25 g (0.81 mmol) of naphthoquinone monoketal 54 was added in a solution of 6 mL of toluene. The resulting dark solution was stirred for 15 min followed by addition of the aryl lithium via a cannula. Upon completion of this addition the reaction was stirred for 45 min followed by additon of 5 mL of water. The cooling bath was removed and the reaction was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of celite which was rinsed with ethyl acetate. The filtrate was dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1, 3:1 and 1:1) to afford 232 mg (47%) of 131 as a tan foam: mp 158-160 °C ; IR (CDCl₃) 1693, 1648 cm⁻¹; ¹H NMR (CDCl₃) δ 1.41 (s, 6H, C(CH₃)₂), 1.42 (s, 6H, C(CH₃)₂), 2.69 (s, 3H, OCH₃), 2.75 (dd, J = 16, 5 Hz, 1H, CH), 2.96 (s, 3H, OCH₃), 3.07 (s, 3H, OCH₃), 3.16 (dd, J = 16, 10 Hz, 1H, CH), 4.01 (s, 2H, OCH₂), 4.08 (d, J = 8 Hz, 1H, OCH), 4.12 (d, J = 8 Hz, 1H, OCH), 4.67 (dd, J = 10, 5 Hz, 1H, CH), 5.18 (d, J = 12 Hz, 1H, OCHPh), 5.30 (d, J = 12 Hz, 1H, OCHPh), 7.00 (d, J = 8 Hz, 1H, ArH), 7.45 (m, 8H, ArH), 7.76 (d, J = 1.6 Hz, 1H, ArH); ¹³C NMR (Acetone-d₆) 28.1 (q), 28.2 (q), 28.3 (q), 30.4 (q), 42.1 (d), 43.7 (t), 49.1 (q), 49.1 (q), 54.4 (q),
49.1 (q), 49.1 (q), 54.4 (q), 68.2 (s), 69.1 (s), 70.8 (t), 79.1 (t), 79.4 (t), 99.9 (s), 112.0 (d), 113.6 (d), 118.3 (d), 121.8 (d), 124.6 (s), 125.7 (s), 127.5 (d), 128.0 (d), 128.5 (s), 128.8 (d), 131.6 (s), 132.0 (d), 132.9 (s), 138.1 (s), 146.1 (s), 156.3 (s), 158.8 (s), 160.8 (s), 195.4 (s); exact mass calcd. for C_{36}H_{40}N_{2}O_{7} m/z 612.2835, found m/z 612.2802.

Anal. calcd. for C_{36}H_{40}N_{2}O_{3}: C, 70.43; H, 6.58. Found: C, 70.43; H, 6.65.

1-Benzyloxy-12-hydroxy-8-(4,4-dimethyl-2-oxazolin-2-yl)-10-methoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one (132). A solution of 292 mg (0.46 mmol) of 131, 10 mL of tetrahydrofuran and 2 mL of 5 N aqueous hydrochloric acid was heated to reflux for 1 h. The reaction was diluted with 50 mL of dichloromethane and washed with 50 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 30-mL portions of dichloromethane and two 30-mL portions of ethyl acetate. The combined organic phases were dried (MgSO_{4}) and concentrated in vacuo to afford an orange solid. This was recrystallized form chloroform-petroleum
ether to afford 175 mg (74%) of 132 as an orange solid: mp 224-226 °C; IR (CH₂Cl₂) 3407, 1726, 1608 cm⁻¹; ¹H NMR δ 1.28 (s, 6H, C(CH₃)₂), 4.15 (s, 3H, ArOCH₃), 4.24 (s, 2H, CH₂O), 5.34 (s, 2H, OCH₂Ph), 7.09 (d, J = 7.9 Hz, 1H, C₂H), 7.50 (s, 6H, ArH), 7.99 (d, J = 1.6 Hz, 1H, C₉H), 8.27 (d, J = 8.4, 1H, C₄H), 8.42 (s, 1H, C₁₁H), 8.76 (d, J = 1.6 Hz, 1H, C₇H), 9.28 (br s, 1H, ArOH); ¹³C NMR (DMSO-d₆ at 333K) δ 23.3 (q), 26.1 (q), 49.0 (s), 56.4 (q), 67.3 (t), 71.0 (t), 73.2 (s), 106.7 (d), 109.2 (d), 113.2 (s), 114.7 (s), 116.4 (s), 116.8 (d), 120.5 (d), 122.4 (d), 124.0 (s), 127.3 (d), 127.6 (d), 128.0 (d), 128.0 (d), 128.4 (d), 130.4 (s), 135.8 (s), 149.6 (s), 154.5 (s), 157.5 (s), 159.3 (s); exact mass calcd. for C₃₀H₂₅N₂O₆ m/z 495.1682, found m/z 495.1691.

![133](image)

1-Benzyloxy-8-methylcarboxalate-10,12-dimethoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one (133). A heterogeneous mixture of 140 mg (0.283 mmol) of 132, 0.450 mL (4.75 mmol) of dimethyl sulfate, 0.82 g (6 mmol) of potassium carbonate and 15 mL of acetone was refluxed for 6 days. The reaction was filtered and the potassium carbonate was rinsed with acetone. The filtrate was concentrated in vacuo dissolved in 30 mL of dichloromethane and washed with 25 mL of 10% aqueous citric acid. The
acidic wash was extracted with two 20-mL portions of dichloromethane. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo to 118 mg (89%) of 133 as an orange solid: mp 251-254 °C; IR 1725 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.96 (s, 3H, OCH$_3$), 4.02 (s, 3H, OCH$_3$), 4.16 (s, 3H, OCH$_3$), 5.22 (s, 2H, OCH$_2$), 7.10 (d, $J$ = 8.8 Hz, 1H, C$_2$H), 7.5 (m, 6H, ArH), 7.97 (d, $J$ = 1 Hz, 1H, C$_9$H), 8.21 (d, $J$ = 10 Hz, 1H, C$_4$H), 8.42 (s, 1H, C$_{11}$H), 8.78 (d, $J$ = 1 Hz, 1H, C$_7$H); $^{13}$C NMR (CDCl$_3$) $\delta$ 52.6 (q), 56.5 (q), 56.6 (q), 71.5 (t), 104.0 (d), 111.0 (d), 112.9 (s), 115.5 (d), 116.6 (d), 1118.8 (s), 123.3 (s), 112.9 (s) 124.3 (d), 126.6 (s), 127.5 (d), 127.0 (d), 127.7 (d), 128.3 (s), 128.4 (d), 130.4 (s), 137.3 (s), 141.9 (s), 153.1 (s), 155.7 (s), 165.7 (s), 177.2 (s); exact mass calcd. for C$_{28}$H$_{22}$O$_7$ m/z 470.1365, found m/z 470.1380.

134

1-Benzyloxy-8-carboxy-10,12-dimethoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one (134) A heterogeneous mixture of 20 mg (0.42 mmol) of 133, 4 mL of tetrahydrofuran-methanol (1:1, degassed with argon for 15 min, and 1 mL of 1.1 methanolic potassium hydroxide (degassed with argon) was heated at reflux for 12 h. The resulting red solution was acidified to a pH of 1 with 10% aqueous hydrochloric acid.
The resulting heterogeneous mixture was diluted with 20 mL of water and extracted with four 100-mL portions of ethyl acetate. The combined organic layers were dried (MgSO₄) and concentrated in vacuo to afford a yellow solid. This solid was recrystallized from ethyl acetate-methanol (10:1) to afford 13 mg (68%) of 134 as a yellow solid: mp 300-302 °C; IR (nujol) 1727, 1681 cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.93 (s, 3H, ArOCH₃), 4.13 (s, 3H, ArOCH₃), 5.22 (s, 2H, OCH₂), 7.45 (m, 7H, ArH), 7.95 (m, 2H, ArH), 8.32 (s, 1H, ArH), 8.40 (s, 1H, ArH), 13.45 (br s, 1H, CO₂H); ¹³C NMR (DMSO-d₆ at 333 K) δ 56.0 (q), 56.5 (q), 70.5 (t), 103.6 (d), 110.8 (d), 112.35 (s), 113.9 (d), 117.0 (d), 117.8 (s), 122.6 (d), 125.6 (s), 126.6 (d), 127.1 (d), 127.5 (d), 127.9 (d), 131.5 (s), 137.1 (s), 140.6 (s), 152.4 (s), 155.2 (s), 157.1 (s), 159.3 (s), 165.5 (s); One singlet in the ¹³C spectrum was not detected; exact mass calcd. for C₂₇H₂₀O₇ m/z 456.1209, found m/z 456.1207.
References


10. McGee, L.R.; Tse-Dinh, Y. Biochemical and Biophysical Research Communications 1987, 143, 808.


51. Swenton, J.S. unpublished results.


Appendix

Selected $^1$H and $^{13}$C Spectra.
61 TM-2-104
(300 MHz, CDCl₃)
OCH3

CH3 O CH O

62 TM-6-134
(250 MHz, CDCl3)
63 TM-6-143
(200 MHz, CDCl₃)
65 TM-6-118
(250 MHz, CDCl₃)

[Chemical structure image]
$OCH_3$

65 TM·6·118
(62.9 MHz, CDCl₃)
60 TM-6-153
(250 MHz, CDCl₃)
54 TM-6-176
(200 MHz, CDCl₃)
$\text{H} - \text{C} = \text{C} - \text{TMS}$

$\text{OCH}_3$

11.0 3.0 10.0

P P M

163
71 TM-1-268
(62.9 MHz, CDCl₃)
72 TM-1-175
(250 MHz, CDCl₃)
72 TM-1-175
(62.9 MHz, CDCl₃)
73 TM-2-41
(62.9 MHz, CDCl₃)
HO
TMS
OCH₃

74 TM-1-260
(300 MHz, CDCl₃)
74 TM-1-260
(52.9 MHz, CDCl₃)
67 TM-2-8
(300 MHz, CDCl₃)
67 TM-2-8
(62.9 MHz, CDCl3)
$\text{H_3C}$

$\text{OCH}_3$

80 TM-4-11-S3

(300 MHz, CDCl$_3$)
80 TM-4-11-S3
(62.9 MHz, CDCl₃)
81 TM-4-11-S2
(300 MHz, CDCl3)
81 TM-4-11-S2
(62.9 MHz, CDCl3)
82 TM-3-212
(300 MHz, CDCl₃)
77 TM-1-295
(300 MHz, CDCl₃)
77 TM-1-295
(62.9 MHz, CDCl₃)
76 TM-4-75
(62.9 MHz, Acetone-d6)
78 TM-1-298
(62.9 MHz, CDCl₃)
88 TM-3-135
(250 MHz, CDCl₃)
88 TM-3-135
(62.9 MHz, CDCl₃)
89 TM-3-148
(250 MHz, CDCl₃)
89 TM-3-148
(62.9 MHz, CDCl₃)
11 TM-3-155

(75.4 MHz, DMSO-d$_6$ at 335 K)
91 TM-2-127-I
(250 MHz, CDCl₃)
91 TM-2-127-1
(62.9 MHz, CDCl₃)
93 TM-2-127-D
(250 MHz, CDCl₃)
93 TM-2-127-D
(62.9 MHz, CDCl₃)
97 TM-3-54
(300 MHz, CDCl₃)
97 TM-3-54
(62.9 MHz, CDCl3)
95 TM-4-106
(300 MHz, CDCl₃)
95 TM-4-106
(62.9 MHz, CDCl$_3$)
98 TM:3-112
(250 MHz, CDCl₃)
98 TM-3-112
(62.9 MHz, CDCl₃)
99 TM-3-184
(300 MHz, CDCl₃)
100 TM-3-267
(300 MHz, CDCl₃)
102 TM-4-80
(300 MHz, CDCl₃)
104 TM-6-221
(300 MHz, CDCl₃)
104 TM-6-221
(62.9 MHz, CDCl₃)
103 TM-4-64
(250 MHz, CDCl₃)
$^{103} \text{TM-4-64}$

(62.9 MHz, CDCl$_3$)
107 TM-4-125
(250 MHz, CDCl₃)
107 TM-4-125
(62.9 MHz, CDCl₃)
108 TM-4-109
(250 MHz, CDCl₃)
109 TM-4-129
(75.4 MHz, CD$_2$Cl$_2$)
109 TM-4-129
(300 MHz, CD₂Cl₂)
138 TM-5-30
(62.9 MHz, CDCl$_3$)
138 TM-5-30
(250 MHz, CDCl₃)
12 TM-4-132
(300 MHz, CD$_2$Cl$_2$)
12 TM-4-132
(75.4 MHz, DMSO-d6 at 333 K)
111 TM-3-165
(300 MHz, CDCl₃)
111 TM-3-165
(62.9 MHz, CDCl₃)
117 TM-4-54
(62.9 MHz, CDCl₃)
Et₂N

Et₂N

OCH₃

118 TM-3-196

(250 MHz, CDCl₃)
119 TM-5-16

(62.9 MHz, CDCl₃)
121 TM-5-16
(250 MHz, CDCl₃)
OH

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

Br

OH

124 TM-5-114
(250 MHz, CDCl$_3$)
125 TM-5-117
(250 MHz, CDCl₃)
126 TM-5-127
(250 MHz, Acetone-d$_6$)
126 TM-5-127
(62.9 MHz, Acetone-d$_6$)
128 TM-5-139-S2
(250 MHz, CDCl$_3$)
HOC, 128 TM-5-139-S2
(62.9 MHz, CDCl₃)
122 TM-5-141
(300 MHz, CDCl₃)
122 TM-5-141
(62.9 MHz, CDCl₃)
130 + 111
(TM-6-106
(250 MHz, CDCl$_3$))
131 TM-6-113
(300 MHz, CDCl₃)
131 TM-6-113
(62.9 MHz, Acetone-d$_6$)
132 TM-6-7
(250 MHz, CDCI3)
132 TM-6-226
(75.4 MHz, DMSO-d$_6$ at 333 K)
133 TM-6-8
(300 MHz, CDCl₃)
133 TM-6-8
(62.9 MHz, CDCl₃)
134 TM-6-252
(300 MHz, DMSO-d$_6$)

1 3 4  T M - 6 - 2 5 2 
(3 0 0 MHz, D M S O - d$_6$)
134 TM-6-256
(75.4 MHz, DMSO-d$_6$ at 333 K)
CH₃ and CH are up
CH₂ are down

OCH₃, OCH₃
CH only

134 TM-6-256
(75.4 MHz, DMSO-d6 at 333 K)

CH, CH₂, CH₃