INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700  800/521-0600
Studies directed towards the synthesis of chrysomycin B

Young, David Gorden J., Ph.D.
The Ohio State University, 1994
STUDIES DIRECTED TOWARDS THE SYNTHESIS OF CHRYSOMYCIN B

DISSERTATION

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

By

David G. J. Young

The Ohio State University

1994

Dissertation Committee:
Dr. David J. Hart
Dr. Viresh H. Rawal
Dr. John S. Swenton

Approved by

David J. Hart
Adviser
Department of Chemistry
To Elizabeth
ACKNOWLEDGEMENTS

I would like to thank Dr. David Hart gave me a chance. He never gave up on me, and allowed me to pursue a number of ideas while developing independent research skills. His patience and self control are marvelous in every aspect of living, with the possible exception of softball (Come on ref, get in the game!).

Anyone who completes a PhD and is married should dedicate at least one paragraph to their spouse. Thank you Elizabeth, you’ve worked every bit as hard at home as I have in the lab, you just don’t get a degree. Perhaps I can repay you some day but I couldn’t have done it without you.

Thank you to my good buddy Tony who I greatly missed during my last year here. Without his skepticism I never would have pursued Chapter III. Alyx, thank you for your kind French ears. I hope they weren’t stuffed with too many four letter American words during your residency in 3027 Evans. Vicky (especially for driving back from Gahanna with a set of keys August 28, 1994), Brian, Dan, and Vincent I hope I was there for you as much as you were for me. The number of former group members is too long to list.

For X-ray crystallographic data I would like to thank Dr. Judith Galluci. For $^1$H NMR and $^{13}$C spectral data I thank Dr. Carl Engelman, Dr. Dirk Friedrich, and Dr. Charles Cottrel. David Chan’s help in acquiring Mass Spectral information is greatly appreciated.

The biggest thanks of all goes to my Grandpa Edson Roush, who died the summer I came here. Of the inumerable pieces of advice he gave me, perhaps the best was "blessed is he who expects nothing, for he shall not be disappointed."
VITA

April 25, 1965.................................................................Born, Sidney, Ohio

B.S. Chemistry, Ohio
Northern University
Ada, Ohio

1988-1991.................................................................Teaching Assistant, The
Ohio State University,
Columbus

1991.................................................................M.S. Organic Chemistry,
The Ohio State University
Columbus

1991-1994.................................................................Research Assistant, The
Ohio State University,
Columbus

PUBLICATIONS


FIELD OF STUDY

Major Field: Chemistry

Studies in Organic Chemistry
# TABLE OF CONTENTS

| DEDICATION | ........................................................................................................... | ii |
| ACKNOWLEDGEMENTS | ............................................................................................................... | iii |
| VITA | ............................................................................................................. | iv |
| TABLE OF CONTENTS | ........................................................................................................... | v |
| LIST OF TABLES | ............................................................................................................. | vii |
| LIST OF FIGURES | ............................................................................................................. | ix |
| LIST OF SCHEMES | ............................................................................................................. | xi |

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td></td>
</tr>
<tr>
<td>STUDIES DIRECTED TOWARDS THE SYNTHESIS OF CHRYSOMYCIN B</td>
<td></td>
</tr>
<tr>
<td>Statement of the Problem</td>
<td>.................................................................</td>
</tr>
<tr>
<td>Introduction to the Gilvocarcins: Structure and Isolation</td>
<td>......................</td>
</tr>
<tr>
<td>The Gilvocarcins: Biosynthesis and Biological Activity</td>
<td>.................</td>
</tr>
<tr>
<td>Recent Advances in the Synthesis of Defucogilvocarcins and C-Aryl Glycosides</td>
<td>..................</td>
</tr>
<tr>
<td>Suzuki's General Solution to the Gilvocarcins, Previous Studies Directed Towards the Synthesis of the Chrysomycins, and a Retrosynthetic</td>
<td>.....</td>
</tr>
</tbody>
</table>
Results and Discussion: Enol Assembly via Bimolecular Coupling

Methods ................................................................................................................21

The Ramberg-Backlund Reaction: An Intramolecular Approach to the
Solubility Problem .............................................................................................31

Experimental ........................................................................................................42

II. STUDIES DIRECTED TOWARDS THE SYNTHESIS OF CHRYSOMYCIN B

Nonclassical Behavior of 1,8-Disubstituted Naphthalenes and Related
Systems .............................................................................................................73

Peri Interaction: Nonclassical Behavior of 1,8-Disubstituted
Naphthalenes......................................................................................................74

Peri Interaction in the Gilvocarcins ....................................................................77

Results and Discussion ....................................................................................83

Selection of the O(1)-protecting group .............................................................99

Experimental ....................................................................................................104

III. X-RAY CRYSTALLOGRAPHY OF 1,8-DISUBSTITUTED NAPHTHALENES

Steric Effects in 1,8-Disubstituted Naphthalenes ...........................................144

Nucleophile-Electrophile Interactions in 1,8-Disubstituted
Naphthalenes ......................................................................................................146

Results and Discussion ....................................................................................150

Conclusion ..........................................................................................................168

Experimental ....................................................................................................171

LIST OF REFERENCES .........................................................................................182
APPENDICES

A. $^1$H and $^{13}$C NMR Spectra of Selected Compounds

186
LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data from Dunitz's 1,8-Disubstituted Naphthalenes</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Correlations to Twist Angle</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Gilvocarcin Family of Antitumor Antibiotics</td>
</tr>
<tr>
<td>2</td>
<td>BE-12406A and BE 12406B</td>
</tr>
<tr>
<td>3</td>
<td>Gilvocarcin V and Trioxsalen</td>
</tr>
<tr>
<td>4</td>
<td>Compounds Containing Essential Features for DNA Nicking</td>
</tr>
<tr>
<td>5</td>
<td>O-C Glycosylation Rearrangement Catalyst</td>
</tr>
<tr>
<td>6</td>
<td>Chrysomycin and Ravidomycin</td>
</tr>
<tr>
<td>7</td>
<td>Transition State for Cyclization of Enol 67</td>
</tr>
<tr>
<td>8</td>
<td>Merriman's Phosphonate</td>
</tr>
<tr>
<td>9</td>
<td>Alternative Ramberg-Backlund Method</td>
</tr>
<tr>
<td>10</td>
<td>1,8-Disubstituted Napthalenes</td>
</tr>
<tr>
<td>11</td>
<td>Alkylation-Dealkylation of Peri Dimethylamino Groups</td>
</tr>
<tr>
<td>12</td>
<td>Comparison of Hₐ in Styrene 166 and Propenylnaphthalene 165</td>
</tr>
<tr>
<td>13</td>
<td>Ground State Conformation of C-Glycoside 171</td>
</tr>
<tr>
<td>14</td>
<td>Stereoscopic View of 1,3,6,8-Tetra(tert)butynaphthalene (208)</td>
</tr>
<tr>
<td>15</td>
<td>1,2,3,4,5,6,7,8-Octamethylnaphthalene (209)</td>
</tr>
<tr>
<td>16</td>
<td>Naphthoic Acid (210)</td>
</tr>
<tr>
<td>17</td>
<td>Stereoview of 8-Methoxy-1-naphthyl methyl ketone (211)</td>
</tr>
</tbody>
</table>
Top View X-Ray of 1,8-Dimethylnaphthalene (212).............................................147
Depiction of Carbonyl Pyramidalization......................................................................148
Angle of Nucleophilic Attack.........................................................................................149
Depiction of Internuclear Distances ..........................................................................149
Displacement of Substituents from the Naphthalene Mean Plane ..................149
Comparison of Substitution Pattern in Aldehyde 75 and Dunitz's
Compounds........................................................................................................................151
Aldehyde 156....................................................................................................................152
ORTEP Plot of Edge On View of Aldehyde 178 Showing Aldehyde and ......
Methoxy Groups................................................................................................................153
Distances of Separation and Pyramidalization in 178 and 221
ORTEP Plot of Top View of Aldehyde 178.............................................................155
ORTEP Plot of Edge On View of Ketone 219 Showing Methoxy and Ketone
Groups...............................................................................................................................157
ORTEP Plot of Top View of Ketone 219.................................................................158
Edge On View of ORTEP Plot of Aldehyde 228 Showing Methoxy and
Aldehyde Groups............................................................................................................160
Top View of Aldehyde 228..........................................................................................161
Top View ORTEP Plot of Aldehyde 158...............................................................163
Edge On View of ORTEP Plot of Aldehyde 158 Showing Aldehyde and
Benzoate Groups.............................................................................................................164
Twist Angle (A) and Bond Length Parameters for Aldehyde Series..............165
Ketone and Aldehyde Analogs...............................................................................166
Nonnucleophilic 1,8-Disubstituted Naphthalenes........................................169
Side and Top Stereoviews of Gilvocarcin M..................................................170
# LIST OF SCHEMES

<table>
<thead>
<tr>
<th>SCHEME</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Biosynthesis of the Gilvocarcins</td>
</tr>
<tr>
<td>II</td>
<td>McGee's DNA Cleaving Experiment</td>
</tr>
<tr>
<td>III</td>
<td>Dave's Synthesis of C-Aryl Glycoside 22</td>
</tr>
<tr>
<td>IV</td>
<td>Parker's Synthesis of 1-O-Methyldefucogilvocarcin V</td>
</tr>
<tr>
<td>V</td>
<td>Martin's Approach to the Defucogilvocarcins</td>
</tr>
<tr>
<td>VI</td>
<td>Suzuki's Synthesis of Gilvocarcin M</td>
</tr>
<tr>
<td>VII</td>
<td>Suzuki's Synthesis of Gilvocarcin V</td>
</tr>
<tr>
<td>VIII</td>
<td>Merriman's Synthesis of Defucogilvocarcin M</td>
</tr>
<tr>
<td>IX</td>
<td>Studies Directed Towards the Synthesis of the Chrysomycins</td>
</tr>
<tr>
<td>X</td>
<td>Retrosynthetic Analysis of the Chrysomycins</td>
</tr>
<tr>
<td>XI</td>
<td>Merriman's Synthesis of Lactone 81</td>
</tr>
<tr>
<td>XII</td>
<td>Attempted Phosphonium Salt Synthesis</td>
</tr>
<tr>
<td>XIII</td>
<td>Proposed Formation Oxetane 93</td>
</tr>
<tr>
<td>XIV</td>
<td>Preparation of a Model for Julia Coupling</td>
</tr>
<tr>
<td>XV</td>
<td>Olefination Studies on Sulfone 97</td>
</tr>
<tr>
<td>XVI</td>
<td>Alternative Disconnection of Olefin 79</td>
</tr>
<tr>
<td>XVII</td>
<td>Preparation of Sulfone 103</td>
</tr>
<tr>
<td>XVIII</td>
<td>Sulfoxide Oxidative Elimination Route to Enol 98</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>XLIV</td>
<td>Synthesis of C-Naphthyl Glycoside 171</td>
</tr>
<tr>
<td>XLV</td>
<td>Mechanisms for Selenoetherification of 170</td>
</tr>
<tr>
<td>XLVI</td>
<td>Disconnection of 1-O-Methyl Chrysomycin B</td>
</tr>
<tr>
<td>XLVII</td>
<td>Functionalization of Naphthaldehyde 158</td>
</tr>
<tr>
<td>XLVIII</td>
<td>Carbohydrate Installation</td>
</tr>
<tr>
<td>XLIX</td>
<td>Installation of the D ring and C Ring Elements</td>
</tr>
<tr>
<td>L</td>
<td>Aldehyde 157 as a Building Block</td>
</tr>
<tr>
<td>LI</td>
<td>Formylation of Propargyl Ether 200</td>
</tr>
<tr>
<td>LII</td>
<td>MAD Mediated Conjugate Addition to Propargyl Ether 201</td>
</tr>
<tr>
<td>LIII</td>
<td>Evaluation of a 1-Trimethylsilylprop-2-yn-3-yl Ether Protecting Group</td>
</tr>
<tr>
<td>LIV</td>
<td>Preparation and Formylation of 206</td>
</tr>
<tr>
<td>LV</td>
<td>Preparation of Aldehyde 228</td>
</tr>
<tr>
<td>LVI</td>
<td>Synthesis of Olefin 229</td>
</tr>
</tbody>
</table>
CHAPTER I.

Studies Directed Towards the Synthesis of the Chrysomycins

Statement of Problem

The gilvocarcins are a family of promising antitumor antibiotic natural products isolated from various strains of streptomycetes. In some cases the fungi which produce the gilvocarcins lose the ability to do so after a relatively short period of time. Since the gilvocarcins are produced naturally in only milligram quantities, an efficient synthesis is desirable so that further biological testing can be evaluated. This dissertation describes efforts towards the synthetic preparation of chrysomycin B, one of the biologically active members of this family.

Introduction to the Gilvocarcins: Structure and Isolation.

The "gilvocarcins" are a family of antitumor antibiotic natural products produced by streptomycetes (curved fungus) which have recently attracted the attention of medicinal and synthetic chemists (Figure I). The gilvocarcins are structurally related and can be partitioned into three components; a polyaromatic aglycone (such as defucogilvocarcin) which embodies a rare glycocyl group at C(4), and a variable substituent at C(8) (methyl, ethyl, and vinyl are known).

Chrysomycins A (6) and B (7) were the first gilvocarcins isolated, found at the New York Botanical Garden in 1955. Their structures, however, remained unsolved for another 27 years. Identification of these C-glycosides was achieved only after isolation and structure elucidation of gilvocarcins V (3) and M (4) by comparison of spectral data. Ravidomycin (8) and gilvocarcin E (5) were discovered in 1981 by separate research laboratories. The aglycone defucogilvocarcin V (2) has also been obtained from natural sources.
More recently, the antitumor compounds BE-12406-A (9) and BE-12406B (10) were isolated from a culture broth of *streptomycetes*. These compounds differ from the gilvocarcins in that they are α-O-rhamnosides rather than C-aryl glycosides. In addition, the sugar is affixed to the C(12) oxygen rather than C(4). Nevertheless 9 and 10 are obvious relatives by virtue of the common 6H-benzo[de]naphtho[1,2b]pyran-6-one ring system.

In general, characterization of the gilvocarcins has not been routine. Six different melting points have been reported for gilvocarcin V, and these range from 220°C to 260°C. This particular problem has been ascribed to the hydration state of the sugar and more recently, to origin of the sample (gilvocarcins M, V, and E are coproduced by *streptomycetes* and separation...
is aridous). Poor solubility makes it difficult to crystallize gilvocarcins and their derivatives and in fact, gilvocarcin M (4) is the lone crystal structure which has been solved. Assignment of absolute stereochemistry has, therefore, been troublesome. Not until Suzuki reported enantioselective syntheses of gilvocarcins V (3) and M (4) starting from optically active L-fucose, could the respective configurations be assigned. The absolute stereochemistry of the chrysomycins (6 and 7) and ravidomycin (8) is still unknown.

The Gilvocarcins: Biosynthesis and Biological Activity.

Biological synthesis of the gilvocarcins is believed to follow the pathway outlined in Scheme I. A polyketide such as 11 is likely the forerunner of the gilvocarcins. Multiple aldol-dehydration cycles leads to the formation of a polyaromatic tetracycle 12. Although it was originally suggested that the C(8) side chain was present prior to polyketide condensation, labeling experiments performed by Takahashi and Tomita suggest this group is assimilated into a preconstructed core. A possible explanation for regiospecific delivery of the side chain is that keto-enol tautomeric equilibria favor a flexible nonenolized D ring as in 13 which avoids bay
region strain present in 12. Dehydration and decarboxylation of the side chain in aldol 14 yields tetracycle 15 that is subsequently transformed into diacid 16 via biological oxidative cleavage of the indicated carbon-carbon double bond. Decarboxylation of the resulting aryl-naphthol followed by carbon-carbon bond rotation completes assembly of the defucogilvocarcin aglycone exoskeleton (17) through lactonization.

Scheme I. Biosynthesis of the Gilvocarcins.
It has been postulated that the carbohydrate is attached to the electron rich A ring via electrophillic aromatic substitution in a subsequent step. This hypothesis is supported by the fact that defucogilvocarcin V (1) has been isolated from fermentation broths in the presence of gilvocarcin V.\textsuperscript{13}

Members of the gilvocarcin family have demonstrated antimicrobial, antiviral, prophage inducing, and antitumor activity.\textsuperscript{15} Another feature of interest is that mice are tolerant to relatively high concentrations (100-400 mg/kg) of these drugs in the bloodstream.\textsuperscript{16} As a consequence, the mode of action of the gilvocarcins has been the subject of numerous studies.\textsuperscript{17}

There is some evidence supporting a photo-initiated mechanism. This theory is supported by McGee's finding that "Gilvocarcin V intercalates into DNA in the dark" and that "strand nicking and covalent modification occur only in the presence of light".\textsuperscript{18} Indeed, irradiation of gilvocarcin V (3) with low energy ultraviolet light, in the presence of calf thymus DNA, leads to [2+2] cycloaddition of the C(8) vinyl moiety to thymidine residues (Scheme II). Syn 1,3-cyclobutane 19 was isolated as the major product in this experiment, while minor products contained a stereochemically identical cyclobutane, and a rearranged sugar.

\textbf{Scheme II. McGee's DNA Cleavage Experiment.}

![Scheme II](image-url)
These data are consistent with the following course of events. A C-glycoside intercalates into DNA such that the C(8) vinyl group is proximate to a thymidine residue. Subsequent exposure to low energy UV light induces cycloaddition of the thymidine and C(8) olefin. Single strand DNA cleavage follows, which liberates chemically altered DNA. Such a photodynamic paradigm is precedented by the action of psoralen, a family of light activated therapeutic agents containing a coumarin ring (20 in Figure 3). It is interesting to note that under optimum conditions of illumination for detection of psoralens, a side-by-side comparison of gilvocarcin V (19) and trioxsalen (20), showed gilvocarcin V to be detectable at concentrations $10^3$ lower, even though 20 has two potentially reactive sites (furan double bond and lactone double bond).

![Figure 3. Gilvocarcin V and Trioxsalen.](image)

In light of the proposed mechanism, the C(8) methyl compounds gilvocarcin M (4) and chrysomycin B (7) would be anticipated to be ineffective DNA cleaving agents. In fact, while gilvocarcin M has practically no activity, chrysomycin B (7) is reported to be active against lymphocytic leukemia in mice. A [2+2] cycloaddition trigger cannot explain the observed biochemistry in this system, and so any pharmacological properties of C(8) methyl compounds are probably derived from their ability to complex DNA. The role of the carbohydrate is less understood, but in the absence of a glycoside, it is known that DNA binding is not as efficient.
Therefore the aglycone is sufficient for activity, but at lower levels of activity than for the C-aryl glycosides.

**Recent Advances in the Synthesis of Defucogilvocarcins and C-Aryl Glycosides.**

Keen interest in biological properties and novel structural features germane to the gilvocarcins has played a role in the development of new methods in C-aryl glycoside synthesis.\(^2^4\) As a result, a number of syntheses of the defucogilvocarcins have been reported, along with one total synthesis of a gilvocarin type C-aryl glycoside. Since earlier work has been adequately reviewed, this section presents more recent activity in the area of synthesis of gilvocarcins and their aglycones.\(^2^5\)

One of two general approaches are usually adopted in C-aryl glycoside synthesis; direct connection of a carbohydrate onto an aromatic backbone, or *de novo* preparation of the C-glycoside. The foremost problem in each approach is stereocontrol of the anomeric position.

Daves' approach to C-aryl glycosides exemplifies the first technique.\(^2^6\) Gilvocardin analogs (21) and (22) were thus prepared by grafting a sugar onto an appropriate aglycone (Figure 3). In the synthesis of 21, stannic chloride catalyzed glycosylation of 23 with 1,2,3,5-HO

![Figure 4. Compounds Containing Essential Features for DNA Nicking.](image_url)
tetra-O-acetyl-D-ribose (24) followed by removal of the triisopropylsilyl group gave C-glycoside 25 in 60% yield as a 1:1 mixture of anomers as shown in equation 1. Higher anomeric selectivity was achieved at -40°C (α:β = 5:1), but unfortunately the product mixture could not be isolated as such under these conditions.

The critical bond in compound 22 was constructed via palladium mediated coupling of iodoaglycone 26 to glycal 27 (Scheme III). Silyl ether 28 was hydrolyzed in the same pot (tetrabutylammonium fluoride-acetic acid) to give furanone 29. Elaboration of C-glycoside 22 was completed via directed reduction of 29 with sodium triacetoxyborohydride, minimal purification, and pivalate cleavage to afford 22 in 91% yield. Although palladium mediated bimolecular coupling was successful in the system in Scheme III, successful implementation in a total synthesis of a gilvocarcin type C-glycoside has not been described. Polyhalogenation problems arise during C(4) halogenation of a fully functionalized defucogilvocarcin. Nonetheless, compounds 21 and 22 represent gilvocarcin prototypes containing the essential features for photolytic cleavage of DNA.

In collaboration with the Upjohn Company, Parker and Coburn have reported a route to ρ-hydroxy C-aryl glycals via reductive aromatization of quinols (equation 2). With the latent sugar acting as the nucleophile, addition of lithiated glycal 30 to naphthoquinone (31) followed by reductive aromatization using aluminum amalgam afforded naphthol glycal 32 in 88% yield.
Scheme III. Daves' Synthesis of C-Aryl Glycoside 22.

Pd(OAc)$_2$, NaOAc, n-Bu$_3$N, DMF;

\[
\text{t-Bu(Ph)$_2$SiO'^{27}} ^{27} \rightarrow \text{NaBH(OAc)$_3$} \rightarrow \text{Na/MeOH} \]

\[
\text{28} \rightarrow \text{n-Bu$_4$NF, AcOH 88%} \rightarrow \text{29}
\]

\[
\text{22} \rightarrow 1) \text{NaBH(OAc)$_3$} \rightarrow 2) \text{Na/MeOH}
\]

1) \[
\text{OTBS} \rightarrow \text{TBSO}, \text{Me} ^{, 0} \rightarrow \text{Li} \rightarrow \text{Al(Hg), THF/H$_2$O \Delta, 22h 88%}
\]

\[
\text{31} \rightarrow 2) \text{Al(Hg), THF/H$_2$O \Delta, 22h 88%} \rightarrow \text{32}
\]
This “reverse polarity” approach to carbohydrate introduction complements the Fischer carbene-aryl acetylene annelation developed by the same authors as potential means of assembling defucogilvocarcin tetracycles (Scheme IV). Methoxyphenyl chromium carbene complex 34 was generated from o-bromoanisole (33). At the annelation stage, refluxing a mixture of 34 and substituted phenylacetylene 35 in heptane produced tricyclic aryl naphthol 36 in 43% yield in a single step. Lactone formation was accomplished using p-toluenesulfonic acid in benzene which afforded 1-O- methyldefucogilvocarcin V (37) in 95% yield.

Scheme IV. Parker’s Synthesis of 1-O-Methyldefucogilvocarcin V.

An efficient method for converting substituted naphthols into defucogilvocarcin tetracycles was described by Martin and coworkers in a short synthesis of the defucogilvocarcin M (3) and E
Readily available benzylated juglone (38) was reductively acetylated to naphthol 39 in 80% yield, and then transformed to 40 in 58% yield using the method of Giles. Installation of the CD-ring system was accomplished using an intramolecular biaryl synthesis protocol. DCC coupling attached trisubstituted benzoic acid 41 to naphthol building block 40, thus securing benzoate 42 in 79% yield. Intramolecular palladium mediated coupling (79%) then completed the two ring annelation. This was a formal synthesis of defucogilvocarcin E (5), since the debenzylation of 43 had been described previously.

Scheme V. Martin’s Approach to the Defucogilvocarcins.
Suzuki's General Solution to the Gilvocarcins, Previous Studies Directed Towards Synthesis of the Chrysomycins, and a Retrosynthetic Analysis of Chrysomycin B.

Martin's two ring anellation was later exploited by Suzuki in a brilliant synthesis of the gilvocarcins (Scheme VI). To date, Suzuki's synthesis is the only total synthesis of a gilvocarcin-type C-aryl glycoside.

Screening of a number of O-C glycoside rearrangement catalysts revealed that a dicyclopentadienylhalfnium dichloride-silver perchlorate system could be used to directly couple carbohydrate 44 to trisubstituted phenol 45 enjoying contrathermodynamic stereoselectivity and ortho regiospecificity. Even higher levels (26:1) of diastereoselection were observed when norbornylsilane 54 was employed as the catalyst (Figure 5). Elaboration of the aromatic region was achieved in a straightforward manner. Phenol 46 was converted to triflate 47 which permitted regiospecific benzyne generation using a metal-halogen exchange trigger. Under these conditions, the lifetime of the intermediate benzyne was sufficient to undergo a Diels-Alder reaction with 2-methoxyluran (48), thus provided naphthol 49 in 88% yield upon quenching with 2N HCl. Although DCC coupling failed with C-naphthyl glycoside 49, complete assembly of the defucogilvocarcin tetracycle could be realized by way of acid chloride 50. Acylation of 49 thus gave benzoate 51 in 91% yield, and application of the Martin protocol afforded fully assembled polyaromatic tetracycle 52 in 90% yield. Exhaustive debenzylation with Raney nickel over a 3 day period furnished gilvocacin M (4) (72%).

Figure 5. O-C Glycosylation Rearrangement Catalyst.

In the synthesis of gilvocacin V, installation of the C-D ring system required some functional group manipulation since the C(8) vinyl substituent would not survive the debenzylation
Scheme VI. Suzuki's Synthesis of Gilvocarcin M.

\[
\begin{align*}
\text{44} & \xrightarrow{\text{Cp}_2\text{HClO}_2,} \text{AgClO}_4 \xrightarrow{\text{CH}_2\text{C}_2, -78\degree -20\degree} \text{45} \\
\text{45} & \xrightarrow{o\text{BuLi, THF,} -78\degree} \text{46} \\
\text{46} & \xrightarrow{\text{Ti}^2\text{O, iPr}_2\text{NEt,} \text{CH}_2\text{C}_2, -78\degree} \text{47}
\end{align*}
\]

87%, \(\alpha:\beta = 8:1\)

\[
\begin{align*}
\text{48} & \xrightarrow{n\text{BuLi, THF,} -78\degree} \text{49} \\
\text{49} & \xrightarrow{i\text{Pr}_2\text{NEt,} \text{4-DMAP, THF}} \text{50} \\
\text{50} & \xrightarrow{(\text{Ph}_3\text{P})_2\text{PdCl}_2, \text{NaOAc, DMA} 125\degree} \text{51} \\
\text{51} & \xrightarrow{\text{H}_2, \text{Raney Ni, EtOH}} \text{52}
\end{align*}
\]

90%, 72%
Scheme VII. Suzuki's Synthesis of Gilvocarcin V.

1. **Chemical Reactions:**
   - **Step 1:** 
     - **Reagent:** EDCI, 4-DMAP, Et₂O
     - **Product:** 54
     - **Yield:** 83%
   - **Step 2:**
     - **Reagents:** 27 mol % (Ph₃P)₂PdCl₂, NaOPiv, DMA, 80°C
     - **Product:** 55
     - **Yield:** 65%
   - **Step 3:**
     - **Reagents:** H₂, Raney Ni, EtOH
     - **Product:** 56
     - **Yield:** 68%
   - **Step 4:**
     - **Reagents:** TMSBr, CH₂Cl₂, -78°C to -10°C
     - **Product:** 57
     - **Yield:** 94%
   - **Step 5:**
     - **Reagent:** NO₂, SeCN, Bu₃P, THF
     - **Product:** 58
     - **Yield:** 95% for two steps
   - **Step 6:**
     - **Reagents:** NaOMe, MeOH
     - **Product:** 3
     - **Yield:** 71%

2. **Chemical Structures:**
   - **Molecules 49-58**
   - **Scheme Diagram:**
     - **Scheme Details:**
       - **1.** Reaction with EDCI and 4-DMAP, Et₂O to form 54.
       - **2.** Reaction with 27 mol % (Ph₃P)₂PdCl₂, NaOPiv, DMA, 80°C to form 55.
       - **3.** Reduction with H₂, Raney Ni, EtOH to form 56.
       - **4.** Reaction with TMSBr, CH₂Cl₂, -78°C to -10°C to form 57.
       - **5.** Reaction with NO₂, SeCN, Bu₃P, THF to form 58.
       - **6.** Neutralization with NaOMe, MeOH to form 3.
conditions (Scheme VII). Furthermore, acylation of 49 was carried out with the water soluble carbodiimide, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), with catalytic 4-DMAP. Under these conditions and employing 6 equivalents of carboxylic acid 54, benzoate 55 was obtained in 83% yield. Unfortunately, the ortho triflate in 55 rendered the ester group highly labile. Hydrolysis of this C-O linkage occurred when 55 was simply heated in the presence of acetate buffer at 100-120°C. To alleviate this problem, the sterically hindered base sodium pivalate was employed as a substitute for sodium acetate. Under these conditions, tetracycle 56 was obtained in 65% yield. Saponification problems persisted, however, and 21% of starting material was also recovered. Benzyl ether 56 was converted to tetraacetate 57 in 68% yield through a debenzylation-acetylation sequence. The task of generating the C(8) vinyl moiety was accomplished by sequential removal of the MOM groups with bromotrimethylsilane in dichloromethane (94%), conversion to an aryl selenide with o-nitrophenyl selenocyanate, and oxidative elimination with 35% hydrogen peroxide (95% for the final two steps). Removal of the acetate protecting groups with sodium methoxide completed the synthesis of gilvocarcin V (3) (71%).

The Hart groups forayed into gilvocarcin studies included a total synthesis of defucogilvocarcin M developed by Merriman (Scheme VII).  In the key bond forming step, MAD mediated conjugate addition of lithiated aryloxazoline 60 to naphthoquinone monoketal 59 gave conjugate adduct 61 in 72% yield. Hydrolysis of the ketal and oxazoline protecting groups was accompanied by dual enolization and subsequent lactonization leading to tetracycle 62. Conversion of 62 to defucogilvocarcin M (2) was accomplished by methylation of the highly hindered C(12) oxygen (heating with dimethyl sulfate at reflux for 72h) followed by reductive deprotection of the benzyl ether (83%).

Our interest in C-aryl glycoside synthesis arose from findings that 6-aryl-5-hexen-2-ols underwent electrophile initiated cyclization to afford 2-aryl pyrans with good control over relative stereochemistry at C(2), C(3), and C(6) (Equations 3 and 4). Thus β-lactam 65 gave bicycle 66
and styrene 67 selectively cyclized to pyran 68 when treated with phenyl selenenyl chloride under conditions of kinetic control.
The idea of using stereocontrolled ring closure as a means of dictating stereochemistry at the anomeric position in the chrysomycins (6 and 7) and ravidomycin (8) was attractive. Unfortunately, it was found that conversion of β-lactam 64 into the tetrahydropyran component of ravidomycin suffered from problems with introducing the C(5) acetate. On the other hand, enol 67 served nicely in model studies directed towards the chrysomycins (Scheme VIII). Selenoetherification of 67 under kinetic conditions selectively generated pyran 68. Under kinetic control it is believed that the favored transition state for this cyclization is a chair in which steric interactions are minimized. Thus the bulkier alkyl groups occupy equatorial sites through the cyclization (Figure 6). Oxidative elimination of the resulting aryl selenide occurred regiospecifically away from the heteroatom, giving rise to glycal 71. The final two oxygenated stereocenters in the chrysomycin model were introduced via osmium tetroxide mediated diol formation, giving 70 as a single diastereomer. The success of the osmylation is consistent with osmium attacking from the less hindered face of the double bond. Diol 70 was converted into...
chrysomycin model 71 in 69% yield via hydrolysis of the methoxymethyl acetal.

Meriman's attempt to combine the aforementioned C-aryl glycoside and defucogilvocarcin studies in a synthesis of chrysomycin B was unsuccessful (Scheme IX).\textsuperscript{42} MAD mediated conjugate addition of 60 to naphthoquinone monoketal 72 was less successful than in the O-benzyl system affording conjugate adduct 73 in moderate yield. Acid hydrolysis of
Scheme IX. Merriman's Chrysomycin Studies.

1) NaBH₄CN, 91% THF, pH~4

2) PBr₃, 81%

MAD, Toluene
-78°C

1) K₂CO₃, Me₂SO₄, Acetone, Δ

2) Cl₂CHO⁻Me, TiCl₄, CH₂Cl₂

83%

N. R.
73 generated pyranone 74 which was methylated with potassium carbonate and dimethyl sulfate in acetone. Formylation of 74 was highly regioselective giving rise solely to aldehyde 75. Chemoselective reduction of the aldehyde was accomplished with sodium cyanoborohydride in acidic media, and the resulting alcohol was converted to bromide 76 using phosphorus tribromide in benzene. Arbuzov rearrangement of 76 occurred under standard conditions to afford phosphonate 77 in good yield. However, the synthesis broke down at this stage when Horner-Emmons reagent 77 would not react with hemiacetal 78.

Failure to couple 77 and 78 prevented meaningful elaboration of the C(4) substituent, which thus rendered Merriman's route to C-aryl glycosides ineffective. However, the ease with which aldehyde 75 had been assembled encouraged us to continue pursuit of the chrysomycins along a similar route employing the "reversed Wittig" approach depicted in Scheme X. The

Scheme X. Retrosynthetic Analysis of the Chrysomycins.
success in converting enol 67 to C-aryl glycoside 71 (Scheme VIII) led us to project that enol 79 could be converted to chrysomycin B (7). In the new route 79 was to be prepared directly from aldehyde 77 by coupling with phosphorous ylid 80. We believed 80 would be available via elementary functional group manipulations of cis-substituted furanone 80, which had already been prepared.43

Results and Discussion: Enol Assembly via Bimolecular Coupling Methods:

To begin our studies, lactone 81 was prepared by scaling up Merriman’s sequence from hydroxy ester 82, previously prepared by Chamberlin (Scheme XI).44 Stereoselective methylation of aldol 82 was followed by ester hydrolysis to afford carboxylic acid 84. Iodolactonization of 84 on large scale was less successful than in Merriman’s studies, but still gave 85 as a single diastereomer. Reduction of 85 with tri-n-butyltin hydride afforded cis-

Scheme XI. Merriman’s Synthesis of Lactone 81.
furanone 86 in 88% yield, and protection of the free hydroxyl group as a MOM acetal completed assembly of lactone 81.

It was next necessary to convert cyclic 81 to the open chain ylid 80 shown in Scheme X. Unfortunately, each step in this scheme was problematic. Lactone 81 was reduced with lithium aluminum hydride as shown in equation 5 (less than 15 min at 0°C), but the polar, low molecular weight nature of resulting diol 87 made isolation and removal of water difficult. The use of a minimum of aqueous ammonium chloride in the workup, and distillation of the final product from calcium sulfate or powdered 4 Å molecular sieves was necessary.

\[
\begin{align*}
\text{81} & \xrightarrow{\text{LAH, THF}} \text{87} \\
& \quad \quad \quad \text{94%} \\
\end{align*}
\]

Having acquired 87, regiospecific conversion of the primary hydroxyl group into its derived tosylate was undertaken. Unfortunately, intramolecular displacement problems stemming from

\[
\begin{align*}
\text{87} & \xrightarrow{\text{TsCl, E_t}_3\text{N., 4-DMAP, rt}} \text{87} + \text{88} + \text{89} \\
& \quad \quad \quad \text{53%} + \text{27%} + \text{20%} \\
\text{89} & \xrightarrow{\text{TBSCI, imid. CH}_2\text{Cl}_2, 0 \degree \text{C}} \text{88} + \text{90} \\
& \quad \quad \quad \text{72%} + \text{28%} \\
\end{align*}
\]
the unprotected C(4) hydroxyl group beleaguered this transformation. Exposure of \textbf{87} to \textit{p}-toluenesulfonyl chloride and triethylamine at room temperature gave the desired tosylate \textbf{89} in poor yield at best, and produced tetrahydrofuran \textbf{88} in greater amounts (Equation 6). Protection of \textbf{89} as a \textit{t}-butyldimethylsilyl ether led to further complications resulting from cyclization (Equation 7). The shelf life of \textbf{89} was less than 24 hours at room temperature.

To minimize time manipulating labile \textbf{89}, a one-pot preparation of \textbf{90} from diol \textbf{87} was developed. Tosylate \textbf{87} was thus generated \textit{in situ}, and then exposed to a fivefold excess of \textit{t}-butyldimethylsilyl chloride. The result was a 70\% yield of silyl ether \textbf{90} (Equation 8).

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{OMOM}
\end{align*}
\]

\[\text{1. p-TsCl, Et$_3$N} \quad \text{4-DMAP, 0°C}
\]

\[\text{2. 5 eq. TBSCI, imidazole, 5 °C}
\]

\[\text{70%}
\]

\[
\begin{align*}
\text{87} & \quad \text{1. p-TsCl, Et$_3$N} \quad \text{4-DMAP, 0°C} \\
\text{Me} & \quad \text{Me} \\
\text{OMOM} & \quad \text{TBSO}
\end{align*}
\]

\[
\begin{align*}
\text{88} & \quad \text{Me} \\
\text{OMOM} & \quad \text{OTos}
\end{align*}
\]

Unfortunately, an efficient synthesis of protected tosylate \textbf{90} was only part of the problem. When the preparation of phosphonium salt \textbf{92} was attempted, neither tosylate \textbf{90} nor iodide \textbf{91} (obtained by the Finkelstein reaction shown in Scheme XII) underwent displacement by triphenylphosphine. Heating tosylate \textbf{90} with triphenylphosphine gave a plethora of products, and when iodide \textbf{91} was used, heating with triphenylphosphine in DMF at reflux led to a 37\% yield of oxetane \textbf{93} (Scheme XIII). Steric hinderance created by \textit{β}-branching was apparently sufficient to impede approach of the incoming nucleophile and, in the latter reaction, the pathway described in Scheme XIII was presumably followed.
Scheme XII. Attempted Phosphonium Salt Synthesis.

\[
\begin{align*}
\text{TBSO} & \quad \text{Me}^+ \quad \text{OTos} \\
\text{Me} & \quad \text{OMOM} \\
90 & \quad \xrightarrow{\text{Nal, acetone}} \quad 94\% \\
\end{align*}
\]

\[
\begin{align*}
\text{TBSO} & \quad \text{Me}^+ \quad \text{P(Ph\textsubscript{3})}^+ \quad \text{Tos}^- \\
\text{Me} & \quad \text{OMOM} \\
92 & \\
\end{align*}
\]

Scheme XIII. Proposed Formation of Oxetane 93.

\[
\begin{align*}
\text{TBSO} & \quad \text{Me}^+ \quad \text{I} \\
\text{Me} & \quad \text{OMOM} \\
91 & \quad \xrightarrow{\text{Ph\textsubscript{3}P, DMF, 165}^\circ\text{C}} \quad 37\% \\
\end{align*}
\]

\[
\begin{align*}
\text{TBSO} & \quad \text{H}^+ \quad \text{O} \\
\text{Me} & \quad \text{Me} \quad \text{Me} \\
93 & \\
\end{align*}
\]

\[
\begin{align*}
\text{TBSO} & \quad \text{Me}^+ \quad \text{I} \\
\text{Me} & \quad \text{OMOM} \\
94 & \quad \xrightarrow{\text{H}_3\text{C}-\text{O}^+} \quad 95 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph\textsubscript{3}P} & \\
\end{align*}
\]
At this point, the latent sugar component had all but eliminated the use of a Wittig reaction to fuse this piece onto the aglycone. Of the potential alternate methods, Julia coupling was attractive because preparation of the necessary glycosyl substrate was most feasible. Thus it was felt that where nucleophilic introduction of phosphorous had failed, thiophenoxide would fare better.

A model β-hydroxysulfone for Julia coupling studies was obtained as shown in Scheme XIV. Tosylate 90 underwent displacement by thiophenoxide to produce sulfide 95 in 96% yield. Oxidation of sulfide 95 to sulfone 96 was accomplished with buffered m-CPBA furnishing 96 in 88% yield. Reaction of the derived anion of 96 with p-anisaldehyde gave a 91% yield of model β-hydroxy sulfone 97 as a mixture of four isomers.

Scheme XIV. Preparation of a Model for Julia Coupling.

\[
\begin{align*}
90 & \xrightarrow{\text{TBSO PhSH, NaH, DMF}}^97\% 95 \\
96 & \xrightarrow{m\text{-CPBA}, CH_2Cl_2, 88\%} 97
\end{align*}
\]
Scheme XV outlines the methods surveyed for stereoselective conversion of sulfone 97 into an E-alkene employing Julia's method. Acylation of 97 followed by reductive elimination of the resulting acetates afforded trans isomer 98 in 32% yield. Alternatively, sodium amalgam promoted reductive elimination of β-hydroxysulfone 97 to give a 64% yield of alkenes on micromolar scale. In addition to poor stereoselectivity (cis:trans = 1:2), however, this method suffered from long reaction times and incomplete conversion of starting material when conducted on larger scales. A better elimination was obtained via the derived O-benzoates. Treatment of the lithium alkoxide derived from 97 with benzoyl chloride afforded an 84% yield of olefin 98, after elimination. In this case an 8:1 mixture of E and Z isomers respectively was obtained (based on $^1$H NMR integration), which could be increased to 34:1 using a free radical isomerization of the double-bond (Equation 9).

Scheme XV. Olefination Studies on Sulfone 97.
Encouraged by the results of the test substrate, we attempted to couple sulfone (96) to formylated aglycone 75. In contrast, these compounds could not be condensed (Equation 10). In fact, aldehyde 75 would not react with the anion of phenyl methyl sulfone, methylidene triphenylphosphorane, or other nucleophiles. Although 75 was a solid, we were unable to identify any derivatives suitable for X-ray analysis. The inert behavior of 75 is probably a function of four factors: (1) seriously adverse solubility properties, (2) triple deactivation by methoxy groups, (3) steric hinderance incurred by the lactone, and (4) an intramolecular nucleophile-electrophile interaction between the lactone oxygen and aldehyde carbonyl.
With respect to the solubility issue, dichloromethane and chloroform provided the highest levels of solubility \( (5 \times 10^{-4} \text{ M}) \). In addition to halocarbons, hot diphenyl ether was the only other solvent in which 75 was soluble. Solubility approached zero for aromatic (toluene, benzene), dipolar aprotic (DMSO, DMF, HMPA.), and ethereal (diethyl ether, tetrahydrofuran) solvents. Solubility was also unaffected by the addition of mild Lewis acids such as \( \text{Ti}(i\text{-OPr})_4 \), and it was suspected that stronger acids would attack the sugar. It was not established that solubility was solely responsible for the reactivity dilemma. After all, Merriman had reduced this substrate in aqueous THF. However, the peculiar reactivity of this substrate served as a launching point for the studies conducted in Chapter 3, and is briefly addressed in the introductory portion of Chapter II.

In an effort to bypass the exceptional unreactivity of 75, we turned to regioselective removal of the 1-O-methyl group. It was anticipated that nucleophilic dealkylation would favor removal of this methyl group by virtue of its stabilization via through resonance conjugation with the aldehyde. A successful dealkylation would potentially allow introduction of a “solubilizing” protecting group at O(1). Unfortunately, boiling 75 with sodium thioethoxide in DMF produced unidentifiable material. In summary, the only useful reaction the intended key intermediate 75 has undergone to date has been acid promoted reduction with sodium cyanoborohydride. Unfortunately, this last result confirmed that the ramifications of our original Julia model did not transfer to the delucogilvocarcin system.

At this point, failure of the Julia coupling necessitated investigation of alternate modes for constructing a “bridging” olefin. Although aldehyde 75 was useless as a coupling component, the reduction and bromination reactions described by Merriman in Scheme IX offered some potential alternatives. \textit{A priori}, the inverse polarity approach outlined in Scheme XVI was devised. A nucleophilic aglycone was to be fastened to the latent carbohydrate in the form of an aldehyde. In support of this process, Merriman had reported the anion of phosphonate 77 to be soluble in tetrahydrofuran (Figure 7). To ensure that coupling was achieved, however, we elected to use a hard sulfonyl anion. Disconnection of target enol 79, with this in mind, revealed the retrons shown in Scheme XVI. Aldehyde 99 had been previously prepared by the author, and it was believed that sulfone 100 could be obtained from bromide 76 via an S_N2 displacement.\textsuperscript{46}
Investigation of this proposal, using benzylic sulfone 103 as a model, was short-lived, however. Treatment of chloride 101 with DBU and thiophenol gave sulfide 102 in 94% yield, and the sulfur was smoothly oxidized to the sulfone oxidation state with "oxone" in aqueous methanol, thus providing 103 in 97% yield. The downfall of this route came when treatment of the anion of 103 with aldehyde 99 resulted in β-elimination of the methoxymethoxy group (Equation 11). Although elimination gave rise to a single double-bond isomer, no effort was made to determine the alkene geometry.

Unfortunately, our method of carbohydrate synthesis was not amenable to installation of the C(3) oxygen subsequent to condensation. As a consequence, all methods involving
nucleophilic addition to aldehyde 99 were eliminated as possible avenues. Once again an insurmountable roadblock forced us to rethink our plans for double bond introduction.

Therefore we reexamined sulfone 97. Although this compound did not react with aglycone 75, it did add to p-methoxybenzaldehyde in good yield, which suggested that it would alkylate benzylic halides well. It was anticipated that elimination of the phenylsulfonyl group from such an alkylation product would regioselectively favor an olefin conjugated with the aromatic ring. Therefore the anion of 97 was generated using the conditions prescribed for Julia coupling, and alkylated with p-methoxybenzyl chloride. Although the low yield of alkylation product could probably have been improved, this point was moot since expulsion of the phenylsulfonyl group could not be achieved (Equation 12). Despite the arylsulfonyl elimination problems with 105, the successful alkylation step immediately directed our
attention to the structurally related sulfoxide (Scheme XVIII). Oxidation of sulfide 96 with one molar equivalent of m-CPBA thus afforded sulfoxide 106 as mixture of diastereomers at sulfur. The derived anion of 106 was alkylated with p-methoxybenzyl chloride followed by heating in refluxing toluene to give olefin 98 in 56% yield as a 1:1 mixture.

With this result in hand, we attempted to alkylate sulfoxide 106 with polyaromatic bromide 76. We were optimistic about bond formation at this site since Arbuzov rearrangement of 76 with triethylphosphite had proceeded well (Scheme IX). It appeared that the only question was how well 76 would react with carbon nucleophiles as opposed to phosphorous nucleophiles. Unfortunately, alkylation of the sulfoxide required use of polar aprotic solvents, and these conditions led to immediate destruction of bromide 76. The proximity of the lactone oxygen and bromomethylene groups could possibly cause intramolecular alkylation problems, however, no polyaromatic degradation products could be isolated, only sulfoxide 106.

The Ramberg-Backlund Reaction: An Intramolecular Solution to the Solubility Problem.

The failure of sulfoxide 106 to undergo alkylation with bromide 76 underscored the difficulties associated with the bond construction we had chosen. It was clear that a fundamentally different approach to carbohydrate connection was needed. Bromide 76 appeared to be a useful coupling component but was sparingly soluble in nonpolar solvents and did not survive in polar media. The fact that 76 was reactive at all, however, suggested that reactions could be negotiated at the C(4) substituent under the right circumstances. On the other hand,
Scheme XVIII. Sulfoxide Alkylative Elimination Route to Enol 98.

\[
\begin{align*}
\text{TBSO} & \quad \text{Me} & \quad \text{OMOM} & \quad \text{95} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{SPh} \\
& \quad \text{m-CPBA}, \text{NaHCO}_3 & \quad \text{CH}_2\text{Cl}_2 & \quad \text{-78°C} & \quad 90\% & \quad \text{90}\% \\
& \quad \text{95} & \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{TBSO} & \quad \text{SPh} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{n-BuLi, THF} & \quad \text{HMPA} & \quad \text{-78°C-rt} & \quad \text{90}\% & \quad \text{48}\% \\
& \quad \text{Me} & \quad \text{OMe} \\
& \quad \text{TBSO} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{98} & \quad \text{65}\% & \quad \text{(E:Z = 1:1)} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{TBSO} & \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{OMe} \\
& \quad \text{TBSO} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{98} & \quad \text{65}\% & \quad \text{(E:Z = 1:1)} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{BDMSO} & \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{OMe} & \quad \text{Me} & \quad \text{OMe} \\
& \quad \text{Br} & \quad \text{O} & \quad \text{Me} \\
& \quad \text{MeO} & \quad \text{OMe} & \quad \text{OMe} \\
& \quad \text{t-BDMSO} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{Me} & \quad \text{OMOM} & \quad \text{Me} \\
& \quad \text{n-BuLi, THF} & \quad \text{HMPA} & \quad \text{-78°C-rt} & \quad \text{Resinification (13)} \\
& \quad \text{96} & \quad \text{76} \\
\end{align*}
\]
replacement of the C(4) bromomethylene with a formyl group gives rise to aldehyde 75, which was inert. At the heart of this reactivity dichotomy was the solubility issue. By removal of this one factor, conclusions could be drawn with respect to the magnitude of steric repulsion from the C(4) lactone oxygen, and possibly allow determination of whether a 1,8-nucleophile-electrophile interaction existed in aldehyde 75.

Therefore we focused on assembling enol 79 through an intramolecular process. In this scenario, unless the reactant were completely insoluble, the requirement of finding a reaction partner would be met intramolecularly.

The fact that a carbon-phosphorus bond had been established at the site for sugar connection suggested that other carbon-heteroatom bonds could be generated. Introduction of the carbohydrate subunit was therefore to be executed via temporary connection to a heteroatom. Extrusion of sulfur dioxide via the Ramberg-Backlund rearrangement has long been recognized as a dependable method of olefination, and so a sulfur atom seemed particularly well suited for acting as the "lynchpin". Furthermore, Ramberg-Backlund reactions involving stabilized sulfone carbanions such as benzyllic sulfones, favor the production of E-alkenes. While the problems associated with olefin geometry had been trivialized at this point by the failure to construct any type of carbon-carbon bond, trans stereochemistry was necessary for stereoselective selenoetherification at a later stage. Consideration of these criteria led to the retrosynthetic analysis of 79 depicted in Scheme XIX. The assemblage of 108 was expected to follow from sulfide 109, which was to be prepared from a reaction between thiol 110 and bromide 76.

To evaluate E-selectivity in the proposed Ramberg-Backlund reaction, model sulfone 113 was prepared from iodide 91 (Scheme IX). Introduction of sulfur was accomplished by reacting 91 with a DBU-thioacetic acid slurry, thus affording an 89% yield of thioester 111. The Finklestein reaction leading to 91 from tosylate 90, however, was capricious and necessitated the development of a more dependable route to the thioester. Originally, displacement reactions of tosylate 90 had been sluggish and turned our attention to more reactive 91. It was discovered, however, that the DBU salt of thioacetic acid reproducibly displaced the tosyl moiety when performed in DMF (8h reaction time). Reduction of 39 with lithium aluminum hydride
subsequently liberated foul smelling thiol 40 in 91% yield. This valuable compound coupled to p-methoxybenzyl chloride to give sulfide prototype 112 in 82% yield. Oxidation of 112 to sulfone 113 was best accomplished with m-CPBA delivering benzylic sulfone 113 in 87% yield. On occasion, it was necessary to conserve the asymmetric glycosyl component. In these instances sulfide 112 was prepared as shown in Scheme XXI. Heating an ethanolic solution of p-methoxybenzyl chloride with thiourea followed by saponification of the intermediate thiouronium salt afforded a 62% yield of benzyl mercaptan 114. Coupling of this material to iodide 91 gave
Scheme XX. Preparation of Thiol 110.

\[
\begin{align*}
\text{TBSO} & \quad \text{Me} \quad \text{MOMO} \\
\text{Me} & \quad \text{I} & \quad \text{DBU, C}_6\text{H}_6 & \quad \text{MeCOSH} \quad 89\% \\
\text{91} & \quad \text{TBSO} & \quad \text{Me} \quad \text{MOMO} \\
\text{Me} & \quad \text{SH} & \quad \text{LAH, THF} \quad 100\% \\
\text{111} & \quad \text{TBSO} & \quad \text{Me} \quad \text{MOMO} \\
\text{Me} & \quad \text{CH}_2\text{Cl} & \quad \text{DBU, C}_6\text{H}_6, \quad 82\% \\
\text{110} & \quad \text{CH}_2\text{Cl} & \quad \text{DBU, C}_6\text{H}_6, \quad 82\% \\
\text{113} & \quad \text{m-CPBA, NaHCO}_3, \text{CH}_2\text{Cl}_2 & \quad 87\% \\
\text{112} & \quad \text{MeO} \quad \text{Me} \quad \text{OMOM} \\
\text{Me} & \quad \text{OMOM} \quad \text{Me} \quad \text{TBSO} \\
\end{align*}
\]

sulfide 112 in 74% yield.

The Ramberg-Backlund rearrangement of 113 was not without problems. Monohalogenation of sulfone 113 following the Regis-Doweyko protocol was unsuccessful.\textsuperscript{49} This procedure is claimed to be catalytic in hydroxide, but in our hands the use of one equivalent of reagent led to the formation of dibromide 116 and recovery of roughly one half of the starting material (Equation 13). Further addition of sodium hydroxide dibrominated the remaining starting material, and then triggered a Ramberg-Backlund reaction (TLC analysis). Crude \textsuperscript{1}H NMR suggested that the olefin-containing rearrangement products were a mixture of E and Z isomers.
Scheme XXI. Alternate Preparation of Sulfide 112.

A more palatable result was obtained when lithium hexamethyldisilazane was used as the base. When the anion of 113 was generated with this reagent and then added dropwise to a vigorously stirred slurry of NBS in tetrahydrofuran, a 2:1 mixture of monobrominated 116a and starting material was obtained (crude $^1$H NMR). Exposure of the resulting mixture to potassium tert-butoxide in THF produced isolable E-olefin 98 in 40% yield for two steps. No Z-isomer was detected.

We next attempted to attach thiol 110 to the unpredictable gilvocarcin aglycone. Thiol 110 coupled to bromide 76 which delivered sulfide 117 in 72% yield. As projected, the incorporation of a greasy sidechain favorably altered the solubility properties of 117. Sulfide 117 was soluble in dichloromethane, tetrahydrofuran, benzene and other typical organic solvents.
Scheme XXII. The Ramberg Backlund Reaction in a Model System.

Oxidation of 117 was carried out with 2 equivalents of m-CPBA, providing extrusion precursor 118 in 85% yield.

In contrast to the benzylic model, when monohalogenation conditions were employed with sulfone 118, only starting material was recovered. A variety of sulfone to olefin conversions were then probed, in each case meeting with failure. Attempted cupric chloride mediated sulfonyl dianion oxidation was met with the recovery of starting material. Examination of the Regis-Doweyko method was precluded by the lability of sulfone 118 to polar aprotic media. The action of freshly ground KOH, CCl₄, and tert-butanol on 118 was subsequently examined. This led to the isolation of aldehyde 75 and an uncharacterized compound tentatively assigned the sulfonic acid structure in Scheme XXIII (based on ¹H NMR). In the latter method, oxidation of the sulfonyl α-carbon was most easily ascribed to halogenation of the presumed carbanion intermediate. Nevertheless, alkene production was not observed in this system either.

It was difficult to appraise why the Ramberg-Backlund reaction succeeded in one case and failed in the other. It is known that aldehydes and ketones are often liberated as hydrolysis products under Ramberg-Backlund conditions, which helps explain the recovery of aldehyde in the latter reaction. This is typically the case when vigorous extrusion methods are employed. These undesired byproducts materialize when adventitious moisture in the reaction vessel reacts
Scheme XXIII. Preparation of Extrusion Precursor 118.

with the intermediate α-halosulfone. Therefore, our results presented a puzzle. The extrusion conditions employed were fairly mild (KOH, t-BuOH, CCl₄, rt), but 75 represented the lone isolable aromatic product. Clearly the halogenation data we had obtained generated plenty of room for speculation.

In comparing sulfones 113 and 118, the lactone oxygen in 118 appears to represent the primary difference. This led us to consider that hydrolysis may be an artifact of neighboring group participation as shown in Scheme XXIV. No deterence to episulfone formation exists on the left hand equation which therefore leads to chelotropic extrusion. On the other hand, a proximate
lone pair in structure 120 might mitigate against extrusion and favor hydrolysis. One would predict that the pathway on the right is adopted by peri-substituted naphthalene derivatives.

Scheme XXIV. Reactivity Comparison of Benzylic and Polyaromatic Sulfones Under Ramberg-Backlund Conditions.

A potential solution to the speculation presented in scheme XXIV was to anneal the leaving group onto the α'-carbon in a prior step (Figure 9). At this site, through space interactions would be less severe. Moreover, our experience in introducing substituents at the site designated α, suggested the regioselectivity problem would be less arduous.

The Fuchs group recently disclosed an olefination method based on contraction of bis-sulfones, which allows stepwise assembly of extrusion precursors from thiosulfonates. By slight alteration of this method, our route took the shape shown in Scheme XXV. The phenylsulfonyl moiety in 123 was thus to serve two roles. It was to serve as a directing group for silylation and as a leaving group for episulfone formation. Structure 122 indicates the downside
of this plan as a vinylic trimethylsilyl group must be removed in a subsequent step.

Scheme XXV. Bissulfone Route.

P = protecting group
R = tert-butyldimethylsilyl
\( p \)-Methoxybenzyl thiol was converted to the derived thiosulfonate (124) by tosylation with triethylamine and tosyl bromide (Equation 15). Silylation of the anion of 96 gave an intermediate whose \(^1\text{H}\) NMR spectrum was consistent with a 1:1 mixture of the anticipated \( \alpha \)-silylsulfones (Equation 16). TLC analysis indicated that deprotonation of this intermediate with \( n \)-BuLi followed by treatment with 124 gave a single new product, which unfortunately decomposed into sulfone 96 and other materials upon workup. Unfortunately, the initially formed product could not be trapped under any circumstances, and the decomposition products could not be identified. Thus, a reordering of events was necessary.

![Chemical reaction diagram]

Therefore, a solution of 124 was added dropwise to a -78°C solution of the anion derived from sulfone 96 (Scheme XXVI). In this instance, difficulties associated with driving the reaction to completion arose and led to a troublesome separation of the intermediate \( \alpha \)-sulfenylsulfone from 96. However, oxidation of the mixture with \( m \)-CPBA, gave isolable bissulfone 126.

Unfortunately, the steric bulk of the sulfone tandem in 126 prohibited the introduction of a trimethylsilyl group. As a final alternative, the Ramberg-Backlund reaction of unshielded 126 was investigated. This reaction provided a low yield of a mixture of products thought to contain vinyl...
sulfone and vinyl chloride by $^1$H NMR spectroscopy of the crude product. Unfortunately, the poor mass balance associated with this reaction discouraged further studies.

Therefore it was concluded that an $\alpha$ leaving group could not be introduced in an efficient manner and reanalysis of the chrysomycin synthesis was necessary.

**Scheme XXVI. Preparation of Sulfone 126.**

[Diagram showing the preparation of sulfone 126]

**Experimental**

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker AC-200, Bruker AM-250, or Bruker AC-300 spectrometers and are recorded in parts per million from internal tetramethylsilane on the $\delta$ scale. The $^1$H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants in hertz, integration, interpretation]. $^{13}$C NMR data were obtained with Bruker AM-250 or Bruker AC-300 spectrometers. Fourier transform infrared spectra were obtained on a Perkin-Elmer 1600 instrument. Mass spectra were obtained on VG 70-250-S or Kralos MS 30 mass spectrometers at an ionization energy of 70 ev. Compounds for which an exact mass is reported exhibited no significant peaks at a $m/e$ greater than that of the parent. Combustion
analyses were performed by Atlantic Microlab Inc., Norcross, Ga.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether, and diglyme were distilled from sodium metal; dichloromethane, pyridine, triethylamine, benzene, and diisopropylamine were distilled from calcium hydride; hexamethylphosphoric triamide, dimethylformamide, and dimethyl sulfoxide were distilled from calcium hydride and stored over 4 angstrom molecular sieves. Tert-butanol was distilled from magnesium sulfate. Trimethylsilyl chloride was distilled from calcium hydride and stored over poly-4-vinyl pyridine for two days prior to use. Tosyl chloride and imidazole were purchased from Aldrich Chemical Co. and recrystallized from benzene. 3,5-Di-tert-butyl-4-hydroxytoluene was recrystallized two to three times from petroleum ether at -60°C and stored under a blanket of argon before use. Trimethylaluminum was purchased from Aldrich Chemical Co. and used as received. Reactions requiring an inert atmosphere were run under a blanket of argon. Analytical thin layer chromatography was conducted using EM Laboratories 0.25 mm thick silica gel 60F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70-230 mesh). All organolithiums were titrated with menthol prior to use using 1,10-phenanthroline as the indicator.52

\[ \text{OMOM} \]

(±)-(2R*,3S*,4S*)-2-Methyl-3-methoxymethoxy-1,4-pentanediol (87). To a solution of 3.00 g (17.2 mmol) of furanone 81 in 290 mL of tetrahydrofuran at -78°C was added 653 mg (17.2 mmol) of lithium aluminum hydride in a single portion. The resulting solution was stirred at -78°C for 30 min, then warmed to room temperature and stirred 1 h. The reaction was quenched by the addition of 3 mL of saturated aqueous ammonium chloride with cooling by an ice bath, and then stirred for 90 min. The resulting slurry was filtered through 10 g of Celite and the filter cake was rinsed with 650 mL of dichloromethane. The filtrate and washings were combined, dried.
(MgSO₄), and concentrated in vacuo to afford 2.85 g (94%) of diol 87 which could be used in subsequent reactions without further purification. If the crude product absorbed moisture (cloudy appearance) distillation from powdered 4A molecular sieves (85°C at 0.05 mm Hg) was necessary. On occasion it was necessary to rigorously dry the diol. This was carried out by refluxing a 0.5 M solution of crude 87 in tetrahydrofuran over about 20 mol% calcium sulfate for 24 h and then distilling under reduced pressure (85°C 0.05 mm Hg) from powdered sieves onto additional sieves and letting stand for 2 days: IR (neat) 3417 (broad) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 1.02 (d, J = 7.0 Hz, 3H, CH₃), 1.19 (d, J = 6.5 Hz, 3H, CH₃), 1.92 (m, 1H, C(2)-H), 3.06 (bs, 2H, OH), 3.24 (t, J = 4.7 Hz, 1H, C(3)-H), 3.43 (s, 3H, OCH₂), 3.68 (dd, J = 11.2, 4.1 Hz, 1H, C(1)-H), 3.56 (dd, J = 11.1, 5.1 Hz, 1H, C(1)-H), 3.86 (m, 1H, C(4)-H), 4.69 (d, J = 6.1 Hz, 1H, OCH₂), 4.74 (d, J = 6.1 Hz, 1H, OCH₂); ¹³C NMR (CDCl₃, 62.9 MHz) δ 15.16 (q), 20.09 (q), 37.27 (d), 56.18 (q), 64.01 (l), 68.19 (d), 88.97 (d), 99.28 (l); exact mass calcd. for C₈H₁₈O₄: m/e 178.1205, found m/e 178.1226.

(±H₂S₃S*,4S*)-3-Methoxymethoxy-4-methyl-5-[[[(4-methylphenyl)sulfonyl]oxy]-2-pentanol (89), and 2-Methyl-3-methoxymethoxy-4-methyltetrahydrofuran (88). To a solution of 178 mg (1.00 mmol) of diol 87 in 10 mL of dichloromethane at -10°C was added 167 μL (121 mg, 1.20 mmol) of triethylamine, and approximately 10 mg of 4-dimethylaminopyridine, followed by 200 mg (1.05 mmol) of p-toluenesulfonyl chloride. The resulting solution was stirred 20 h at 0°C or less and diluted with 10 mL of dichloromethane. The organic phase was washed with 10 mL of 1N HCl, and 10 mL of saturated aqueous brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 7 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:1) to afford 60 mg of p-toluenesulfonyl chloride, followed by 43 mg (27%) of cis-
substituted tetrahydrofuran 88: IR (neat) 2964, 1039 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.08 (d, \(J = 6.6\) Hz, 3H, CH\(_3\)), 1.27 (d, \(J = 7.0\), 3H, CH\(_3\)), 2.45 (m, 1H, C(3)-H), 3.34 (s, 3H, OCH\(_3\)), 3.54 (dd, \(J = 10.0\), 8.8 Hz, 1H, C(2)-H), 3.92 (m, 2H, C(4)-H), 4.05 (m, 1H, C(1)-H), 4.65 (m, 2H, OCH\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 62.9 MHz) \(\delta\) 11.29 (q), 15.33 (q), 39.22 (d), 56.03 (q), 72.50 (t), 78.81 (d), 80.97 (d), 97.05 (t).

Continued elution afforded 66 mg (20%) of slightly impure tosylate 89 as a colorless oil: IR (neat) 3448 (broad), 3120, 2976, 1738, 1177 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.98 (d, \(J = 6.1\) Hz, 3H, CH\(_3\)), 1.14 (d, \(J = 6.6\) Hz, 3H, CH\(_3\)), 2.12 (m 1H, C(2)-H), 2.45 (s, 3H, ArCH\(_3\)), 2.55 (bs, 1H, OH), 3.14 (t, \(J = 4.4\) Hz, 1H, C(3)-H), 3.39 (s, 3H, OCH\(_3\)), 3.73 (qu, \(J = 6.2\) Hz, 1H, C(4)-H), 3.95 (dd, \(J = 10.6\), 7.0 Hz, 1H, C(1)-H), 4.11 (dd, \(J = 10.6\), 4.4 Hz, 1H, C(1)-H), 4.60 (d, \(J = 6.6\) Hz, 1H, OCH\(_2\)), 4.67 (d, \(J = 6.6\) Hz, 1H, OCH\(_2\)), 7.45 (d, \(J = 7.9\) Hz, 2H, Ar(3)-H, Ar(5)-H), 7.78 (d, \(J = 7.9\) Hz, 2H, Ar(2)-H, Ar(6)-H); \(^{13}\)C NMR (CDCl\(_3\), 62.9 MHz) \(\delta\) 14.78 (q), 19.58 (q), 21.59 (q), 35.07 (d), 56.04 (q), 67.67 (d), 72.47 (t), 88.07 (d), 99.03 (t), 127.87 (d), 129.81 (d), 133.06 (s), 144.75 (s); exact mass calcd. for C\(_{15}\)H\(_{23}\)O\(_6\)S (M-1) \(m/e\) 331.1215, found \(m/e\) 331.1265.

Further elution provided 35 mg (20%) of diol 87.

\(\pm\)-(2\(S^*, 3S^*, 4S^*\))-4-[(tert-Butylsilyl)oxy]-3-methoxymethoxy-2-methyl-1-[[([4-methylphenyl)sulfonyl]oxy]pentane (90). Method A: To a solution of 177 mg (530 \(\mu\)mol) of freshly prepared tosylate 89 in 1.5 mL of dichloromethane at -30°C was added 100 mg (670 \(\mu\)mol) of tert-butyldimethylsilyl chloride followed by 57 mg (800 \(\mu\)mol) of imidazole resulting in the immediate production of a white precipitate. The slurry was stirred at 0°C or below for 12 h, then
an additional equivalent each of tert-butyldimethylsilyl chloride and imidazole were added. The resulting slurry was stirred for 2 h, diluted with 5 mL of dichloromethane, and washed with 3 mL of saturated aqueous brine. The aqueous layer was extracted with two 10-mL portions of dichloromethane and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:4) to afford 61 mg (72%) of tetrahydrofuran 88.

Continued elution gave impure 90 contaminated with tert-butyldimethylsilyl residues. This material was purified by placing under high vacuum for 24 h to furnish 61 mg (28%) of tosylate 90 as a colorless oil: IR (neat) 3050, 2930, 2889, 1177 cm⁻¹; \(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) 0.02 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.87 (s, 9H, CCH₃), 1.01 (d, \(J = 6.9\) Hz, 3H, CH₃), 1.09 (d, \(J = 6.4\) Hz, 3H, CH₃), 2.09 (m, 1H, C(2)-H), 2.44 (s, 3H, ArCH₃), 3.19 (dd, \(J = 5.9, 5.1\) Hz, 1H, C(3)-H), 3.31 (s, 3H, OCH₃), 3.91 (m, 1H, C(4)-H), 3.99 (dd, \(J = 9.4, 6.8\) Hz, 1H, C(1)-H), 4.13 (dd, \(J = 8.4, 4.1\) Hz, 1H, C(1)-H), 4.54 (d, \(J = 6.7\) Hz, 1H, OCH₂), 4.61 (d, \(J = 6.7\) Hz, 1H, OCH₂), 7.33 (d, \(J = 8.3\) Hz, 2H, Ar(3)-H, Ar(5)-H), 7.80 (d, \(J = 8.3\) Hz, 2H, Ar(2)-H, Ar(6)-H); \(^1^3\)C NMR (CDCl₃, 62.9 MHz) \(\delta\) -4.83 (q), -4.61 (q), 15.22 (q), 17.95 (q), 18.95 (q), 21.59 (q), 25.81 (q), 33.99 (d), 55.85 (q), 69.60 (d), 72.86 (t), 84.25 (d), 98.19 (t), 127.92 (t), 129.75 (d), 133.32 (s), 144.56 (s).

**Method B:** To a solution of 1.78 g (10.0 mmol) of dry diol 87 in 40 mL of dichloromethane at \(-10^\circ\)C was added 3.80 g (20.0 mmol) of \(p\)-toluenesulfonyl chloride in a single portion. The slurry was stirred 5 min followed by the addition of 140 mg of 4-dimethylaminopyridine and 2.80 mL (2.02 g, 20.0 mmol) of triethylamine. The resulting solution was gradually warmed to \(0^\circ\)C over a 9 h period after which 7.52 g (50.0 mmol) of tert-butyldimethylsilyl chloride and 4.08 g (60.0 mmol) of imidazole were added. The entire brew was stirred for 9 h at \(0^\circ\)C or lower, then 2 h at room temperature. The reaction mixture was diluted with 75 mL of dichloromethane and washed with 35 mL of water. The aqueous phase was extracted with three 50-mL portions of dichloromethane, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:6) to furnish 90 contaminated with tert-butyldimethylsilyl residues. This
material was purified by storing under high vacuum for 24 h to afford 3.14 g (70%) of pure 90 as a colorless oil.

\[ \text{TBSO} \quad \text{OMOM} \quad 91 \]

\((\pm)-\text{tert-Butyl} \quad [(1R^*,2R^*,3S^*)-4\text{-iodo-2-(methoxymethoxy)-1,3-dimethylbutoxy}]\) dimethylsilane (91). To a solution of 1.21 g (2.71 mmol) of tosylate 90 in 25 mL of acetone at 0°C was added 4.50 g (30.0 mmol) of sodium iodide in five portions over ten minutes. The ice bath was removed and the orange solution was stirred at room temperature for 48 h. The resulting slurry was carefully concentrated and the residue was extracted with two 50-mL portions of diethyl ether. The combined ether layers were concentrated \textit{in vacuo}, and the residue was chromatographed over 10 g of silica gel (eluted with diethyl ether-petroleum ether, 1:25) to afford 1.02 g (94%) of iodide 91 as a colorless oil: \(\text{IR (neat) } 2930, 2857, 1041 \text{ cm}^{-1}; \text{^1H NMR (CDCl}_3, 250 \text{ MHz}) } \delta 0.07 (s, 6\text{H, SiCH}_3), 0.89 (s, 9\text{H, CCH}_3), 1.10 (d, J = 6.7 \text{ Hz, } 3\text{H, CH}_3), 1.17 (d, J = 6.4 \text{ Hz, } 3\text{H, CH}_3), 1.72 (m, 1\text{H, C(3)-H}), 3.18 (dd, J = 8.1, 4.4 \text{ Hz, } 1\text{H, C(4)-H}), 3.30 (dd, J = 9.5, 6.8 \text{ Hz, } 1\text{H, C(2)-H}), 3.35-3.43 (m, 4\text{H, OCH}_3, C(4)-H), 4.00 (m, 1\text{H, C(1)-H}), 4.64 (s, 2\text{H, OCH}_2); \text{^{13C NMR (CDCl}_3, 62.9 \text{ MHz}) } \delta -4.76 (q), -4.52 (q), 15.60 (t), 17.98 (s), 18.66 (q), 18.92 (q), 25.84 (q), 36.08 (d), 55.92 (q), 67.59 (d), 85.55 (d), 98.30 (t); \text{exact mass calcd. for C}_{13}\text{H}_{28}\text{O}_2\text{Sil (M-15) } m/e 371.0881, \text{found } m/e 371.0886. \]

\[ \text{t-BDMSO} \quad \text{OM} \quad 93 \]

\((\pm)-\text{tert-Butyl} \quad [(1R^*,2R^*,3R^*)-1,3\text{-dimethyl-2,4-dioxybutoxy}]\text{dimethylsilane (93). To a} \]
solution of 402 mg (1.0 mmol) of iodide 91 in 1.0 mL of dimethylformamide was added 288 mg
(1.1 mmol) of triphenylphosphine in a single portion. The resulting solution was heated at reflux
for 3 h, cooled to room temperature, and diluted with 3 mL of diethyl ether. The reaction mixture
was concentrated to approximately one fourth of the original volume, and the residue was
chromatographed over 10 g of silica gel (eluted with petroleum ether-diethyl ether 6:1) to afford
85 mg (37%) of material tentatively assigned structure 93: IR (neat) 2958, 1036 cm⁻¹; ¹H NMR
(CDCl₃, 250 MHz) δ 0.05 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.94 (s, 9H, CCH₃), 0.98 (d, J =
6.8 Hz, 3H, CH₃), 1.17 (d, J = 6.3 Hz, 3H, CH₃), 2.33 (m, 1H, C(2)-H), 3.52 (dd, J = 10.0, 7.5 Hz,
1H, C(3)-H), 3.85 (t, J = 7.7 Hz, 1H, C(1)-H), 3.92-4.05 (m, 2H, C(3)-H, SiOCH); ¹³C NMR
(CDCl₃, 62.9 MHz) δ -4.36 (q), 11.28 (q), 15.73 (q), 18.27 (s), 25.95 (q), 40.10 (d), 72.29 (t),
75.39 (t), 79.60 (d); exact mass calcd. for C₁₂H₂₆O₂Si m/e 230.1653, found m/e 230.1663.

\[
\begin{align*}
\text{TBSO} & \quad \text{SPh} \\
\text{Me} & \quad \text{OMOM} \\
\text{Me} & \quad \text{OMOM}
\end{align*}
\]

(±)-tert-Butyl [(1'R,2'R,3'S)-2-(methoxymethoxy)-1,3-dimethyl-4-thiophenyl]butoxy
dimethylsilane (95). Method A: To a solution of 206 µL (220 mg, 2.00 mmol) of thiophenol in 4
mL of benzene was added 298 µL (2.00 mmol, 304 mg) of DBU. The solution was stirred 5 min
at 4°C and a solution of 804 mg (2.00 mmol) of iodide 91 in 2 mL of benzene was added over a 5
min period. The resulting slurry was stirred at 4°C for 3 h, filtered, and the filtrate was
concentrated in vacuo. Chromatography of the residue over 50 g of silica gel (diethyl ether-
petroleum ether, 1:20 as eluant) furnished 699 mg (91%) of 95 as a colorless oil: IR (neat) 3059,
2955, 1584, 1037 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.06 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃),
0.87 (s, 9H, CCH₃), 1.08 (d, J = 6.4 Hz, 3H, CH₃), 1.16 (d, J = 6.8 Hz, 3H, CH₃), 2.03 (m, 1H,
C(3)-H), 2.74 (dd, J = 12.7, 9.3 Hz, 1H, C(4)-H), 3.24 (m, 2H, C(2)-H, C(4)-H), 3.39 (s, 3H,
OCH₃), 3.97 (m, 1H, C(1)-H), 4.63 (d, J = 6.8 Hz, 1H, OCH₂), 4.76 (d, J = 6.8 Hz, 1H, OCH₂),
7.1-7.45 (m, 5H, 5Ar-H); \(^{13}\text{C}\) NMR (CDCl\(_3\), 62.9 MHz) \(\delta\) -4.74 (q), -4.59 (q), 17.41 (q), 17.97 (s),
19.35 (q), 25.84 (q), 34.17 (d), 37.07 (t), 55.96 (q), 69.98 (d), 86.31 (d), 98.34 (t), 125.66 (d),
128.80 (d), 129.06 (d), 137.39 (s); exact mass calcd. for \(\text{C}_{20}\text{H}_{36}\text{O}_{3}\text{SiS}\) \(\text{m/e}\) 384.2154, found
\(\text{m/e}\) 384.2163.

**Method B:** To a slurry of 140 mg (3.5 mmol) of sodium hydride (60% oil dispersion) in
17 mL of dimethylformamide was added thiophenol dropwise. The resulting bright yellow
thiophenoxide solution was stirred at room temperature until \(\text{H}_2\) evolution ceased (30 min). To
the resulting solution was added tosylate 90 dropwise, and the mixture was stirred 4 h at room
temperature. The reaction was diluted with 50 mL of diethyl ether, washed with 50 mL of water,
and the resulting aqueous wash was extracted with three 50-mL portions of diethyl ether. The
organic phases were combined, washed with 50 mL of brine, dried (MgSO\(_4\)), and concentrated in
vacuo. The residue was chromatographed over 70 g of silica gel (eluted with diethyl ether-
petroleum ether, 1:10) to afford 1.23 g (92%) of the phenylsulfide as a colorless oil.

\[
\text{t-BDMSO} \quad \text{OMOM}
\]

\[
96
\]

(\(\pm\))-**tert-Butyl\([(1R^*,2R^*,3S^*)-2-(\text{methoxymethoxy})-1,3\)-dimethyl-4-\(\text{(phenylsulfanyl)butoxy}\)] dimethylsilane (96). Method A: To an emulsion of 699 mg (1.82
mmol) of sulfide 95 in 47 mL of 6% wt. aqueous acetone was added 600 \(\mu\)L of a 0.9 M aqueous
solution of ammonium molybdate and 9.3 mL of 30% aqueous hydrogen peroxide. The bright
yellow solution was stirred at room temperature for 96 h and 4.6 mL of hydrogen peroxide was
added every 24 h. The acetone was removed via rotary evaporation and the aqueous residue
was extracted with three 300-mL portions of diethyl ether. The organic phases were washed with
100 mL of saturated aqueous brine, dried (MgSO\(_4\)), and concentrated in vacuo. The residue was
chromatographed over 20 g of silica gel (eluted with ethyl acetate-pentane, 1:10) to afford 656 mg
(87%) of the desired sulfone 27 as a colorless oil: IR (neat) 3062, 2955, 1305 1035,
cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.00 (s, 3H, SiCH₃), 0.01 (s, 3H, SiCH₃), 0.83 (s, 9H, CCH₃), 0.97 (d, J = 6.2 Hz, 3H, CH₃), 1.20 (d, J = 6.8 Hz, 3H, CH₃), 2.32 (m, 1H, C(3)-H), 2.92 (dd, J = 14.5, 9.7 Hz, 1H, C(4)-H), 3.11 (dd, J = 6.2, 3.9 Hz, 1H, C(2)-H), 3.32 (s, 3H, OCH₃), 3.36 (d, J = 14.5 Hz, 1H, C(4)-H), 3.72 (qu, J = 6.2 Hz, 1H, C(1)-H), 4.53 (d, J = 6.7 Hz, 1H, OCH₂), 4.70 (d, J = 6.7 Hz, 1H, OCH₂), 7.13 (m, 1H, Ar(4)-H), 7.28 (m, 2H, Ar(3,5)-H), 7.38 (m, 2H, Ar(2,6)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.82, (q), -4.61 (q), 17.90 (s), 18.95 (q), 19.25 (q), 25.76 (q), 29.40 (d), 55.91 (q), 55.82 (t), 69.66 (d), 86.33 (d), 98.21 (l), 127.92 (d), 129.24 (d), 133.51 (d), 140.08 (s); exact mass calcd. for C₁₉H₃₃O₄SiS (M+15) m/e 385.1869, found m/e 385.1864.

Method B: To a slurry of 1.89 g (22.54 mmol) of sodium bicarbonate in 33 mL of dichloromethane was added 1.23 g (3.23 mmol) of phenylsulfide 95 followed 5 min later by a solution of 1.11 g (6.44 mmol) of 99% m-CPBA in 32 mL of dichloromethane. The resulting slurry was stirred for 1 h at 0°C, followed by 5 h at room temperature, and then quenched by the addition of 10 mL of saturated aqueous sodium bisulfite. The mixture was diluted with 100 mL of dichloromethane and washed with 50 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three 100-mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried (MgSO₄), and concentrated in vacuo to afford 1.32 g (99%) of the sulfone as a colorless oil. This material could be used in subsequent reactions without further purification.

![Chemical Structure](image)

(±)-tert-Butyl[(1R*,2R*,3S*)-5-hydroxy-2-(methoxymethoxy)-1,3-dimethyl-5-phenyl-4-phenylsulfonyl]pentoxy] dimethylsilane (97). To a solution of 208 mg (500 μmol) of sulfone 96
in 1.6 mL of tetrahydrofuran and 440 µL of hexamethylphosphorictriamide at -78°C was added
dropwise 405 µL (600 µmol) of a solution of 1.48 M n-butyllithium in hexanes over 5 min. The
bright yellow solution was stirred at or below -72°C for 30 min followed by the addition of a
solution of 84 µL (112 mg, 600 µmol) of 4-methoxybenzaldehyde in 900 µL of tetrahydrofuran
over a 5 min period. The resulting solution was stirred at -78°C for 90 min and quenched with 1
mL of saturated aqueous ammonium chloride. The mixture was diluted with 10 mL of water and
extracted with three 20-ML portions of diethyl ether. The combined organic extracts were dried
(MgSO₄) and concentrated in vacuo.

The residue was chromatographed over 20 g of silica gel (eluted with petroleum ether-ethyl acetate, 20:1) to afford 129 mg (47%) of a single β-
hydroxysulfone: IR (neat) 3518 (broad), 3020, 2956, 1514 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ
0.01 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.83 (s, 9H, CH₃), 0.97 (d, J = 6.3 Hz, 3H, CH₃), 1.58
(d, J = 7.3 Hz, 3H, CH₃), 2.56 (m, 1H, SCCH), 3.28 (s, 3H, CH₃), 3.74 (s, 3H, ArOCH₃), 3.83 (m,
2H, OH, OCH), 4.02 (m, 2H, SiOCH, SCH), 4.66 (d, J = 6.2 Hz, 1H, OCH₂) 4.7 (d, J = 6.2 Hz, 1H,
OCH₂), 5.12 (t, J = 0.9 Hz, 1H, ArCH), 6.72 (m, 2H, Ar(3,5)-H), 7.0 (m, 2H, Ar(2,6)-H), 7.5-7.75
(m, 3H, Ph-H), 8.07 (m, 2H, Ph-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ -5.10 (q), -3.85 (q), 14.51 (q),
19.10 (q), 25.86 (q), 29.18 (s), 31.85 (d), 55.12 (q), 55.96 (q), 66.78 (d), 68.32 (d), 71.39 (d),
66.30 (d), 98.79 (l), 113.59 (d), 127.01 (d), 128.36 (d), 129.10 (d), 131.41 (s), 133.59 (d), 139.90
(s), 158.84 (s); exact mass calcd. for C₂₈H₄₄O₅SiS m/e 520.2679, found m/e 520.2679.

Continued elution with petroleum ether-ethyl acetate, 8:1, gave 25 mg (9%) of a second
β-hydroxysulfone: IR (neat) 3510 (broad), 2950, 1505 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.07
(s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.91 (s, 9H, CCH₃), 1.19 (d, J = 6.4 Hz, 3H, CH₃), 1.44 (d,
J = 7.2 Hz, 3H, CH₃), 3.24 (m, 1H, SCCH), 3.38 (s, 3H, OCH₃), 3.59 (dd, J = 8.5, 4.3 Hz, 1H,
OCH), 3.74 (s, 3H, OCH₃), 3.85-4.15 (m, 3H, SiOCH, SCH, OH), 4.69 (d, J = 6.1 Hz, 1H, OCH₂),
4.72 (d, J = 6.1 Hz, 1H, OCH₂), 5.13 (bd, J = 8.8 Hz, 1H, ArCH), 6.6 (m, 2H, Ar(3)-H, Ar(5)-H),
7.06 (m, 2H, Ar(2)-H, Ar(6)-H), 7.25-7.45 (m, 5H, Ph-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.82
(q), -4.44 (q), 13.66 (q), 18.00 (s), 18.86 (q), 25.84 (q), 29.10 (s), 32.02 (d), 55.20 (q), 55.68 (q),
68.76 (d), 69.37 (q), 70.95 (d), 86.06 (d), 98.69 (l), 113.58 (d), 127.41 (d), 128.48 (d), 128.89 (d),
Further elution with petroleum ether-ethyl acetate, 4:1 furnished 96 mg (35%) of the final two diastereomers as an inseparable mixture for a total of 250 mg (91%) of coupling product 97:

$^1$H NMR (CDCl$_3$ 250 MHz) diagnostic signals at δ: -0.12 (s, 3H, SiCH$_3$), -0.50 (s, 3H, SiCH$_3$), -0.49 (s, 3H, SiCH$_3$), -0.20 (s, 3H, SiCH$_3$), 0.73 (s, 9H, C(CH$_3$)$_3$), 0.81 (s, 9H, C(CH$_3$)$_3$), 0.98 (d, J = 6.2 Hz, 6H, CH$_3$), 0.99 (d, J = 6.4 Hz, 3H, CH$_3$), 1.26 (d, J = 6.8 Hz, 3H, CH$_3$), 2.05 (m, 1H, C(3)-H), 2.60 (m, 2H, C(3)-H, OH), 3.30 (s, 3H, OCH$_3$), 3.38 (s, 3H, OCH$_3$), 3.78 (s, 6H, ArOCH$_3$), 3.70-3.90 (m, 1H, C(1)-H), 3.90-4.05 (m, 1H, C(1)-H), 4.10 (m, 1H, C(2)-H), 4.30 (m, 1H, C(2)-H), 4.47 (d, J = 4.4 Hz, 1H, OCH$_2$), 4.55 (d, J = 4.4 Hz, 1H, OCH$_2$), 4.74 (d, 5.2 Hz, 1H, OCH$_2$), 4.79 (d, 5.2 Hz, 1H, OCH$_2$), 6.8 (m, 4H, Ar-H), 7.16 (m, 2H, Ar-H), 7.28 (m, 3H, Ar-H), 7.45-7.55 (m, 7H, Ar-H), 7.80 (m, 2H, Ar-H), 8.05 (m, 1H, Ar-H).

($\pm$)-tert-Butyl (1R *,2R *,3R *)-cis, and trans-2-(methoxymethoxy)-5-(p-methoxyphenyl)-1,3-dimethyl-4-butenyloxy] dimethylsilane (98). To a solution of 19 mg (37 µmol) of 28 in 600 µL of methanol at -10°C was added 25 mg of sodium hydrogen phosphate followed by 240 mg of 5% sodium amalgam. The resulting slurry was stirred at -10°C for 16 h, diluted with 1 mL of diethyl ether, and decanted. The organic phase was concentrated to one quarter of the original volume and directly chromatographed over 2.5 g of silica gel (eluted with petroleum ether-ethyl acetate, 8:1) to afford 11 mg (63%) of a 1:2 mixture of inseparable cis-trans
isomers of 98 as a colorless oil: $^1$H NMR (CDCl$_3$, 250 MHz) δ (peaks due to cis isomer), 0.03 (s, 3H, SiCH$_3$), 0.09 (s, 3H, SiCH$_3$), 0.90 (s, 9H, CCH$_3$), 0.95 (d, $J = 6.5$ Hz, 3H, CH$_3$), 1.16 (m, 3H, CH$_3$), 3.13 (m, 1H, =CCH), 3.23 (m, 1H, C(2)-H), 3.45 (s, 3H, OCH$_3$), 3.82 (s, 3H, ArOCH$_3$), 3.85 (m, 1H, C(1)-H), 4.67 (d, $J = 6.8$ Hz, 1H, OCH$_2$), 4.80 (d, $J = 6.8$ Hz, 1H, OCH$_2$), 5.67 (t, $J = 10.5$ Hz, 1H, =CH), 6.37 (apparent d, 10.5 Hz, 1H, ArCH), 6.85 (m, 2H, Ar(3)-H, Ar(5)-H), 7.27 (m, 2H, Ar(2)-H, Ar(6)-H); (peaks due to trans isomer), 0.04 (s, 3H, SiCH$_3$), 0.05 (s, 3H, SiCH$_3$), 0.88 (s, 9H, CCH$_3$), 1.16 (m, 6H, CH$_3$, CH$_3$), 2.57 (m, 1H, =CCH), 3.25 (m, 1H, C(2)-H), 3.41 (s, 3H, OCH$_3$), 3.81 (s, 3H, ArOCH$_3$), 3.88 (m, 1H, C(1)-H), 4.66 (d, $J = 6.6$ Hz, 1H, OCH$_2$), 4.82 (d, $J = 6.6$ Hz, 1H, OCH$_2$), 6.13 (dd, $J = 17.4$, 8.5 Hz, 1H, =CH), 6.3 (d, $J = 17.4$ Hz, 1H, ArCH), 6.83 (m, 2H, Ar(3,5)-H), 7.29 (m, 2H, Ar(2,6)-H).

![Chemical structure of 98](image)

(±)-tert-Butyl (1$^R$,2$^R$,3$^R'$)-trans-2-(methoxymethoxy)-5-(p-methoxyphenyl)-1,3-dimethyl-4-butenyloxy] dimethylsilane (98). Method A. To a solution of 104 mg (250 μmol) of sultone 96 in 500 μL of tetrahydrofuran at -78 °C was added dropwise 156 μL (250 μmol) of a solution of 1.60 M n-butyllithium in hexanes over 2 min. The resulting bright yellow solution was stirred for 25 min at -78 °C, then added dropwise via cannula over a 5 min period to a solution of 32 μL (33 mg, 240 μmol) of p-methoxybenzaldehyde in 250 μL of tetrahydrofuran at -78°C. The resulting solution was maintained between -78°C and -65°C for 45 min followed by the dropwise addition of 67 μL (73 mg, 0.72 mmol) of acetic anhydride. The resulting solution was stirred at -78°C for 4 h, then warmed to 0°C and stirred 1 h. The reaction mixture was diluted with 5 mL of
diethyl ether and washed with 2 mL of water. The aqueous phase was extracted with three 10-
ml portions of ethyl acetate and the combined organic phases were dried (MgSO₄) and
concentrated to dryness. A slurry of 35 mg (59 μmol) of the resulting acetates in 780 μL of a 2:1
mixture of methanol-ethyl acetate was prepared at 0°C and treated with 400 mg of 5% sodium
amalgam. The resulting mixture was stirred 1 h at 0°C then gradually warmed to room
temperature and stirred 8 h. The reaction mixture was diluted with 10 mL of diethyl ether and
decanted from the residual pool of mercury. The resulting organic phase was washed with 5 mL
of water, and the resulting aqueous layer was extracted with two 10-mL portions of diethyl ether.
The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was
chromatographed over 1 g of silica gel (eluted with pentane-ethyl acetate, 10:1) to afford impure
alkene, then chromatographed over 1 g of silica gel (eluted with pentane-ethyl acetate, 100:1) to
afford 8 mg (32%) of exclusively the trans isomer: 

1H NMR (CDCl₃, 250 MHz) δ 0.04 (s, 3H, SiCH₃), 0.05 (s, 3H, SiCH₃), 0.88 (s, 9H, CCH₃), 1.16 (m, 6H, CH₃), 2.57 (m, 1H, =CCH), 3.25 (m, 1H, C(2)-H), 3.41 (s, 3H, OCH₃), 3.81 (s, 3H, ArOCH₃), 3.88 (m, 1H, C(1)-H), 4.66 (d, J = 6.6 Hz, 1H, OCH₂), 4.82 (d, J = 6.6 Hz, 1H, OCH₂), 6.13 (dd, J = 17.4, 8.5 Hz, 1H, =CH), 6.3 (d, J = 17.4 Hz, 1H, ArCH), 6.83 (m, 2H, Ar(3)-H, Ar(5)-H), 7.29 (m, 2H, Ar(2)-H, Ar(6)-H). 

13C NMR (CDCl₃, 62.9 MHz) δ -4.69 (q), -4.59 (q), 18.00 (s), 19.09 (q), 19.66 (q), 25.89 (q), 38.77 (d), 55.29 (q), 55.98 (q), 70.69 (d), 86.44 (d), 98.35 (t), 113.89 (d), 127.13 (d), 129.07 (d), 130.64 (d), 130.72 (s), 158.70 (s).

**Method B:** To a solution of 45 mg (82 μmol) of 97 and approximately 2 mg of 1,10-
phenanthroline in 300 μL of tetrahydrofuran at -78°C was added dropwise a solution of 1.48 M n-
butyllithium in hexanes until a dark color persisted (approximately 55-60 μL were required). The
resulting solution was stirred 5 min at -78°C and 19 μL (23 mg, 164 μmol) of benzoyl chloride
was added. After warming to room temperature over a 3 h period, the reaction mixture was
stirred for 2 h and then directly chromatographed over 8 g of silica gel (eluted with petroleum
er ether-ethyl acetate, 8:1) to afford diastereomeric benzoates. The residue was redissoved in 1.5
mL of methanol and treated with 55 mg of sodium hydrogen phosphate. The resulting solution
was cooled to -18°C and 450 mg of 5% sodium amalgam was added. The resulting mixture was stirred at -18°C for 5.5 h, diluted with 5 mL of diethyl ether, and decanted from the residual mercury. The ether layer was washed with 5 mL of water, and the resulting aqueous layer was extracted with three 5-mL portions of diethyl ether. The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 2 g of silica gel to afford 27 mg (84%) of an approximately 1:8 mixture of cis-trans isomers as a colorless oil.

Free radical Isomerization of (±)-tert-Butyl (1 R*,2R*,3R*)-trans-2-(methoxymethoxy)-5-(p-methoxyphenyl)-1,3-dimethyl-4-butenyloxy) dimethylsilane (98). To a solution of 31 mg (79 µmol) of an approximately 1:8 cis-trans mixture of 98 in 2.5 mL of benzene was added 5.0 µL (5.0 mg, 40 µmol) of thiophenol followed by 8 mg (47 µmol) of AIBN. The resulting solution was heated to 50°C for 14 h, cooled to room temperature, and directly chromatographed over 1 g of silica gel (eluted with petroleum ether-diethyl ether, 50:1) to afford 16 mg (52%) of a 1:34 mixture of cis-trans isomers of 98 by G.C. analysis: phenyl-methyl silicone gum; temperature range 100-300°C; rate of heating 10°C/min; Z-olefin RT = 14.23 min, E-olefin RT = 15.29 min.
4-Methoxybenzyl phenyl sulfide (102). To a solution of 1.0 mL (1.10 g, 10.0 mmol) of thiophenol and 1.49 mL (1.52 g, 10.0 mmol) of DBU in 30 mL of benzene at room temperature was added 1.54 g (10.0 mmol) of \( p \)-methoxybenzyl chloride in a single portion. The resulting slurry was stirred at room temperature for 3 h and filtered. The filtrate was washed with 10 mL of water, dried (\( \text{MgSO}_4 \)), and concentrated \textit{in vacuo} to afford 2.10 g (92%) of phenyl sulfide 102 as a white solid (mp 79-82°C) which was used in the next reaction without further purification. An analytical sample was obtained by recrystallization from ethanol, affording white needles: mp 84.5-85.5°C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 250 MHz) \( \delta \) : 3.77 (s, 3H, OCH\textsubscript{3}), 4.08 (s, 2H, CH\textsubscript{2}), 6.82 (d, \( J = 7.9 \text{ Hz} \), 2H, Ar(3)-H, Ar(5)-H), 7.1-7.4 (m, 7H, Ph-H, Ar(2)-H, Ar(6)-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.9 MHz) \( \delta \) 38.43 (t), 55.22 (q), 113.88 (d), 126.21 (d), 128.77 (d), 129.76 (s), 129.76(d), 129.89 (d), 136.54 (s), 158.74 (s); exact mass calcd. for C\textsubscript{14}H\textsubscript{14}O\textsubscript{5}S \textit{m/e} 230.0766, found \textit{m/e} 230.0756.

Anal. calcd. for C\textsubscript{14}H\textsubscript{14}O\textsubscript{5}S: C, 73.00; H, 6.13; found C, 72.88; H, 6.15.

4-Methoxybenzyl phenyl sulfone (103). Method A: To a solution of 228 mg (1.00 mmol) of phenylsulfide 35 in 3.5 mL of dichloromethane at room temperature was added over 5 min a solution of \( m \)-CPBA in 5 mL of dichloromethane. The resulting solution was stirred 20 min at room temperature producing a white precipitate. The resulting slurry was stirred for 1 h,
filtered, and washed with 2 mL of 10% aqueous sodium sulfite followed by two 3.5-mL portions of saturated aqueous sodium bicarbonate. The combined organic layers were dried (MgSO₄) and concentrated to afford 194 mg (74%) of a white solid: mp 128-133°C. This material was used in subsequent reactions without further purification. An analytical sample was prepared by recrystallization from ethanol which afforded white needles: mp 139-140°C; ¹H NMR (CDCl₃, 300 MHz) δ 3.79 (s, 3H, OCH₃), 4.22 (s, 2H, SCH₂), 6.80 (d, J = 8.8 Hz, 2H, Ar (3)-H, Ar(5)-H), 6.95 (d, J = 8.8 Hz, 2H, Ar(2)-H, Ar(6)-H), 7.4-7.5 (m, 2H, Ph-H), 7.55-7.7 (m, 3H, Ph-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 55.23 (q), 62.19 (t), 114.0 (d), 119.95 (s), 128.61 (d), 128.84 (d), 131.98 (d), 133.58 (d), 137.97 (s), 159.99 (s); exact mass calcd. for C₁₄H₁₄O₃S m/e 262.0664, found m/e 262.0676.

Anal. calcd. for C₁₄H₁₄O₃S: C, 64.11; H, 5.38; found C, 63.95; H, 5.11.

Method B: To a solution of 1.14 g (5.00 mmol) of phenyl sulfide 35 in a solution of 136 mL of methanol and 11 mL of dichloromethane was added a solution of 4.57 g of "oxone" in 27 mL of water. The resulting solution was stirred at 0°C for 1 h, then warmed to room temperature and stirred 14 h. The reaction mixture was diluted with 100 mL of water and the aqueous phase was extracted with three 110-mL portions of dichloromethane. The combined organic phases were washed with 100 mL of saturated aqueous ammonium chloride, dried (MgSO₄), and concentrated to afford 1.26 g (97%) of sulfone 103 (mp 135-138°C).

4-[(tert-Butyldimethylsilyl)oxy]-2-methyl-2-pentenal (104). To a solution of 21 mg (72 µmol) of sulfone 103 in 150 µL of tetrahydrofuran at -78°C was added 185 µL of a 0.43 M (80.0 µmol) stock solution of lithium diisopropylamide. The resulting solution was stirred at -78°C
for 1 h and a solution of 21 mg (72 µmol) of aldehyde 99 in 100 µL of tetrahydrofuran was added dropwise over a 2 min period. This solution was stirred at -78°C for 30 min, then warmed to room temperature and stirred for 2 h. The reaction was quenched with 3 mL of diethyl ether and washed with 5 mL of water. The aqueous phase was extracted with three 10-mL portions of diethyl ether and the combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ether-petroleum ether, 1:10) to afford 15 mg (64%) of aldehyde 33: 

\[ ^1H \text{NMR (CDCl}_3, 250 \text{ MHz) } \delta 0.02 \text{ (s, 3H, SiCH}_3), 0.05 \text{ (s, 3H, SiCH}_3), 0.87 \text{ (s, 9H, CCH}_3), 1.28 \text{ (d, } J=1.4 \text{ Hz, 3H, =CCH}_3), 1.75 \text{ (d, } J=1.4 \text{ Hz, 3H, =CCH}_3), 4.75 \text{ (m, 1H, CH}_2CH)), 6.43 \text{ (dq, } J=7.7, 1.4 \text{ Hz, 1H, =CH), 9.41 \text{ (s, 1H, CHO).} \]

Continued elution gave 20 mg (95%) of starting sulfone 96.

\[ (+)-\text{tert-Butyl(1R*,2R*,3S*)-4-}p\text{-methoxybenzyl)-2-(methoxymethoxy)-1,3-dimethyl-4-}p\text{-phenylsulfonyl)butoxy] \text{ dimethylsilane (105).} \]

To a -78°C solution of 192 mg (500 µmol) of sulfone 96 in 2.5 mL of tetrahydrofuran and 430 µL of hexamethylphosphoric triamide was added 328 µL (525 µmol) of a 1.6 M solution of n-butyllithium in hexanes over a 5 min period. The resulting bright yellow reaction mixture was stirred 45 min at -78°C and then treated all at once with 68 µL (78 mg, 500 µmol) of \( p \)-methoxybenzyl chloride. The reaction mixture was stirred for 2 h with warming to 0°C and then diluted with 20 mL of diethyl ether. The resulting mixture was washed with 10 mL of water, and the aqueous phase was extracted with three 30-mL portions of ether. The combined organic extracts were washed with 50 mL of brine, dried (MgSO₄), and
concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with petroleum ether-ethyl acetate, 10:1) to afford 88 mg (35%) of the benzylated sulfone 105 as a colorless oil: IR (neat) 2958, 1613 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ -0.02 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃), 0.88 (s, 9H, CCH₃), 0.98 (d, J = 6.4 Hz, 3H, CH₃), 1.25 (d, J = 6.8 Hz, 3H, CH₃), 2.73 (m, 1H, C(3)-H), 2.95 (m, 1H, C(2)-H), 3.14 (m, 1H, C(4)-H), 3.38 (s, 3H, OCH₃), 3.70-3.95 (m, 2H, C(1)-H, C(H₂), 3.68-3.78 (m, 1H, CH₂), 3.75 (s, 3H, ArOCH₃), 3.88 (m, 1H, C(5)-H), 4.74 (d, J = 5.8 Hz, 1H, OCH₂), 4.48 (d, J = 5.8 Hz, 1H, OCH₂), 6.68 (d, 2H, Ar(2,5)-H), 7.03 (d, 2H, Ar(2,6)-H), 7.50 (m, 3H, Ph-H), 7.78 (d, 2H, Ph-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -5.05, -4.78, 12.62, 17.84, 25.68, 29.05, 32.01, 44.99, 55.12, 55.67, 65.49, 69.35, 84.99, 97.87, 99.53, 113.68, 128.32, 128.67, 129.83, 129.96, 130.36, 132.85, 139.50, 158.07; exact mass calcd. for C₂₇H₄₁O₅Si (M-31) m/e 505.2494, found m/e 505.2469.

![TBSO](https://example.com/image1)

(±)-tert-Butyl [(1R*,2R*,3S*)-2-(methoxymethoxy)-1,3-dimethyl-4-(phenylsulfinyl)butoxy] dimethylsilane (106). To a -78°C slurry of 650 mg (1.69 mmol) of phenylsulfide 95 and 994 mg (11.8 mmol) of sodium bicarbonate in 15 mL of dichloromethane was added 291 mg (1.69 mmol) of m-chloroperbenzoic acid as a solution in 10 mL of dichloromethane. After stirring 3 h at -78°C, the reaction mixture was quenched with 15 mL of saturated aqueous sodium bisulfite. The resulting mixture was further diluted by the addition of 50 mL of saturated aqueous sodium bicarbonate and extracted with three 50-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:10), to afford 607 mg (90%) of the diastereomeric sulfoxides as a colorless oil: IR (neat) 2956, 2931,
$1583 \text{ cm}^{-1}$; $^1\text{H NMR (CDCl}_3, 250 \text{ MHz}) \delta 0.05 \text{ (s, 12H, SiCH}_3\text{)}, 0.80 \text{ (s, 18H, SiC(CH}_3\text{)}_2\text{)}, 0.98 \text{ (d, } J = 6.4 \text{ Hz, 3H, CH}_3\text{)}, 1.11 \text{ (d, } J = 7.2 \text{ Hz, 3H, CH}_3\text{)}, 1.18 \text{ (d, } J = 7.8 \text{ Hz, 3H, CH}_3\text{)}, 1.25 \text{ (d, } J = 7.2 \text{ Hz, 3H, CH}_3\text{)}, 2.12 \text{ (m, 1H, C(3)-H)}, 2.41 \text{ (m, 1H, C(3)-H)}, 2.58 \text{ (m, 1H, C(4)-H)}, 2.79 \text{ (dd, } J = 12.9, 8.1 \text{ Hz, 1H, C(4)-H)}, 2.93 \text{ (dd, } J = 12.1, 2.9 \text{ Hz, 2H, C(4)-H)}, 3.00 \text{ (dd, } J = 12.9, 4.1 \text{ Hz, } 3.15 \text{ (m, 1H, C(2)-H)}, 3.24 \text{ (m, 1H, C(2)-H)}, 3.33 \text{ (s, 3H, OCH}_3\text{)}, 3.81 \text{ (m, 2H, C(1)-H, C(1)-H)}, 4.57 \text{ (m, 2H, OCH}_2\text{)}, 4.73 \text{ (m, 2H, OCH}_2\text{)}, 7.51 \text{ (m, 6H, Ar-H)}, 7.64 \text{ (m, 4H, Ar-H)}; ^{13}\text{C NMR (CDCl}_3, 75.5 \text{ MHz) } \delta -4.76 \text{ (q), -4.64 (q), 17.901 (q), 19.19 (q), 19.27 (q), 19.50 (q), 25.79 (q), 29.65 (d), 29.95 (d), 55.90 (q), 55.94 (q), 61.75 (l), 62.16 (l), 69.83 (d), 62.16 (d), 86.56 (d), 86.66 (d), 98.31 (l), 98.41 (l), 123.94 (d), 124.21 (d), 129.21 (d), 130.75 (d), 131.08 (d), 144.80 (s), 144.90 (s); exact mass calcd. for C$_{26}$H$_{36}$O$_4$Si (M+1) $m/e$ 401.2218, found $m/e$ 401.2200.

\[ \text{OMe} \]

\[ \text{TBSO} \]

\[ \text{Me} \]

\[ \text{OMOM} \]

\[ \text{98} \]

\((\pm)\text{-tert-Butyl } (1\text{ R}^*,2\text{R}^*,3\text{R}^*)\text{-trans-2-(methoxymethoxy)-5-(p-methoxyphenyl)-1,3-dimethyl-4-butenyloxy] dimethylsilane (98).}\) A solution of 103 mg (198 \mu mol) of sulfoxide in 5 mL of tetrahydrofuran was heated under reflux for 20 h and cooled to room temperature. The reaction mixture was diluted with 20 mL of dichloromethane and washed with 10 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three additional 20-mL portions of dichloromethane and the combined organic phases were dried (MgSO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1) to afford 46 mg (60%) of a 1:1 mixture of 98 as a 1:1 mixture of E- and Z- isomers.
(±)-tert-Butyl [(1R*,2R*,3S*)-2-(methoxymethoxy)-1,3-dimethyl-4-(thioacetoxy)-butoxy] dimethylsilane. **Method A:** To a solution of 300 mg (0.75 mmol) of iodide 91 in 2.25 mL of benzene was added 54 µL (57 mg, 0.75 mmol) of thioacetic acid followed by 112 µL (0.75 mmol) of DBU. The resulting slurry was stirred at room temperature for 6 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over 15 g of silica gel (eluted with petroleum ether-diethyl ether, 20:1) to afford 235 mg (89%) of thioester 111 as a colorless oil.

**Method B:** To a solution of 2.12 g (1.95 mL, 35.4 mmol) of thioacetic acid in 15 mL of N,N-dimethylformamide at 0°C under argon was added 5.43 g (5.3 mL, 35.4 mmol) of DBU. The resulting dark blue solution was stirred for 15 min. To the resulting solution was added a solution of 4.51 g (10.11 mmol) of tosylate 90 in 30 mL of N,N-dimethylformamide. The reaction was stirred 8 h while warming to room temperature and then diluted with 250 mL of dichloromethane. The resulting solution was washed with five 100-mL portions of water, then dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate; 40:1) to afford 3.30 g (93%) of thioester 111 as an oil. IR (neat) 2932, 1693, 1037 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.06 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃), 0.88 (s, 9H, C(CH₃)₃), 1.04 (d, J = 6.9 Hz, 3H, CH₃), 1.16 (d, J = 6.4 Hz, 3H, CH₃), 1.94 (m, 1H, SCCH), 2.32 (s, 3H, COCH₃), 2.75 (dd, J = 13.4, 8.9 Hz, 1H, SCH₂), 3.19 (m, 2H, SCH₂, OCH), 3.39 (s, 3H, OCH₃), 4.00 (qu, J = 6.2 Hz, 1H, SiOCH), 4.62 (d, J = 6.7 Hz, 1H, OCH₂), 4.76 (d, J = 6.7 Hz, 1H, OCH₂); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.73 (q), -4.62 (q), 17.19 (q), 17.97 (s), 19.33 (q), 25.85 (q), 30.56 (q), 32.14 (t), 34.45 (d), 55.96 (q), 70.08 (d), 86.27 (d), 98.34 (t), 195.50 (s); exact mass calcd. for C₁₅H₃₁O₃SSi (M-31) m/e 319.1763, found m/e 319.1733.
To a -78°C solution of 3.04 g (8.68 mmol) of thioacetate 111 in 80 mL of diethyl ether was added 650 mg (17.1 mmol) of lithium aluminum hydride in two portions. The resulting slurry was stirred 5 min at -78°C then warmed to room temperature and stirred 30 min. The reaction was carefully neutralized by the cautious dropwise addition of 1.3 mL of 3N aqueous HCl. The resulting foamy solution was stirred for 2h at 0°C and then filtered through a cake of Celite. The filter cake was rinsed with 100 mL of diethyl ether, and then 200 mL of dichloromethane. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with petroleum ether-ether, 50:1) to afford 2.42 g (91%) of the thiol 110 as a foul smelling oil: IR (neat) 2995, 2800, 1050 cm⁻¹; \(^1\)H NMR (CDCl₃, 250 MHz) \(\delta\) 0.07 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.89 (s, 9H, CCH₃), 1.09 (d, \(J = 6.7\) Hz, 3H, CH₃), 1.15 (d, \(J = 8.0\) Hz, 3H, CH₃), 1.35 (t, \(J = 8.1\) Hz, 1H, SH), 1.94 (m, 1H, C(2)-H), 2.54 (m, 1H, SCH₂), 2.75 (ddd, \(J = 12.0, 8.0, 3.3\) Hz, 1H, SCH₂), 3.27 (dd, \(J = 6.0, 3.3\) Hz, 1H, OCH), 3.39 (s, 3H, OCH₃), 3.96 (m, 1H, SiOCH), 4.63 (d, \(J = 6.7\) Hz, 1H, OCH₂), 4.73 (d, \(J = 6.7\) Hz, 1H, OCH₂); \(^{13}\)C NMR (CDCl₃, 62.9 MHz) \(\delta\) -4.77 (q), -4.57 (q), 16.08 (q), 17.98 (s), 19.10 (q), 25.84 (q), 28.02 (t), 36.87 (d), 55.95 (q), 69.74 (d), 85.28 (d), 98.09 (t); exact mass calcd. for C₁₄H₃₁O₃SSi (M-1) \(m/e\) 307.1863, found \(m/e\) 307.1814.
(±)-tert-Butyl [(1R',2R',3S')-4-[(p-methoxybenzyl)sulfenyl]-2-(methoxymethoxy)-1,3-dimethylbutoxy] dimethylsilane (112) and di-(±)-(2S*,3R*,4R*)-4-[(tert-Butyldimethylsilyloxy]-3-(methoxymethoxy)-2-methylpentyl disulfide (112a). Method A: To a solution of 103 mg (334 µmol) of thiol 110 in degassed benzene was added 52 mg (334 µmol) of p-methoxybenzyl chloride followed by 50 µL (334 µmol) of DBU. The resulting solution was stirred at room temperature for 3 h and directly chromatographed over 10 g of silica gel (eluted with petroleum ether-diethyl ether, 15:1) to afford 125 mg (87%) of an inseparable mixture of sulfide 112 contaminated with a small amount (approximately 5%) of disulfide 112a: IR (neat) 2930, 1462, 1100, 1036 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.05 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.90 (s, 9H, CCH₃), 1.13 (d, J = 6.4 Hz, 3H, CH₃), 1.18 (d, J = 6.7 Hz, 3H, CH₃), 2.07 (m, 1H, C(2)-H), 2.52 (m, 1H, C(1)-H), 3.00 (m, 1H, C(1)-H), 3.22 (m, 1H, C(3)-H), 3.40 (s, 3H, OCH₃), 3.95 (m, 1H, C(4)-H), 4.65 (d, J = 6.4 Hz, 1H, OCH₂), 4.77 (d, J = 6.4 Hz, 1H, OCH₂); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.71 (q), -4.62 (q), 17.26 (q), 17.96 (s), 19.47 (q), 25.84 (q), 34.07 (d), 34.22 (d), 41.99 (t), 42.77 (t), 55.90 (q), 70.16 (d), 86.45 (d), 98.37 (l); exact mass calcd. for C₁₄H₃₁O₃SSi m/e 307.1863, found m/e 307.1814. This material could be used in subsequent reactions without further purification. However, complete removal of 112a could be effected in the following manner. A -78°C solution of the above material in 3 mL of tetrahydrofuran was treated with 10 mg (226 µmol) of lithium aluminum hydride and warmed to room temperature. After 30 min, g.c. analysis (phenyl methyl silicone gum; 100-300°C; 10°C/min; initial time 2.00 min; thiol Rₜ = 8.38 min, sulfide Rₜ = 16.60 min, disulfide Rₜ = 19.92), indicated 112a had been quantitatively converted to thiol 110. The reaction mixture was quenched with one drop of saturated aqueous ammonium chloride with cooling by an ice bath. The resulting slurry was stirred 10 min and filtered through a cake of celite. The residue was
chromatographed over 10 g of silica gel (eluted with petroleum ether-diethyl ether 30:1) to first afford 6 mg of thiol 110. Further elution afforded 117 mg (82%) of disulfide free 112.

Method B: To a solution of 154 mg (1.0 mmol) of DBU in 3.0 mL benzene was added 154 mg (1.0 mmol) of thiol 114 in a single portion. The resulting solution of thiolate anion was stirred for 5 min and then 384 mg (1.0 mmol) of iodide 91 was added. The reaction mixture was stirred 8 h at room temperature and filtered through 2 g of silica gel. The filter plug was washed with 50 mL of diethyl ether and the combined filtrate and washings were concentrated in vacuo affording 317 mg (74%) of 112 that could be used in subsequent reactions without further purification: IR (neat) 3050, 2956, 1728, 1253 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.87 (s, 9H, CCH₃), 1.08 (m, 6H, CH₃, CH₃), 1.91 (m, 1H, C(3)-H), 2.31 (dd, J = 12.6, 9.2 Hz, 1H, C(4)-H), 2.67 (dd, J = 12.6, 3.5 Hz, 1H, C(4)-H), 3.15 (t, J = 5.5 Hz, 1H, C(2)-H), 3.33 (s, 3H, OCH₃), 3.64 (s, 2H, ArCH₂), 3.78 (s, 3H, OCH₃), 3.89 (m, 1H, SiOCH), 4.58 (d, J = 6.7 Hz, 1H, OCH₂), 4.69 (d, J = 6.7 Hz, 1H, OCH₂), 6.8 (m, 2H, Ar(3,5)-H), 7.24 (m, 2H, Ar(2,6)-H); ¹³C NMR (CDCl₃, 75.47 MHz) δ -4.73 (q), -4.61 (q), 17.38 (q), 17.99 (s), 19.45 (q), 25.87 (q), 34.41 (d), 34.79 (t), 36.35 (t), 55.28 (q), 55.86 (q), 69.93 (d), 86.25 (d), 98.27 (t), 113.85 (d), 129.94 (d), 130.67 (s), 158.60 (s) exact mass calcd. for C₂₀H₃₆O₃SSi (M-44) m/e 384.2220, found m/e 384.2187.

(+)-tert-Butyl [(1R*,2R*,3S*)-4-[(p-methoxybenzyl)sulfonyl]-2-(methoxymethoxy)-1,3-dimethylbutoxy]dimethylsilane (113). To a solution of 120 mg (280 µmol) of sulfide 112 in 2.5 mL of chloroform containing 172 mg (1.92 mmol) of solid sodium bicarbonate was added dropwise a solution of 143 mg (560 µmol) of 80% m-chloroperbenzoic acid in 3.0 mL of chloroform. The resulting slurry was stirred 2 h and diluted with 25 mL of saturated aqueous
sodium bicarbonate. The entire mixture was extracted with four 40-mL portions of dichloromethane, and the combined organic phases were washed with 50 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-diethyl ether, 10:1, followed by ethyl acetate-petroleum ether, 4.5:1) to afford 94 mg (73%) of desired sulfone 42 as a colorless oil: IR (neat) 3020, 2956, 1727, 1514, 1258 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.88 (s, 9H, CCH₃), 1.08 (d, J = 6.4 Hz, 3H, CH₃), 1.28 (d, J = 7.2 Hz, 3H, CH₃), 2.46 (m, 1H, C(3)-H), 2.58 (dd, J = 15.3, 8.0 Hz, 1H, C(4)-H), 3.13 (m, 2H, C(2)-H, C(4)-H), 3.34 (s, 3H, OCH₃), 3.65-3.85 (m, 1H, C(1)-H), 3.82 (s, 3H, ArOCH₃), 4.16 (s, 2H, ArCH₂), 4.56 (d, J = 6.4 Hz, 1H, OCH₂), 4.73 (d, J = 6.4 Hz, 1H, OCH₂), 6.92 (m, 2H, Ar(3,5)-H), 7.34 (m, 2H, Ar(2,6)-H); ¹³C NMR (CDCl₃, 62.90 MHz) δ -4.84 (q), -4.71 (q), 17.87 (s), 18.82 (q), 19.27 (q), 25.74 (q), 28.82 (d), 53.16 (t), 55.21 (q), 55.86 (q), 60.08 (t), 69.67 (d), 86.12 (d), 98.15 (t), 114.13 (t), 120.00 (s), 131.82 (d), 160.09 (s); exact mass calcd. for C₂₁H₁₇O₅Si (M-31) m/e 429.2069, found m/e 429.2100.

4-Methoxybenzylthiol (114). To a slurry of 760 mg (10 mmol) of thiourea in 5 mL of ethanol was added 1.56 g (10.0 mmol) of p-methoxybenzyl chloride. The slurry was heated under reflux for 4 h, and the resulting thiouronium salt was subsequently hydrolyzed by the addition of a solution of 600 mg of sodium hydroxide in 4 mL of water. The reaction mixture was then warmed under reflux for 2 h during which a white precipitate formed and gradually redissolved. The reaction mixture was cooled to room temperature and the lower mercaptan layer was decanted. The aqueous residue was acidified with 1.5 mL of 2.5 M sulfuric acid, and extracted with one 5-mL portion of benzene. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was distilled bulb-to-bulb affording 956 mg (62%) of thiol.
43: b.p. 80-90°C 2 mm Hg: $^1$H NMR (CDCl₃, 300 MHz) $\delta$ 1.68 (t, $J = 6.8$ Hz, 1H, SH), 3.68 (d, 2H, CH₂SH), 3.75 (s, 3H, OCH₃), 6.81 (d, $J = 8.2$ Hz, 2H, Ar(3,5)-H), 7.20 (d, $J = 8.2$ Hz, 2H, Ar(2,6)-H).

$$\text{(±)- tert-Butyl [(1R,2R,3S*)-4,4-dibromo-4-[(p-methoxybenzyl)sulfonyl]-2-(methoxymethoxy)-1,3-dimethylbutoxy] dimethylsilane (116).}$$

To a stirred solution of 4.4 mg (110 µmol) of freshly powdered sodium hydroxide in 200 mL of dimethylformamide at 0°C was added 40 mg (120 µmol) of carbon tetrabromide. The resulting yellow solution was stirred 5 min and a solution of 46 mg (100 µmol) of sulfone 113 in 50 µL of dimethylformamide was added dropwise imparting a bright green color to the reaction mixture, turning brown after 2 min. The resulting solution was stirred at 0°C for 1 h, then directly chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 15:1) to afford 16 mg (26%) of slightly impure α,α-dibromosulfone 116: $^1$H NMR (CDCl₃, 300 MHz) $\delta$ 0.05 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.88 (s, 9H, CCH₃), 1.12 (d, $J = 5.6$ Hz, 3H, CH₃), 1.29 (d, $J = 6.8$ Hz, 3H, CH₃), 2.55 (m, 1H, C(3)-H), 3.25 (m, 2H, C(4)-H, C(2)-H), 3.33 (s, 3H, OCH₃), 3.72-3.85 (m, 2H, C(1)-H, C(4)-H), 3.82 (s, 3H, OCH₃), 4.61 (d, $J = 6.4$ Hz, 1H, OCH₂), 4.76 (d, $J = 6.4$ Hz, 1H, OCH₂), 6.93 (m, 2H, Ar(2)-H, Ar(6)-H), 7.95 (m, 2H, Ar(3)-H, Ar(5)-H): $^{13}$C NMR (CDCl₃, 62.9 MHz) $\delta$ -4.76 (q), -4.64 (q), 17.96 (s), 18.90 (q), 19.24 (q), 25.81 (q), 29.59 (d), 48.69 (t), 55.50 (q), 56.13 (q), 69.78 (d), 77.84 (s), 86.04 (d), 98.19 (l), 113.24 (d), 124.45 (s), 132.92 (d), 161.62 (s); exact mass calcd. for C$_{21}$H$_{27}$Br$_{79}$BrO$_5$Si (M-39) m/e 578.9641, found m/e 578.9668.
Continued elution of the column with the same solvent system afforded 24 mg (54%) of starting sulfone 113:

\[
\begin{align*}
\text{OMOM} & \quad \text{CH}_3 \\
\text{OTBS} & \quad \text{OMe} \\
\text{98}
\end{align*}
\]

(±)-(2R*,3R*,4S*)-trans-5-[(tert-Butyldimethylsilyl)oxy]-1-(p-methoxyphenyl)-4-(methoxymethoxy)-3-methyl-5-hexene (98). To a solution of 56 mg (122 µmol) of sulfone 42 in 400 µL of tetrahydrofuran and 50 µL of hexamethylphosphoramide at 0°C was added 235 µL (146 µmol) of a 0.625 M stock solution of lithium hexamethyldisilazane in tetrahydrofuran. The resulting dark red solution was stirred 1 h at 0°C, then added dropwise via cannula to a vigorously stirred solution of NBS in 200 µL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 h, diluted with 5 mL of diethyl ether and washed with 5 mL of water. The aqueous phase was extracted with two 10-mL portions of diethyl ether and the combined organic phases were washed with 10 mL of saturated aqueous brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel to afford 6.0 mg (8%) of dibromide 116: Continued elution gave 39 mg of an inseparable mixture composed of an approximately 2:1 ratio of bromide 116a and sulfone 113, respectively.

A 20 mg sample of the mixture was dissolved in tetrahydrofuran and treated with 11 mg of potassium tert-butoxide in a single portion. The resulting solution was stirred 2 h and filtered through 1 g of silica gel. The silica gel was washed with 30 mL of diethyl ether and the combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (eluted with diethyl ether-petroleum ether, 1:20) to afford 6.0 mg (63%) of the trans alkene 98. Continued elution afforded 6.1 mg of sulfone 42.
(±)-4-[[[(2R*,3S*,4S*)-4-(tert-Butyldimethylsiloxy)-3-(methoxymethoxy)-2-methylpentyl]thio)methyl]-1,10,12-trimethoxy-8-methyl-6H-benzo[cd]naphtho[1,2,3]pyran-6-one (117). To a slurry of 11 mg (26 µmol) of bromide 76 in 400 µL of benzene was added 8.0 mg (26 µmol) of thiol 110 followed by 4.0 µL (4.0 mg, 26 µmol) of DBU. The yellow slurry was stirred at room temperature for 3 h, diluted with 250 µL of chloroform and chromatographed over 3 g of silica gel (eluted with diethyl ether-chloroform, 1:50) to afford 12 mg (72%) of sulfide 117 as a yellow green oil that slowly solidified: mp 106-115°C; IR (neat) 2930, 1718 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.03 (s, 3H, SiCH₃), 0.05 (s, 3H, SiCH₃), 0.86 (s, 9H, C(CH₃)₃), 1.03 (d, J = 6.8 Hz, 3H, CH₃), 1.08 (d, 3H, J = 6.3 Hz, CH₃), 1.92 (m, 1H, C(2')-H), 2.35 (dd, J = 12.4, 9.4 Hz, 1H, C(1')-H), 2.49 (s, 3H, ArCH₂), 2.81 (dd, J = 12.6, 3.4 Hz, 1H, C(1')-H), 3.13 (t, J = 5.5 Hz, 1H, C(3')-H), 3.32 (s, 3H, OCH₃), 3.93 (m, 1H, C(4')-H), 3.98 (s, 3H, ArOCH₃), 4.02 (s, 3H, OCH₃), 4.08 (s, 3H, ArOCH₃), 4.48-4.71 (m, 4H, OCH₂, OCH₂, ArCH₂, ArCH₂), 6.86 (d, J = 8.1 Hz, 1H, Ar(3)-H), 7.17 (s, 1H, Ar(9)-H), 7.32 (d, J = 8.3 Hz, 1H, Ar(2)-H), 7.95 (s, 1H, Ar(7)-H), 8.55 (s, 1H, Ar(11)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 4.71 (q), -4.63 (q), 17.37 (q), 17.97 (s), 19.58 (q), 21.61 (q), 25.87 (q), 34.59 (d), 34.77 (t), 40.36 (t), 55.81 (q), 56.32 (q), 56.68 (q), 57.21 (q), 70.03 (d), 86.54 (d), 98.31 (t), 106.12 (d), 107.26 (d), 114.85 (s), 118.14 (d), 119.54 (s), 122.12 (s), 122.48 (d), 122.77 (s), 124.66 (s), 127.45 (s), 130.84 (d), 139.85 (s), 142.16 (s), 153.14 (s), 156.27 (s), 157.28 (s), 160.62 (s).
(±)-4-[[[(2'R,3'S,4'S*)-4'-[tert-Butyldimethylsiloxy]-3'-(methoxymethoxy)-2'-methylpentyl)sulfonyl]methyl]-1,10,12-trimethoxy-8-methyl-6H-benzo[d]naphtho[1,2,b]pyran-6-one (118). To a solution of 16.8 mg (25 pmol) of sulfide 117 in 250 µL of chloroform was added 10.5 mg (125 pmol) of sodium bicarbonate followed by a solution of 12.5 mg (62.5 mmol) of m-chloroperbenzoic acid in 250 µL of chloroform. The resulting solution was warmed to room temperature and stirred for 3h, then directly chromatographed over 6 g of silica gel (eluted with chloroform-diethyl ether, 30:1) to afford 15.0 mg (85%) of the sulfone 118 as a yellow green oil. The oil crystallized on standing to afford a yellow green solid: mp 192-195°C; IR (neat) 2990, 2970, 1750, 1720 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.04 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.88 (s, 9H, CCH₃), 1.10 (d, J = 6.3 Hz, 3H, CH₃), 1.31 (d, J = 6.8 Hz, 3H, CH₃), 2.50 (s, 3H, ArCH₃), 2.45-2.6 (m, 1H, C(2')-H), 3.07 (dd, J = 13.9, 9.8 Hz, 1H, C(1')-H), 3.18 (dd, J = 6.6, 3.7 Hz, 1H, C(3')-H), 3.33 (s, 3H, OCH₃), 3.53 (d, J = 6.7 Hz, 1H, C(4')-H), 4.00 (s, 6H, ArOCH₃, ArOCH₃), 4.06 (s, 3H, ArOCH₃), 4.54 (d, J = 6.7 Hz, 1H, OCH₂), 4.75 (d, J = 6.7 Hz, 1H, ArCH₂), 5.30 (d, J = 13.5 Hz, 1H, ArCH₂), 5.42 (d, J = 13.5 Hz, 1H, ArCH₂), 6.97 (d, J = 8.3 Hz, Ar(2)-H), 7.17 (s, 1H, Ar(9)-H), 7.52 (d, J = 8.3 Hz, 1H, Ar(3)-H), 7.90 (s, 1H, Ar(7)-H), 8.55 (s, 1H, Ar(11)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.73 (q), 17.92 (s), 19.30 (q), 19.59 (q), 21.61 (q), 25.85 (q), 28.68 (d), 28.97 (s), 55.21 (t), 55.85 (q), 56.35 (q), 56.50 (q), 57.23 (q), 61.78 (t), 70.22 (d), 87.19 (d), 98.49 (t), 106.21 (d), 107.40 (d), 114.82 (s), 115.19 (s), 118.37 (d), 119.17 (s), 122.02 (s), 122.43 (d), 122.65 (s), 125.44 (s), 135.20 (d), 140.09 (s), 141.56 (s), 153.35 (s), 157.42 (s), 157.93 (s), 160.40 (s); C₂₂H₁₈O₆Si (M-324) m/z 378.1085, m/z found 378.1094 (corresponds to aldehyde 75).
S-(p-Methoxybenzyl) thiobenzenesulfonate (124). To a solution of 561 mg (2.4 mmol) of tosyl bromide in 15 mL of carbon tetrachloride at 0°C was added 334 mL (242 mg, 2.4 mmol) of triethylamine. To the resulting solution was added 308 mg (2.4 mmol) of p-methoxybenzyl thiol in 5 mL of carbon tetrachloride over a 30 min period. The reaction mixture was maintained at or below 5°C for 1 h, then diluted with 500 mL of dichloromethane, washed with 25 mL of 5% aqueous HCl, 40 mL of saturated aqueous sodium bicarbonate, and finally 50 mL of saturated aqueous brine. The organic portion was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 30g of silica gel (eluted with petroleum ether-diethylether, 10:1) to afford 554 mg (90%) of thiosulfonate as a white solid. An analytical sample was prepared by recrystallization from chloroform-petroleum ether which gave white platelets: mp 58-59°C; IR (CH₂Cl₂) cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.43 (s, 3H, CH₃), 3.76 (s, 3H, OCH₃), 4.21 (s, 2H, CH₂), 6.74 (d, J = 8.5 Hz, 2H, Ar(3,5)-H), 7.09 (d, J = 8.5 Hz, 2H, Ar(2,6)-H), 7.27 (d, J = 8.2 Hz, 2H, SO₂Ar(3,5)-H), 7.73 (d, J = 8.2 Hz, 2H, SO₂Ar(2,6)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 21.51 (q), 39.82 (t), 55.17 (q), 114.09 (d), 125.25 (s), 126.87 (d), 129.64 (d), 130.28 (d), 142.00 (s), 144.50 (s), 159.29 (d); exact mass calcd. for C₁₅H₁₆O₃S₂ m/z 308.0541, found m/z 308.0569.

Anal. calcd. for C₁₅H₁₆O₃S₂: C, 58.42; H, 5.23; found C, 58.23; H, 5.28.
(±)-tert-Butyl [(1R*,2R*,3S*)-4-[(p-methoxybenzyl)sulfonyl]-2-(methoxymethoxy)-1,3-dimethyl-4-(phenylsulfonyl)butoxy]dimethylsilane (126). To a solution of 53 mg (127 μmol) of sulfone 96 in 630 mL of tetrahydrofuran and 110 mL of hexamethyl phosphoramidate at -78°C was added 87.5 mL (140 μmol) of n-butyllithium as a 1.6 M solution in hexanes. The bright yellow solution was stirred 30 min at -78°C before 37 mg (127 μmol) of thiosulfonate 124 was added in a single portion. The resulting mixture was stirred for 1 h and then warmed to room temperature over a 1 h period. The mixture was diluted with 25 mL of diethyl ether and washed with 10 mL water followed by 10 mL of saturated brine. The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:5) to afford 44 mg (61%) of the desired benzylic sulfide as an oil (¹H NMR), contaminated with unreacted sulfone. The impure material was dissolved in 1.5 mL of dichloromethane at 0°C and treated with 45 mg of solid sodium bicarbonate. To the resulting slurry was added 33 mg (155 μmol) of 80% m-CPBA in one portion. The reaction was stirred for 4.5 h and quenched by the addition of 10 mL of saturated aqueous sodium bicarbonate. The resulting emulsion was extracted with three 15-mL portions of dichloromethane and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was crystallized from petroleum ether-ethyl acetate and then recrystallized from methanol to afford 38 mg (83%) of the bissulfone as white needles: mp 145-147°C; IR (CH₂Cl₂) cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ -0.09 (s, 3H, SiCH₃), 0.05 (s, 3H, SiCH₃), 0.84 (s, 9H, CCH₃), 0.97 (m, 6H, CH₃), 2.64 (m, 1H, C(3)-H), 3.23 (s, 3H, OCH₃), 3.49 (dd, J = 9.8, 2.5 Hz, 1H, C(2)-H), 3.82 (s, 3H, ArOCH₃), 3.94 (m, 2H, C(1)-H, ArCH₂), 4.20 (d, J = 6.5 Hz, 1H, ArCH₂), 4.60 (d, J = 13.6 Hz,
1H, OCH₂), 4.99 (d, J = 13.6 Hz, 1H, OCH₂), 5.12 (s, 1H, C(4)-H), 6.95 (m, 2H, Ar(3,5)-H), 7.57 (m, 2H, Ar(2,6)-H), 7.60 (m, 2H, SO₂Ar(3,5)-H), 7.71 (m, 1H, SO₂Ar(4)-H), 8.06 (m, 2H, SO₂Ar(2,6)-H); ¹³C NMR δ -5.02 (q), -4.31 (q), 11.67 (q), 17.86 (s), 18.04 (q), 25.75 (q), 35.30 (d), 55.26 (q), 55.54 (q), 62.61 (t), 68.31 (d), 76.89 (d), 85.23 (d), 98.79 (t), 114.39 (d), 119.18 (s), 128.96 (d), 130.16 (d), 132.74 (d), 134.50 (d), 137.06 (s), 160.37; exact mass calcd. for C₂₇H₄₁O₈Si m/e (M - 15) 585.2012, found m/e 585.2011.

Anal. calcd. for C₂₈H₄₄O₈Si: C, 55.97; H, 7.38; found C, 55.96; H, 7.35.
Nonclassical Behavior of 1,8-Disubstituted Naphthalenes and Related Systems.

During the synthetic studies described in Chapter I, we gradually became aware of reactivity differences between benzylic systems and C(4) substituted substrates derived from defucogilvocarcin M. In fact, every convergent step explored as a potential route to the chrysomycins met with success in a benzylic models, while every attempt to couple a carbohydrate surrogate to a defucogilvocarcin derived tetracycle failed. Three of the unsuccessful coupling reactions are shown below. Aldehyde 75 was resistant to nucleophilic attack (Equation 17), bromide 76 was delicate (Equation 18), and under Ramberg-Backlund rearrangement conditions, sulfone 118 gave an aldehyde (Equation 19).
We suspected involvement of the C(4b) lactone oxygen in the reactivity problems although its exact role was not clear. Over the course of our studies, however, evaluation of the primary literature began to shed light upon the situation. The unorthodox chemistry associated with these systems was evidently related to the peri interaction which arises in simpler 1,8-disubstituted naphthalenes.

**Perl Interaction: Nonclassical Behavior of 1,8-Disubstituted Naphthalenes.**

The inflexible carbon skeleton associated with aromatic systems imparts rigid geometry to ring substituents. In 1,8-disubstituted naphthalenes, ligands are forced into extremely close proximity. The distance separating these ligands is generally less than the sum of their combined Van der Waals radii. This lack of “elbow room” imparts ground state strain energy to the molecule, and special reactivity to the substituents. Traditional organic chemistry is therefore not always observed in these systems and instead, a driving force to remain or return to sp² hybridization operates.

Equation 20 depicts Kirby’s finding that treatment of methyl ketone 127 with methyllithium leads only to enolization. Addition to the carbonyl would result in sp³ hybridization of a peri
substituent and is therefore not observed.

In Scheme XXVIII, elimination of the tertiary alcohol in 129 affords styrene 130. In Scheme XXVIII, elimination of the tertiary alcohol in 129 affords styrene 130. Chemoselective hydrogenation of the double bond in 130, however, leads to ring reduction to the tetralin 131. It is feasible that in this particular system the double bond is reduced first, however, equation 21 further illustrates the propensity of strained naphthalenes to relieve peri strain. Attempted C-O bond cleavage in 129 thus liberates dihydronaphthalene 132.

Scheme XXVIII. Peri Strain Promoted Reduction of a Naphthalene Ring.

In Scheme XXIX, dihydronaphthalene 133 is oxidized to naphthalene 134 with DDQ, benefiting from a gain in resonance energy. Nevertheless, exposure of 134 to dilute mineral acid results in loss of the isopropyl group prior to MOM hydrolysis. This unusually easy retro Friedel-Crafts reaction is clearly driven by the release of peri strain.
During a total synthesis of aaptamine, Joule noted that condensation with the formyl group in quinoline 136 was abnormally challenging (Equation 22). Treatment of 136 with the anion derived from nitromethane (and further activated by the addition of DMPU) gave alcohol 137 in 15% yield. Although nitromethane readily forms 1,2-addition products with aldehydes, in this peri substituted quinoline the use of sodium methoxide, potassium tert-butoxide, triethylamine, or diisopropylamine as an alternative base did not improve matters.

The disubstituted naphthalenes in Figure 10 exhibit unusual reactivity. The borane substructure of naphthalene 138 defies oxidation by hydrogen peroxide even under forcing conditions. It is believed that this compound contains a nucleophile-electrophile interaction (Chapter III) and the vacant p-orbital on boron is actually filled by the nonbonding nitrogen lone pair. The $^1$H NMR spectrum of compound 139 in deuterotrifluoroacetic acid indicates the amino
methyl groups are diastereotopic. Apparently naphthalene 139 is largely ring closed in acidic media and exists primarily as the hemiaminal.

![Figure 10. 1,8-Disubstituted Naphthalenes.](image)

Proximity effects of the MOM acetal in naphthalene 140 deter alkylation of the nitrogen atom (Figure 11). To methylate this compound, Meerwein's salt must be employed. On the other hand, although conditions for ammonium salt dealkylation are usually brutal, water made weakly basic by the addition of triethylamine is sufficient to dealkylate 141 within 30 minutes.

![Figure 11. Alkylation-Dealkylation of Peri Dimethylamino Groups.](image)

**Peri Interaction in the Gilvocarcins.**

Natural products that exhibit a peri interaction are few in number. Of the known C-aryl glycosides, only the gilvocarcin family embodies the strain problem associated with 1,8-disubstituted naphthalenes. Nonetheless, this interaction may be responsible for a number of chemical properties of the gilvocarcins.
As shown in (Scheme XXX), treatment of gilvocarcin V (toromycin) (3) with a catalytic amount of p-toluenesulfonic acid in acetonitrile results in ring expansion and anomerization of the carbohydrate. At least two other compounds are produced by this rearrangement, but to date structures of these compounds have not been delineated.

Acid catalyzed reactions are standard chemistry within the context of O-glycosides. C-glycosides, however, lack a geminal oxygen at the anomeric position, and are therefore less susceptible to modification by acid. This raises an interesting question as to what particular trait related to the gilvocarcins serves to facilitate rearrangement.

Quinone methide 144 has been proposed as an intermediate in the rearrangement of 3 to 142 and 143.\textsuperscript{54} However, for 144 to be involved, stereoelectronic requirements dictate that the C(2') C-O bond be aligned with the aromatic pi system. As bond breakage occurs, an intrusive methine proton must be rotated towards the C(4b) lactone oxygen until ultimately coplanarity is
achieved (Scheme XXXI). X-ray crystallography experiments conducted by the author (Chapter III) suggest that a proton attached to a freely rotating carbon at this site should prefer to be out of the naphthalene plane.

Scheme XXXI. Quinone Methide Mediated Rearrangement of Gilvocarcin V.

An alternative rearrangement pathway is portrayed in Scheme XXXII. C-O bond cleavage is facilitated by neighboring group participation of the C(4b) lactone oxygen, and takes place through a conformation in which the C-O linkage is orthogonal to the aromatic π framework. In this mechanism, a three component equilibrium serves to alleviate charge-density build up at the peri position. Thus peri strain is relieved via incipient bond formation. It is notable that structures 146 and 147 differ only by the position of a single lone pair of electrons and all atoms remain intact. Therefore 146 and 147 are resonance structures.

The quinone methide model presented in Scheme XXXI is inconsistent with the data in Equations 21 and 22. Suzuki reported that equilibration of C-phenyl glycoside 46 with protic acid is achieved under relatively vigorous conditions (equation 21).[^9] This epimerization likely proceeds through a quinone methide intermediate. In equation 22, the C-naphthyl glycoside 49 could also epimerize by way of a quinone methide, however, the aforementioned steric problems diminish the likelihood of this pathway. Therefore if a quinone methide were involved in these transformations, equilibration of 46 should be expected to occur under milder conditions than 49.
This is not the case. Indeed the effects of a perioxy substituent are far reaching. After 49 stood in CDCl₃ for 1 hour (containing a trace of acid), the furanose ring of 49 was completely equilibrated. Under the same conditions, monocyclic C-glycoside 49 was unaffected. It is counterintuitive to believe a quinone methide mediates the conversion of naphthyl glycoside 49 and not 46. On the contrary, a quinone methide would be a more likely intermediate if 46 had epimerized and not 49. Differences in the mechanisms in Scheme XXX and Scheme XXXI are academic in nature, but it is important to recognize that distinctly different conformations are necessary for each mechanism, and that only one mode may operate.
Alkoxide Mediated Rearrangements of the Gilvocarcins.

The degradative rearrangement of ravidomycin (8) under the influence of base has also been described. Alkaline fusion of 8 in 50% KOH at reflux for 6h gave rise to two products of interest, defucogilvocarcin V (1) (13%), and hemiacetal 149 (45%) (Scheme XXXIII). Loss of the carbohydrate component to give the aglycone 1 was explained invoking the mechanism in Scheme XXXIV. Ground state strain is relieved through protonation of the ravidomycin A ring, which leads to formation of quinone methine 151. Interception of 151 by hydroxide accomplishes an overall "inverse" electrophilic aromatic substitution.

The formation of 149 has been postulated to arise via quinone methide 152 as shown in Scheme XXXV. Deprotonation of the C(1) hydroxyl in ravidomycin first triggers ejection of the pyranose ring oxygen, and under the basic conditions, a Grob fragmentation of the resulting
Scheme XXXIII. Base Mediated Rearrangement of Ravidomycin.

quinone methide 151 rearomatizes the A-ring generating an enol (not pictured) which tautomerizes to aldehyde 153. Ring closure of naphthyloxy aldehyde 153 produces hemiacetal 149.
It is possible once again however, that a peri substituent plays a critical role. An alternate mode of hemiacetal formation is shown in Scheme XXXVI. Thus alkaline conditions favor a ring open form of the ravidomycin pyranone as in structure 154. The liberated alkoxide substituent intramolecularly displaces the pyranose ring oxygen. A fragmentation similar to the one proposed in Scheme XXXV then leads to the common intermediate 153 en route to lactol 149.

Results and Discussion.

It was anticipated that a better understanding of the reactivity of 1,8-disubstituted naphthalenes would assist in the chrysomycin studies. Sulfone 118 (Scheme XXIV), for example, had hydrolyzed to an aldehyde under Ramberg-Backlund conditions. Since α-halosulfones are notoriously resistant to hydrolysis, it was quite interesting that the only isolable polyaromatic product was aldehyde 75.
Scheme XXXVI. Base Mediated Rearrangement of Ravidomycin Involving the C(4b) Lactone.

The mechanism proposed in Scheme XXIV and reiterated in Scheme XXXVII explains this result on the basis of relief of strain energy. In halosulfone 120, for example, strain relief is achieved via five membered ring formation (Scheme XXXVII). Labile 120a would then be hydrolyzed on workup to afford the aldehyde.

Originally, when sulfone 118 failed to contract to an olefin, installation of a leaving group within the carbohydrate skeleton prior to sulfur extrusion was attempted. In this manner, introduction of a leaving group at the highly hindered sulfonyl α carbon could be avoided. In addition, it was felt that a leaving group at the ω'-sulfonyl carbon would be effected by neighboring group participation to a lesser degree. This chemistry was never actually studied in great detail, however, since a benzylic model was not encouraging. However, in retrospect, these arguments
Scheme XXXVII. Possible Decomposition Step in Ramberg-Backlund Reaction of 118.

ignored the peri interaction problem.

To relieve ground state strain, a free naphthoxide at C(8) would likely have displaced the bridging sulfone moiety (Scheme XXXVIII). In fact, any leaving group at C(2') would likely succumb to peri strain under alkaline conditions, based on the hypothetical model described in Scheme XXIV.

Scheme XXXVIII. Projected Result of Ramberg-Backlund Reaction of Bissulfone 153.

Little evidence supported the proposed degradation model, but on the other hand, no evidence refuted it. The critical point was whether a neighboring group coerced displacement of C(4) substituents, and if so, what groups at C(4b) could act as nucleophiles.
In Equation 18, bromide 76 decomposed upon exposure to the reaction mixture. One possibility, therefore, was that the oxygen of an unopened lactone was enough to discharge a leaving group. If this was the case, then the route to chrysomycin B would need major reworking.

In coupling reactions of defucogilvocarcin derived substrates examined thus far, aldehyde 75 represented the only polyaromatic product actually observed. Therefore, there was no reason to believe that defucogilvocarcin derived substrates would provide evidence in the displacement matter. In light of this, some analogous substituted naphthalenes were prepared to serve as mechanistic probes.

The first target was a C(4b)-naphthol benzoate which carried a peri sulfone (Scheme XXXIX). If the proposed mechanism was accurate, then this system should liberate 8-hydroxynaphthaldehyde, benzoic acid, and ethyl sulfinic acid under Ramberg-Backlund conditions.

Scheme XXXIX. Projected Reactivity of a Peri Substituted Dialkyl Sulfone.

A potential precursor of this benzoate sulfone, aldehyde 158, was prepared by the sequence outlined in Scheme XL. Exhaustive methylation of 1,5-dihydroxynaphthalene (154) gave a bis methyl ether which was formylated using a Vilsmeier reaction.\textsuperscript{60,61} Regioselective demethylation of the resulting aldehyde (156) afforded 4-methoxy-8-hydroxy-1-naphthaldehyde (157).\textsuperscript{61} Acylation of 157 was achieved with benzoyl chloride and Hunig's base to give benzoate 158. Unfortunately, reduction of 158 gave a complex mixture of products.
It was possible that the alcohol which was generated during the reduction process was intramolecularly hydrolyzing the ester. To eliminate this possibility, a geometrically constrained ester was devised. The ester was fastened back to the B-ring so that neighboring group participation was not feasible. As depicted in Scheme XLI Pechman condensation of ethyl acetoacetate with 1,5-dihydroxynaphthalene gave tricyclic naphthol 159. Methyl ether formation was conducted using dimethyl sulfate and potassium carbonate in acetone giving 160 in 88% yield. Unfortunately, this substrate was labile to formylation conditions and a C(4) aldehyde could not be introduced.

It was becoming clear that evidence for the hydrolysis model in Scheme XXIV would not come easily. We therefore turned our attention towards a complimentary aspect of the problem by using sulfone 161 (Scheme XLII). In contrast to the substrates in Schemes XL and XLI, this new target would support the mechanism if it did yield an olefin. It would be difficult ascertain whether a lactone was open or closed under a given set of reaction conditions, but in 161, the
Scheme XLI. Preparation of Formylation Precursor.

methoxy group represented a lactone which was "locked" shut. Thus a peri alkoxide mediated pathway was ruled out here, and normal behavior was expected for projected intermediate α-halosulfone 161a, unless a peri ether substituent was capable of altering reactivity.

Scheme XLII. Projected Reaction Pathway for Sulfone 161.
Scheme XLIII outlines the preparation of sulfone 161. Reduction of aldehyde 156 with sodium cyanoborohydride in aqueous THF gave alcohol 162 in 94% yield. Conversion of 162 to bromide 163 was accomplished in 74% yield using phosphorous tribromide in benzene. A thioethyl group was attached to 163 using ethanethiol and DBU, to furnish sulfide 164 in 76% yield. Oxidation of 164 was best achieved with oxone, delivering 161 in quantitative yield.

Scheme XLIII. Olefination of Sulfone 161.

The stage was now set for the olefination. Treatment of 161 with carbon tetrachloride, freshly ground potassium hydroxide, and tert-butanol produced trans-alkene 165 in 74% yield, contaminated with an inseparable impurity. Extrusion occurred in this system at room temperature and was complete in 4 hours. The contaminant appeared to contain a methyl doublet at δ 1.5 and a methyl ether singlet at δ 4.1 in the 250 MHz 1H NMR spectrum. However, the vinyl region was free of peaks due to the impurity and mass spectral analysis showed the
absence of chlorine. Therefore it was unlikely that the contaminant was cis or chlorinated olefin.

The stereochemistry of the major product was established as trans based on the 13 Hz coupling constant between vinyl protons $H_a$ and $H_b$. The chemical shift of $H_a$ in 165 seemed to underscore the phenomenon we had struggled against. While $H_a$ in styrene 166 appears at $\delta$ 6.25, $H_a$ in naphthalene 165 is observed at $\delta$ 7.50, apparently as a result of severe crowding. It is noteworthy that olefin production in naphthalene 165 was consistent with the mechanism proposed in Scheme XXIV, but offered no proof by itself.

Figure 12. Comparison of $H_a$ in Styrene 166 and Propenylnaphthalene 165.

The successful synthesis of olefin 165 prompted us to examine olefination in a substrate containing more functionality in the sidechain. In particular, the consequences of carrying a peri substituent through the selenium mediated ring closure step needed to be evaluated since the outcome was not necessarily predictable. Such a transformation would apparently violate the reactivity principles that had been established ($sp^2 \Rightarrow sp^3$ at a peri carbon), and neighboring group participation by the C(8) oxygen in this reaction would severely complicate our studies. To clarify this matter we examined the sequence outlined in Scheme XLIV.

As in the reaction with ethanethiol, bromide 163 was a potent alkylating reagent. Treatment of 163 with thiol 110 furnished dialkyl sulfide 167 in 76% yield. Oxidation of the resulting sulfide was best accomplished using $m$-CPBA at $0^\circ$C. In contrast to the earlier benzylic
models in Chapter I, 168 behaved as ethyl sulfone 161. Trans olefin 169 was obtained in 72% yield. No contaminant was present in this product. Once again, the vinyl proton adjacent to the naphthalene was found downfield, appearing at δ 7.8. This is 1.5 ppm downfield with respect to substituted styrene 166.

Scheme XLIV. Synthesis of C-Naphthyl Glycoside 171.

The apparently general solution to olefination in 8-substituted naphthaldehydes permitted examination of an electrophile initiated cyclization. Removal of the tert-butyl(dimethyl)silyl group in 171 was slow (48h with 5 equivalents of TBAF), but delivered enol 170 in 94% yield. Cyclization of alkene 170 under Merriman's prescribed conditions for kinetic control delivered a single diastereomeric selenide 171. Data is consistent with the stereochemistry, regiochemistry and
conformation depicted in Figure 13. Evidence for the regio and stereochemistry of 171 is provided by the chemical shift of H_b (δ 3.5) and the 11 Hz coupling constant between H_a and H_b. The downfield shift of H_a (δ 6.2) is nearly 2 ppm, from C-phenyl glycoside 68 in Scheme VIII, and is consistent with a conformation in which the hydrogen atom is pointed at the peri methoxy group. Consideration of competing steric effects, lone pair-lone pair interactions, and the known crystal structure of gilvocarcin M, the anomeric hydrogen and oxygen atoms are projected to lie below the mean plane of the naphthalene ring system and the C(5) methoxy group is likely to be wedged between the C(2)-C(3) bond and the anomeric carbon-hydrogen bond, closer to the hydrogen atom.

Figure 13. Ground State Conformation of C-glycoside 171.

The stereo and regiochemistry in 171 agrees with the results obtained in benzylic models which suggests a similar transition state may be involved in the cyclization. A mode of cyclization consistent with the transition state in Figure 4 and the stereochemistry of 171 is outlined in Scheme XLV. The hydroxyl group adds to the olefin opposite the face of the methoxy group. Steric repulsion between H_b and the peri methoxy group is significant, however, some overlap between the ethenyl π system and the aromatic ring is maintained. The potential for neighboring group participation by the methoxy group is minimized in this cyclization since the methoxy lone
pair is nearly orthogonal to the olefin pi system. The extraordinarily downfield chemical shift of the crowded proton in enol 170 suggests that the vinyl proton lies in approximately the naphthalene plane in its ground state conformation.

Scheme XLV. Mechanisms for Selenoetherification of 170.

The primary implication of the naphthalene enol cyclization was that the carbohydrate could be attached to a polyaromatic core in the presence of a peri substituent under the right circumstances. The pyranone ring of the gilvocarcins was absent in studies conducted in Scheme XLIV. This piece would simply have to be assembled subsequent to installation of the glycoside. We therefore turned to the issue of aglycone assembly. Natural chrysomycin B carries a hydroxyl group at C(1). Protection of this site had some complications associated with it, however. A 1-O-methyl derived substrate was adequate for studying aglycone construction and the preparation of such a substrate from aldehyde 158 appeared to be straightforward. Therefore, the hydroxyl protection problem was postponed until liberation of the tetracycle could be achieved in the presence of the sugar, and compound 6a was set as the next target for synthesis.

A retrosynthesis of 1-O-methyl chrysomycin B (6a) is shown in Scheme XLV. Thus, installation of the C and D rings was to be achieved using a MAD-mediated conjugate addition of aryl oxazoline 60 to highly functionalized naphthoquinone monoacetal 174, followed by lactonization. We envisioned assembly of the carbohydrate from enol 175 using the technology
Scheme XLVI. Disconnection of 1-O-Methyl Chrysomycin B.

previously developed in Scheme XLIV. Enol 175 was to be prepared from aldehyde 158.

We initiated these studies by constructing tetrasubstituted naphthalene building block 180 as described in Scheme XLVII. Aldehyde 158 was transformed into naphthol 176 using Rapoport’s method. A p-toluenesulfonate was employed to protect the naphthol since electron withdrawing properties of the sulfonate were expected to decrease electron density in the B-ring. This electronic requirement was necessary for regioselective A ring formylation. Heating a slurry of naphthol 176, potassium carbonate and acetone thus delivered 177 in 88% yield as a highly crystalline solid. Formylation indeed occurred regioselectively para to the C(8) methoxyl affording
aldehyde 178 in 93% yield. Reduction with sodium cyanoborohydride in acidic aqueous tetrahydrofuran was followed by conversion of the resulting alcohol to bromide 180 using phosphorus tribromide in benzene (83% yield for two steps).

Scheme XLVII. Functionalization of Naphthaldehyde 158.

Carbohydrate installation was accomplished as shown in Scheme XLVIII. Sulfide connection occurred instantly upon addition of DBU to a benzene slurry of bromide 180 and thiol 110. Following oxidation of sulfur to sulfone 182, Ramberg-Backlund rearrangement to trans-olefin 183 was achieved using the method which had succeeded in the preparation of sulfone 168. Removal of the silicon protecting group in 183 was accomplished using tetra-n-butylammonium fluoride in tetrahydrofuran to give a quantitative yield of alcohol 184. Selenoetherification of 184 delivered selenide 185 in 71% yield. Oxidation and elimination of selenide 185 was highly regioselective as had been previously observed.

It is notable that C-aryl glycal 186, produced by the selenoxide elimination, was labile and
appeared by $^1$H NMR to epimerize at the anomeric center after standing a short time in CDCl$_3$. In the absence of solvent, epimerization was not observed. Assembly of the tetrahydropyran was completed via osmylation of the trisubstituted olefin, thus affording chrysomycin B analog 187 as a single diastereomer in 94% yield.

We were now ready to complete preparation of the aglycone. As depicted in Scheme XLIX the vicinal glycol was protected using chloromethyl methyl ether and Hunig’s base. These conditions avoided degradation of the sugar and gave tris-MOM ether 188 in quantitative yield. One of the MOM methoxy singlets in 188 was observed at δ 2.85. This is presumably the C(3) MOM ether which is forced to reside over the naphthalene π system. Reduction of the sulfur-
oxygen bond was achieved with 5.25% sodium amalgam in methanolic tetrahydrofuran which gave naphthol 189 in 90% yield. Anodic oxidation of the B-ring produced naphthoquinone monoketal 174 in 76% yield. Enone 174 was treated with a freshly prepared stock solution of MAD in toluene which gave a dark purple aluminum complex. Addition of anion 60 to this complex produced a light red-brown solution. Workup and isolation provided conjugate adduct 191 in 30% yield.

Scheme XLIX. Installation of the D Ring, and C-Ring Elements.
It is noteworthy that the conjugate addition succeeded on such a highly oxygenated substrate. Moreover, evidence suggests that nucleophilic additions in MAD mediated conjugate additions are directed by the ketal oxygens. It is therefore noteworthy that the yield of conjugate adduct is comparable to the yield for the conversion $72 \rightarrow 73$ in Scheme IX (Chapter 1). However, we briefly examined the potential cause of yield moderation using the reaction shown in Equation 23. Dropwise addition of a solution of phenyllithium in ether-cyclohexane to a MAD complex of 190 gave conjugate adduct 192 in 84% yield. This result indicates that under the right circumstances 1-O-methyl substrates can react quite well. Swenton and coworkers noted marked increases in yields when ether was employed as solvent as opposed to THF. In the transformation $190 + 60 \rightarrow 191$ the reaction was run in toluene, but lithiated oxazoline 60 was generated in THF since lithiation was capricious in ether.

Unfortunately, before cyclization studies could be conducted on 191, the small amount of material at our disposal decomposed. While conjugate adduct 191 is indefinitely stable in an isolated state, it is apparently quite sensitive to acid. We were able to collect data in deuterated chloroform, however, after standing in CDCl$_3$ for 6h no 191 remained. TLC analysis indicated that conversion of 191 to the decomposition product was highly efficient, however, $^1$H NMR indicates that two very similar products are present (possibly diastereomers). One would anticipate that ketal hydrolysis in 191 would effect dual enolization of the resulting dione, such that the B-ring would aromatize. Indeed, in the $^1$H NMR of the decomposition products, two
signals consistent with hydrogen bonded naphthol protons are present at δ 10.6, two methoxy singlets are missing, as is the benzylic B-ring proton previously at δ 4.5. However, the anomeric proton appears to be missing as well, which may indicate that during B-ring enolization, the sugar unraveled. It is, however, difficult to say exactly what series of transformations took place.

Therefore, the B-ring dimethylketal group appears to be quite sensitive to acid. While this suggests that the ketal can indeed be removed, in the long run this could prove detrimental to the synthetic route since subsequent undesirable reactions apparently take place.

Nonetheless, we are currently preparing more cyclization precursor to evaluate the potential use of an acid mediated cyclization as a means of achieving C,D-ring system installation in the chrysosmycins.

Selection of the O-1 Protecting Group.

The final problem was selection of a protecting group for the C(1)-hydroxyl group. For example, assuming 191 could be cyclized, O(12) would have to be methylated, the MOM groups would have to be removed, and then selective removal of the O(1) hydroxyl would have to be achieved. Although pyranone formation could probably be made to succeed, methylation of hydrogen bonded O(12) would be more difficult, and selective demethylation would be next to impossible. Therefore either the 1-O-methyl group had to be removed and replaced by an adequate protecting group, or a suitable protecting group had to be instituted from the beginning. The latter scenario was adopted because this route minimized steps and also because 4-methoxy-8-hydroxy-1-naphthaldehyde (157) was readily available. This material would presumably allow convenient installation of a protecting group through alkylation of the free naphthol (Scheme LI).
Scheme L. Aldehyde 157 as a Building Block.

Alkylation of peri substituted naphthols requires highly reactive species. It was also necessary that once installed, the protecting group had to direct electrophilic attack to the naphthalene A ring. This essentially restricted possibilities to ethers, silyl ethers, and acetals. Acetals were precluded by virtue of their acid sensitive nature. It was questionable whether silylation of this hindered position would succeed employing bulky silanes, and smaller ones, like trimethylsilyl, might not survive formylation. Introduction of a silyl ether would also generate a chemoselectivity problem since a tert-butyldimethylsilyl ether was already present in the sugar.

This narrowed the possibilities to ethers which could be cleaved. Suzuki had employed a benzyl ether in the synthesis of gilvocarcin. Unfortunately, Merriman's studies demonstrated that this group was incompatible with formylation. Allylic ethers have seen use as protecting groups, but our scheme for carbohydrate introduction involved osmylation of a trisubstituted olefin. It was more than likely, therefore, that the protecting group would be oxidized first. Thus a host of protecting groups have been developed, but it did not appear that any published ones were suitable for our needs.

We therefore evaluated the potential of using a propargyl ether as a protecting group. Two questions were how acidity of the acetylenic proton would effect the MAD reaction, and whether it would survive formylation conditions.

The studies shown in Scheme LII were conducted to evaluate the outcome of formylation.
Alkylation of naphthol **157** with 3-bromo-1-trimethylsilylpropyne followed by desilylation with methanolic potassium hydroxide gave terminal acetylene **196** in 84% yield. Baeyer-Villiger oxidation of **196** followed by saponification of the resulting formate gave naphthol **198** in 50% recrystallized yield for two steps. The naphthol was protected as a sulfonate ester by treating a 0°C solution of the derived naphthoxide with tosyl chloride in acetonitrile in the presence of 18-crown-6. Formylation of tosylate **199** gave aldehyde **200** in quantitative yield. Thus the propargyl group clearly did not interfere with formylation.

**Scheme LI. Formylation of Propargyl Ether 200.**

Turning to the MAD reaction, naphthol **198** was electrochemically oxidized in a 1% solution of lithium perchlorate in methanol to afford naphthoquinone monoketal **201** in 75% yield. MAD-mediated conjugate addition of **60** to **201**, however, gave a complex mixture from which a 6% yield of **202** was isolated after an acidic workup. The adverse solubility properties of this
yellow solid made characterization difficult. However, infrared, $^1$H NMR, and mass spectral data are consistent with structure 202. In addition to 202, 50% of the starting naphthoquinone monoketal 201 and oxazoline 60 were recovered. It was concluded that deprotonation of the acetylene was an issue and so the terminal acetylene had to be blocked.

**Scheme LII. MAD Mediated Conjugate Addition to Propargyl Ether 201.**

The first choice for a blocking unit was a trimethylsilyl group. Thus silylacetylene 203 was subjected to Baeyer-Villiger oxidation followed by reduction of the crude formate with sodium borohydride. The trimethylsilyl group, however, was not very stable to the oxidation and only a 24% yield of 204 was obtained. However, the MAD reaction was conducted anyway, in an attempt to discern the potential use of less labile silicon groups. Anodic oxidation of 204 gave naphthaleneone 205 in 80% yield. Addition of lithiated aryl oxazoline 60 to 204, however, gave no conjugate adduct. Desilylated ketal 201 was present in the crude product ($^1$H NMR), indicating that desilylation was a problem.

A more stable group was therefore needed at the acetylene terminus, and thus a methyl group was evaluated. As shown in Scheme LV, tosylate 199 was deprotonated at -60°C and methylated without competing sulfonate cleavage. The resulting butynyl ether 206 directed formylation to C(5) in 69% yield.
Scheme LIII. Evaluation of a 1-Trimethylsilyl-3-propynyl Ether Protecting Group.

\[
\begin{align*}
&\text{HO CHO} \\
&\text{TMS} \\
&\text{K}_2\text{CO}_3, \Delta \\
&84\% \\
\end{align*}
\]

\[
\text{157} \xrightarrow{\text{TMS} \equiv \text{Br}} \text{157} \xrightarrow{\text{1. m-CPBA}} \text{1. m-CPBA} \\
\text{CH}_2\text{Cl}_2 \xrightarrow{\text{2. NaBH}_4} \text{2. NaBH}_4 \text{MeOH} \\
24\%
\]

\[
\text{Decomposition} \xrightarrow{\text{MAD, -78°C}} \text{L}^{60} \xrightarrow{\text{MeO}} \text{OMe} \xrightarrow{\text{TMS}} 205
\]

Scheme LIV. Preparation and Formylation of 206.

\[
\begin{align*}
&\text{OMe} \\
&\text{1. n-BuLi, -60°C;} \\
&\text{Me}, 90\% \\
\end{align*}
\]

\[
\text{199} \xrightarrow{1. n-\text{BuLi, -60°C;}} \text{199} \xrightarrow{\text{Me}, 90\%} \text{206} \\
\text{206} \xrightarrow{\text{TiCl}_4, \text{Cl}_2\text{CHMe}} \text{207}
\]

In conclusion, a triple bond derived protecting group has been installed which tolerates formylation conditions, and no problems in the MAD-mediated conjugate addition are foreseeable. Problems that will have to be addressed, however include selectivity in the electrophile initiated
cyclization and osmylation reactions. Preliminary results indicate that in the selenium mediated cyclization, some addition across the triple bond does occur, however slow addition of the electrophile suppresses this side reaction. Success in the osmylation reaction is projected on the basis of osmylation studies conducted by Corey.

Removal of this group will also have to be addressed. Two potential methods include formation of a cobalt complex followed by solvolysis in methanol, or alternatively the institution of palladium chemistry in a manner consistent with allylic ether cleavage.

Experimental.

A general experimental section is presented at the beginning of the Chapter 1 Experimental section.

8-Hydroxy-4-methoxy-1-naphthaldehyde, benzoate (158). To a solution of 202 mg (1 mmol) of naphthol 158 in 5 mL of tetrahydrofuran was added 177 μL (1.0 mmol) ethylidisopropylamine followed 5 min later by 116 μL (140 mg, 1.0 mmol) of benzoyl chloride. The resulting reaction mixture was stirred 3h and 0.1 mmol of benzoyl chloride was added. After an additional 30 min the suspension was quenched with 10 mL of 1N HCl and extracted with three 50-mL portions of dichloromethane. The combined extracts were dried (MgSO₄), and concentrated to afford 274 mg (90%) of the benzoate as a yellow solid. An analytical sample was recrystallized from chloroform-petroleum ether to afford colorless crystals suitable for X-ray analysis: mp 173-174.5°C; IR (CH₂Cl₂) 3020(w), 1744, 1727 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 4.09 (s, 3H, OCH₃), 6.93 (d, J = 8.3 Hz, 1H, Ar(3)-H), 7.51-7.59 (m, 5H, Ar-H), 8.15 (d, J =8.2
Hz, 1H, Ar-H), 8.22-8.26 (m, 2H, Ar-H), 8.33 (d, J = 8.2 Hz, 1H, Ar(5)-H), 10.78 (s, 1H, CHO); 
\(^{13}\)C NMR (CDCl\(_3\), 62.8 MHz) \(\delta\) 56.01 (q), 103.72 (d), 121.23 (d), 122.77 (d), 125.46 (d), 125.97 
105 (s), 126.48 (s), 127.51 (s), 128.84 (d), 128.98 (s), 131.83 (d), 134.01 (d), 146.57 (s), 160.03 
(s), 165.07 (s); exact mass calcd. for C\(_{19}\)H\(_{14}\)O\(_4\) \(m/e\) 306.0892, found \(m/e\) 306.0892.

7-Hydroxy-4-methyl-2-oxo-2H-naphtho[1,2\(b\)]pyran (159).\(^{62}\) To a 0°C slurry of 4.00 g 
(25 mmol) of bisnaphthol 154 in 3.69 g, (28.4 mmol) of ethyl acetoacetate was added 10 mL of 
concentrated H\(_2\)SO\(_4\) dropwise over 25 min. The mixture was stirred for about 45 min and then 
allowed to stand for 2 h. The resulting mixture was poured into 200 mL of ice-water and 
exttracted with four 300-mL portions of diethyl ether. The ether layers were dried (MgSO\(_4\)) and 
concentrated in vacuo. The residue was chromatographed over 150 g of silica gel to afford 200 
mg (3.5%) of the lactone as a yellow solid. A sample recrystallized from acetone gave: mp 261-
265°C; \(^1\)H NMR (DMSO, 250 MHz) \(\delta\) 2.45 (d, J = 1.2 Hz, 3H, CH\(_3\)), 6.35 (d, J = 1.2 Hz, 1H, 
C(3)-H), 7.05 (d, J = 7.8 Hz, 1H, C(8)-H), 7.40 (m, 1H, C(9)-H), 7.55 (d, J = 9.0 Hz, 1H, C(5)-H), 
7.80 (d, J = 9.0 Hz, 1H, C(6)-H), 8.0 (d, J = 8.9 Hz, 1H, C(10)-H), 10.3 (s, 1H, OH).
7-Methoxy-4-methyl-2-oxo-2H-naphtho[1,2b]pyran (160). To a solution of 40 mg (177 mmol) of naphthol 159 in 3 mL of acetone was added 110 mg of potassium carbonate and 89 mg (708 μmol) of dimethyl sulfate. The resulting slurry was heated at reflux for 4h, cooled to room temperature, and concentrated. The residue was directly chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1) to afford a yellow solid. The solid was precipitated from chloroform-petroleum ether to afford 31 mg (74%) of the methyl ether: m.p. 177-180°C; 1H NMR (CDCl₃, 300 MHz) δ 2.53 (d, J = 1.2 Hz, 3H, CH₃), 4.03 (s, 3H, OCH₃), 6.37 (d, J = 1.2 Hz, 1H, =CH), 6.98 (d, J = 7.7 Hz, 1H, Ar-H), 7.51-7.59 (m, 2H, Ar-H), 8.10-8.16 (m, 2H, Ar-H); 13C NMR (CDCl₃, 75.0 MHz) δ 19.08 (q), 55.60 (q), 98.55 (s), 106.57 (d), 114.46 (d), 114.56 (d), 118.20 (d), 119.30 (d), 126.71 (s), 127.26 (d), 150.26 (s), 153.20 (s), 155.08 (s), 160.79 (s) one aromatic singlet was not observed; exact mass calcd. for C₁₅H₁₂O₃ m/z 240.0799, found m/z 240.0792.

4,8-Dimethoxy-1-naphthylmethanol (161). To a slurry of 1.09 g (5.05 mmol) of aldehyde 156 in 50 mL of a 5:1 mixture of tetrahydrofuran-methanol was added a small amount of bromocresol green, 1.59 g (25.3 mmol) of sodium cyanoborohydride, and 4 drops of 5% aqueous HCl such that the green solution turned yellow. The resulting solution was stirred at
room temperature for 6h with additional HCl being added at appropriate intervals such that the solution remained yellow. The reaction mixture was diluted with 100 mL of dichloromethane and washed with two 100-mL portions of water. The aqueous washes were extracted with three 50-mL portions of dichloromethane, and the extracts were combined, dried (MgSO₄), and concentrated in vacuo to afford 963 mg (88%) of the alcohol. This material was of sufficient purity to be used in subsequent reactions without further purification. However, an analytical sample was prepared by precipitation from dichloromethane-petroleum ether to afford a white solid: mp 144.5-147 °C, IR (neat) 3579 (narrow), 3068 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.2 (bs, 1H, OH), 3.98 (s, 3H, OCH₃), 4.03 (s, 3H, OCH₃), 4.98 (s, 2H, ArCH₂), 6.75 (d, J = 7.9 Hz, 1H, Ar(3)-H) 6.98 (d, J = 7.8 Hz, 1H, Ar(7)-H), 7.34 (d, J = 7.9 Hz, 1H, Ar(2)-H), 7.40, (m, 1H, Ar(6)-H), 7.98 (d, J = 8.5 Hz, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 55.52 (q), 55.90 (q), 67.08 (t), 103.81 (d), 106.99 (d), 115.80 (d), 124.62 (s), 125.04 (d), 128.16 (s), 128.38 (d), 128.68 (s), 155.21 (s), 155.67 (s); exact mass calcd. for C₁₃H₁₄O₃ m/e 218.0942, found m/e 218.0939.

Anal. calcd. for C₁₃H₁₄O: C, 71.54; H, 6.46; found C, 71.45; H, 6.27.

![Image of chemical structure](image_url)

(4,8-Dimethoxy-1-naphthyl)bromomethane (163). To a slurry of 485 mg (2.22 mmol) of alcohol 162 in 22 mL of benzene was added 628 µL (1.79 g, 6.67 mmol) of phosphorous tribromide. The resulting homogeneous solution was stirred for 1h, diluted with 100 mL of dichloromethane, and washed with three 100-mL portions of water. The combined aqueous phases were extracted with 50 mL of dichloromethane and the combined organic layers were washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo affording 500 mg (80%) of the bromide as a pale green solid: mp 111-113 °C (decomp); IR (CH₂Cl₂) 3075, 2304, cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.98 (s, 3H, OCH₃), 4.03 (s, 3H, OCH₃), 5.29 (s, 2H, CH₂Br), 6.72 (d,
\[ J = 8.8 \text{ Hz}, 1\text{H}, \text{Ar}(3)-\text{H}], 6.96 \text{ (d, } J = 8.5 \text{ Hz}, 1\text{H}, \text{Ar}(7)-\text{H}], 7.3-7.45 \text{ (m, } 2\text{H, Ar(2,6)-H}], 7.92 \text{ (d, } J = 8.8 \text{ Hz}, 1\text{H, Ar(5)-H]}; ^{13}\text{C NMR (CDCl}_3, 75.47 \text{ MHz)} \delta 38.49 \text{ (q), 55.54 \text{ (q), 55.68 \text{ (q), 103.80 \text{ (d), 107.46 \text{ (d), 114.96 \text{ (d), 123.89 \text{ (s), 125.63 \text{ (s), 125.91 \text{ (s), 128.07 \text{ (s), 130.30 \text{ (d), 155.97 \text{ (s), 156.73 \text{ (s); exact mass calcd. for C}_{13}\text{H}_{13}\text{OBr}^{79} m/e 282.0031, found m/e 282.0055.}}}

\[ \text{OMe} \]

(4,8-Dimethoxy-1-naphthyl)methyl ethyl sulfide (164). To a slurry of 305 mg (1.09 mmol) of bromide 163 in 1 mL of benzene was added 68 mg (81 \mu\text{L, 1.09 mmol}) of ethanethiol, followed by 166 mg (1.09 mmol) of DBU. The resulting slurry was stirred 5 min, filtered through a glass wool plug, and concentrated in vacuo. The crude red oil was dissolved in ether, and the insoluble material was removed by filtration. Concentration of the filtrate gave 175 mg (61%) of slightly impure sulfide as a light green solid: \text{mp 59-61 °C, IR (CHCl}_3) 3080, 2930, 1514 \text{ cm}^{-1}; ^{1}\text{H NMR (CDCl}_3, 200 \text{ MHz)} \delta 1.25 \text{ (t, } J = 7.6 \text{ Hz, 3H, CH}_3], 2.48 \text{ (q, } J = 7.6 \text{ Hz, 2H, SCH}_2], 3.95 \text{ (s, 6H, OCH}_3], 4.34 \text{ (s, 2H, ArCH}_2], 6.69 \text{ (d, } J = 8.2 \text{ Hz, 1H, Ar(3)-H], 6.90 \text{ (d, } J = 7.9 \text{ Hz, 1H, Ar(7)-H], 7.08 \text{ (d, } J = 8.2 \text{ Hz, 1H, Ar(2)-H], 7.38 \text{ (m, 1H, Ar(6)-H], 7.90 \text{ (d, } J = 8.8 \text{ Hz, 1H, Ar(5)-H]}; ^{13}\text{C NMR (CDCl}_3, 62.9 \text{ MHz)} \delta 14.61 \text{ (q), 24.84 \text{ (t), 38.38 \text{ (t), 55.47 \text{ (q, 2 carbons, 103.31 \text{ (d), 106.88 \text{ (d), 114.89 \text{ (d), 124.32 \text{ (s), 125.26 \text{ (d), 127.18 \text{ (s), 127.67 \text{ (d), 128.49 \text{ (s), 154.56 \text{ (s), 157.13 \text{ (s); exact mass calcd. for C}_{15}\text{H}_{18}\text{O}_2\text{S} m/e 262.1028, found m/e 262.1035.}}}

\[ \text{OMe} \]
To a solution of 85 mg (324 μmol) of sulfide 164 in 3 mL of dichloromethane at 0°C was added 196 mg (2.27 mmol) of sodium bicarbonate, and then 112 mg (649 μmol) of 90% m-CPBA in one portion. The resulting solution was stirred at 0°C for 2h, then warmed to room temperature over 5 min, and then quenched with 5 mL of saturated aqueous sodium bisulfite. The resulting biphasic mixture was vigorously stirred for 20 min and diluted with 25 mL of dichloromethane. The organic layer was washed sequentially with 15 mL of saturated aqueous sodium thiosulfate, 15 mL of saturated aqueous sodium bicarbonate, 15 mL of saturated brine, dried (MgSO₄) and concentrated to dryness giving 85 mg (85%) of the sulfone as an off white solid. An analytical sample was prepared by recrystallization from methanol as white needles: mp 124-125°C; IR (neat) 3040, 2939, 1516 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.24 (t, J = 7.6 Hz, 3H, CH₃), 2.78 (q, J = 7.6 Hz, 2H, CH₂), 3.99 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 5.15 (s, 2H, ArCH₂), 6.83 (d, J = 8.1 Hz, 1H, Ar(3)-H), 6.95 (d, J = 7.6 Hz, 1H, Ar(7)-H), 7.40-7.43 (m, 2H, Ar(2,6)-H), 7.96 (d, J = 8.8 Hz, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, MHz) δ 5.40 (q), 44.98 (t), 55.41 (q), 55.61 (q), 59.96 (t), 104.10 (d), 107.37 (d), 115.53 (d), 115.65 (s), 124.60 (s), 125.45 (d), 127.96 (s), 132.33 (d), 156.09 (s, 2 carbons); exact mass calcd. for C₁₅H₁₈O₄S m/e 294.0926, found m/e 294.0940.

trans-1-(4,8-Dimethoxynaphthyl)propene (165). To a slurry of 40 mg (136 µmol) of sultone 161 and 460 mg (8.1 mmol) of freshly ground KOH in 1.8 mL of t-BuOH at room temperature was added 4.3 mL of carbon tetrachloride in one portion. The reaction mixture was stirred for 2h at room temperature with a gas being evolved. The mixture was diluted with 20 mL of ether and washed with three 10-mL portions of water. The organic phase was washed with 10 mL of brine, dried (MgSO₄), and concentrated in vacuo to afford 28 mg (90%) of the trans alkene 165 as a yellow solid containing an unidentified impurity: IR (neat) 3020, 2960, 1516 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 1.91 (m, 3H, =CCH₃), 3.92 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 5.75 (m, 1H, =CH), 6.75 (d, J = 8.0 Hz, 1H, Ar-H), 6.89 (d, J = 7.6 Hz, 1H, Ar-H), 7.27-7.39 (m, 2H, Ar-H), 7.48 (d, J = 13.1 Hz, 1H, ArCH), 7.88 (m, 1H, Ar-H); exact mass calcd. for C₁₅H₁₆O₂ m/e 228.1150, found m/e 228.49.

(±)-tert-Butyl [(1R*,2R*,3S*)-4-[[4,8-Dimethoxy-1-naphthyl]methyl]thio]-2-(methoxy-methoxy)-1,3-dimethylbutoxy]dimethylsilane (167). To a solution of 308 mg (1.0 mmol) of thiol 110 in 2 mL of degassed benzene was added 152 mg (1.0 mmol) of DBU which imparted a
yellow color to the solution. To the resulting solution of thiolate anion was added 280 mg (1.0 mmol) of bromide 163. The resulting slurry was stirred for 5 min, filtered through a glass wool plug, and the filtrate was concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (eluted with petroleum ether-ether, 15:1) to give 352 mg (69%) of sulfide 167 as a colorless oil: IR (neat) 3080, 2956, 2856 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.07 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.91 (s, 9H, SiC(CH₃)₃), 1.11 (m, 6H, CH₃), 1.95 (m, 1H, C(2)-H), 2.33 (dd, J = 12.6, 12.4, 1H, SCH₂), 2.78 (dd, J = 12.6, 3.4, 1H, SCH₂), 3.18 (t, J = 5.56, 1H, C(3)-H), 3.35 (s, 3H, OCH₃), 3.95-4.03 (m, 1H, C(4)-H), 3.96 (s, 3H, ArOCH₃), 3.97 (s, 3H, ArOCH₃), 4.23 (d, J = 13.1, 1H, ArCH₂), 4.43 (d, J = 13.1, 1H, ArCH₂), 4.58 (d, J = 6.6, 1H, OCH₂), 4.67 (d, J = 6.6, 1H, OCH₂), 6.70 (d, J = 7.9, 1H, Ar(3)-H), 6.90 (d, J = 7.7, 1H, Ar(7)-H), 7.15 (d, J = 7.9, 1H, Ar(2)-H), 7.37 (m, 1H, Ar(6)-H), 7.93 (d, J = 8.4, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -4.78 (q), -4.69 (q), 17.33 (q), 17.90 (s), 19.37 (q), 25.80 (q), 34.31 (t), 34.59 (d), 39.24 (t), 55.39 (q), 55.44 (q), 55.70 (q), 69.91 (d), 86.26 (d), 98.17 (t), 103.26 (d), 106.85 (d), 114.87 (d), 124.41 (s), 125.19 (d), 127.16 (s), 127.84 (d), 128.44 (s), 154.54 (s), 157.15 (s); exact mass calcd. for C₂₇H₄₄O₅SSi m/e 508.2670, found m/e 508.2674.

\[
\text{Me} \quad \text{OMOM} \quad \text{OTBS} \quad \text{OMe} \\
\text{O=SO} \quad \text{Me} \quad \text{OMe} \\
\text{MeO} \quad \text{Me} \\
\text{168}
\]

(±)-\textit{tert}-Butyl [(1\textit{R},2\textit{R},3\textit{S}*)-4-[[4,8-dimethoxy-1-naphthyl]methyl]sulfonyl]-2-(methoxymethoxy)-1,3-dimethylbutoxy]dimethylsilane (168). To a solution of 325 mg (639 \(\mu\)mol) of sulfide 167 in 17 mL of dichloromethane at 0°C was added 366 mg (1.6 mmol) of 75% \textit{m}-CPBA in one portion. The mixture was stirred 3 h at 0°C, for 3 h at room temperature, and
then 30 mL of 10% aqueous sodium bisulfite was added. The resulting mixture was stirred for 2 h and extracted with 100 mL of dichloromethane. The organic phase was washed sequentially with 50 mL of 10% aqueous sodium bisulfite, 50 mL of saturated aqueous sodium bicarbonate, and 50 mL of brine. The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to afford 301 mg (87%) of sulfone 168 as a colorless oil. IR (neat) 2934, 2893, 1597, 1560 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ -0.06 (s, 3H, SiCH₃), -0.05 (s, 3H, SiCH₃), 0.82 (s, 9H, SiC(CH₃)₃), 0.95 (d, J = 6.3, 3H, CH₃), 1.20 (d, J = 6.7 Hz, 3H, CH₃), 2.41 (m, 1H, C(2)-H), 2.59 (dd, J = 13.8, 9.9 Hz, 1H, SCH), 3.06 (m, 2H, SCH, C(1)-H), 3.19 (s, 3H, OCH₃), 3.58 (m, 1H, C(4)-H), 3.96 (s, 3H, ArOCH₃), 3.97 (s, 3H, ArOCH₃), 4.41 (d, J = 6.6 Hz, 1H, OCH₂), 4.57 (d, J = 6.6 Hz, 1H, OCH₂), 5.02 (d, J = 13.9 Hz, 1H, ArCH₂), 5.18 (d, J = 13.9 Hz, 1H, ArCH₂), 6.80 (d, J = 8.1 Hz, 1H, Ar(3)-H), 6.92 (d, J = 8.2 Hz, 1H, Ar(7)-H) 7.34-7.41 (m, 2H, Ar(2,6)-H), 7.94 (d, J = 8.5 Hz, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ -4.93 (q), -4.88 (q), 17.77 (s), 19.02 (q), 19.08 (q), 25.68 (q), 28.14 (d), 52.61 (t), 55.29 (q), 55.50 (q), 55.62 (q), 61.65 (t), 69.77 (d), 86.37 (d), 98.06 (t), 104.00 (d), 107.28 (d), 115.50 (d), 115.90 (s) 124.61 (s), 125.34 (d), 127.91 (s), 132.27 (d), 155.98 (s), 156.03 (s); exact mass calcd. for C₂₇H₄₄O₇SSi m/z 540.2553, found m/z 540.2565.

(±)-tert-Butyl [[(1'R,2'R,3'R)-5-(4,8-dimethoxy-1-naphthyl)-2-(methoxymethoxy)-1,3-dimethyl-4-pentenyl]oxy]dimethylsilane (169). To a solution of 270 mg (500 µmol) of sulfone 168 in 2.1 mL of tert-butanol and 5.2 mL of carbon tetrachloride at room temperature under argon was added 1.68 g (30 mmol) of freshly ground potassium hydroxide. The reaction mixture was
stirred for 4 h, diluted with 100 mL of ether, and washed with three 50-mL portions of water and
one 50-mL portion of saturated brine. The organic phase was dried (MgSO$_4$) and concentrated
in vacuo. The resulting material was suitable for use in further reactions without purification,
however, an analytical sample was prepared by silica gel chromatography (eluted with petroleum
ether-ethyl acetate 5:1) to afford 147 mg (62%) of alkene 169: IR (neat) 3080, 2990, 2920, 1590,
1514 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 0.07 (s, 6H, SiCH$_3$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 1.20-1.24
(m, 6H, CH$_3$), 2.67 (m, 1H, C(3)-H), 3.29 (m, 1H, C(2)-H), 3.42 (s, 3H OCH$_3$), 3.87-3.98 (m, 1H,
C(1)-H), 3.91 (s, 3H, ArOCH$_3$), 3.98 (s, 3H, ArOCH$_3$), 4.68 (d, $J = 6.8$ Hz, 1H, OCH$_2$), 4.86 (d, $J$
= 6.9 Hz, 1H, OCH$_2$), 5.80 (dd, $J = 15.4$, 8.6 Hz, 1H, C(4)-H), 6.78 (d, $J = 8.1$ Hz, 1H, Ar(3)-H),
6.87 (d, $J = 7.7$ Hz, 1H, Ar(7)-H), 7.30-7.38 (m, 2H, Ar(2,6)-H), 7.40 (d, $J = 15.4$ Hz, 1H, C(5)-H),
7.93 (d, $J = 8.4$ Hz, 1H, Ar(5)-H); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) $\delta$ -4.67 (q, 2 carbons), 17.95 (s),
19.21 (q), 19.19 (q), 25.86 (q), 38.56 (d), 55.41 (q), 55.44 (q), 55.81 (q), 71.00 (d), 86.98 (d),
98.53 (t), 104.32 (d), 106.66 (d), 114.75 (d), 124.36 (s), 124.96 (d), 125.85 (d), 127.37 (s), 129.11
(s), 130.02 (d), 133.69 (d), 154.42 (s), 157.34 (s); exact mass calcd. for $m/e$ C$_{27}$H$_{42}$O$_5$Si
474.2819, found $m/e$ 474.2810.

OMOM
Me Me
OMe
MeO
170

(±)-(2$R$*,3$R$*,4$R$*)-trans-6-(4,8-dimethoxy-1-naphthyl)-3-(methoxymethoxy)-4-methyl-
5-hexen-2-ol (170). To a solution of 130 mg (274 mmol) of silyl ether 169 in 700 $\mu$L of
tetrahydrofuran was added 1.4 mL of 1.37 M tetrabutylammonium fluoride in tetrahydrofuran in
one portion. The resulting solution was stirred for 10 h, diluted with 50 mL of dichloromethane,
washed with three 20-mL portions of water, 20 mL of brine, dried (MgSO$_4$) and concentrated in
vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethylacetate, 1:1) to afford 98 mg (99%) of enol 170 as a gum: mp 43-47°C; IR (neat) 3443 (broad), 3055, 1614, 1592, 1514 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.21-1.25 (m, 6H, CH₃), 2.60-2.71 (m, 1H, C(4)-H), 3.22-3.36 (m, 1H, C(3)-H), 3.40 (bs, 1H, OH), 3.47 (s, 3H, OCH₃), 3.78-3.81 (m, 1H, C(2)-H), 3.92 (s, 3H, ArOCH₃), 3.98 (s, 3H, ArOCH₃), 4.74 (d, J = 6.9 Hz, 1H, OCH₂), 4.79 (d, J = 6.9 Hz, 1H, OCH₂), 5.72 (dd, J = 8.4, 15.4 Hz, 1H, C(5)-H), 6.75 (d, J = 7.8 Hz, 1H, Ar(3)-H), 6.86 (d, 1H, Ar(7)-H), 7.25-7.38 (m, 3H, Ar(2,6)-H, C(6)-H), 7.90 (d, J = 8.4 Hz, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 18.42 (q), 19.01 (q), 39.44 (d), 55.44 (q), 55.53 (q), 55.87 (q), 68.57 (d), 91.32 (d), 99.00 (l), 104.32 (d), 106.70 (d), 114.79 (d), 124.32 (s), 125.09 (d), 126.04 (d), 127.40 (s), 128.64 (d), 128.80 (s), 134.48 (d), 154.6 (s), 157.27 (s); exact mass calcd. for C₂₁H₂₉O₅ (M+1) m/e 361.1918, found m/e 361.1966; exact mass calcd. for C₂₁H₂₈O₅ m/e 360.1932, found m/e 360.1934.

(±)-(2R⁺,3R⁺,4S⁺,5R⁺,6S⁺)-Tetrahydro-6-(4,8-dimethoxy-1-naphthyl)-3-(methoxymethoxy)-2,4-dimethyl-5-(phenylselenyl)-2H-pyran (171). To a -78°C solution of 98 mg (272 μmol) of enol 170 in 2.5 mL of dichloromethane was added 104 mg (544 μmol) of phenylselenenyl chloride in one portion. The resulting solution was stirred for 2h, diluted with 10 mL of dichloromethane and washed with 5 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two 10-mL portions of dichloromethane and the combined extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed
over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1) to afford 117 mg (84%) of
the aryl selenide 171 as a colorless oil. IR (neat) 3070, 1599, 1519 cm⁻¹; ¹H NMR (CDCl₃, 250
MHz) δ 1.26 (d, J = 6.5 Hz, 3H, CH₃), 1.37 (d, J = 6.7 Hz, 3H, CH₃), 1.97-2.11 (m, 1H, C(4)-H),
3.42 (t, J = 11.2 Hz, 1H, C(5)-H), 3.46-3.50 (m, 1H, C(3)-H), 3.48 (s, 3H, OCH₃), 3.78 (m, 1H,
C(2)-H), 3.92 (s, 3H, ArOCH₃), 3.93 (s, 3H, ArOCH₃), 4.73 (d, J = 6.9 Hz, 1H, OCH₂), 4.79 (d, J
= 6.9 Hz, 1H, OCH₂), 6.16 (d, J = 10.8 Hz, 1H, C(6)-H), 6.66 (d, J = 8.3 Hz, 1H, Ar(3)-H), 6.92 (d,
J = 8.1 Hz, 1H, Ar(7)-H), 6.94-7.15 (m, 5H, SeAr-H), 7.36 (m, 1H, Ar(6)-H), 7.60 (d, J = 8.3 Hz,
1H, Ar(2)-H), 7.95 (d, J = 8.5 Hz, 1H, Ar(5)-H); ¹³C NMR (CDCl₃, 75.47 MHz) δ 18.09 (q), 18.21
(q), 42.69 (d), 53.96 (d), 55.23 (q), 55.43 (q), 56.34 (q), 76.50 (d), 80.11 (d), 81.09 (d), 98.78 (t),
103.98 (d), 107.11 (d), 115.02 (d), 124.31 (d), 125.38 (s), 126.05 (d), 126.79 (d), 127.41 (s),
128.11 (d), 129.44 (s), 129.70 (s), 134.94 (d), 154.74 (s), 157.12 (s); exact mass calcd. for
C₂₇H₃₂O₅²²Se m/e 517.1397, found m/e 517.1445; exact mass calcd. for C₂₇H₃₂O₅⁸⁰Se m/e
516.1419, found m/e 516.1417.

2-(3-Methoxy-5-methyl)phenyl-4,4-dimethyl-Δ²-oxazoline (60).⁴¹b To a solution of
2.00 g of 3-methoxy-5-methyl benzoic acid in 15 mL of benzene was added 2.65 mL (36.6 mmol)
of thionyl chloride in a single portion via syringe.⁴¹b The resulting solution was heated at reflux
for 2.5 h, cooled to room temperature and concentrated in vacuo. The residue was dissolved in
10 mL of dichloromethane and added to a solution of 2.3 mL (24.2 mmol) of 2-amino-2-methyl-1-
propanol in 20 mL of dichloromethane over a 5 min period. The resulting solution was stirred at
room temperature for 3 h, diluted with 50 mL of dichloromethane and washed with 20 mL of 10%
citric acid. The aqueous phase was extracted with three 30-mL portions of dichloromethane and
the combined organic layers were dried (MgSO₄), and concentrated in vacuo. The residue was
treated with 5 mL of thionyl chloride, stirred 30 min, and diluted with 75 mL of ether. After stirring 3 h, the reaction mixture was filtered and the filter cake was rinsed with 50 mL of diethyl ether. The solid was collected and dissolved in 30 mL of 10% aqueous sodium hydroxide. The aqueous layer was extracted with three 30-mL portions of dichloromethane. The combined organic phases were dried (MgSO4) and concentrated in vacuo. The resulting crude orange oil was distilled under reduced pressure (70-72°C/0.5 mm Hg) to afford a water white solid: mp 43.5-45°C; 1H NMR (CDCl3, 250 MHz) δ 1.34 (s, 6H, CHg), 2.30 (s, 3H, ArCHg), 3.78 (s, 3H, OCHg), 4.05 (s, 2H, CH2), 6.79 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.36 (s, 1H, ArH).

Anal. calcd. for C13H17NO2: C, 71.21; H, 7.81; found C, 71.43; H, 7.87.

4,8-Dimethoxy-1-naphthol, p-toluenesulfonate (177). To a solution of 1.00 g (4.9 mmol) of naphthol 176 in 20 mL of acetone at room temperature was added 6.76 g (49 mmol) of K2CO3 and 650 mg (3.18 mmol) of tosyl chloride in one portion. The resulting mixture was heated under reflux for 0.5 h, and an additional 650 mg (3.18 mmol) of tosyl chloride was added. The slurry was then heated under reflux for 8 h, cooled to room temperature, and filtered. The filter cake was rinsed with 50 mL of acetone, and the filtrate was washed with 100 mL of 10% citric acid, 100 mL of water and 100 mL of brine. The resulting organic phase was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate-dichloromethane, 10:1:1) to afford 1.34 g (82%) of tosylate 177 as white needles: mp 109-110°C; IR (neat) 3000, 2955, 1599 cm⁻¹; 1H NMR (CDCl3, 300 MHz) δ 2.40 (s, 3H, CH3), 3.86 (s, 3H, OCH3), 3.94 (s, 3H, OCH3), 6.60 (d, J = 8.5 Hz, 1H, Ar(3)-H), 6.85 (m, 2H, Ar(2,7)-H), 7.28 (d, J = 8.8 Hz, 2H, SAr(3,5)-H), 7.35 (t, J = 8.5 Hz, 1H, Ar(6)-H), 7.71 (d, J = 8.8 Hz, 2H, SAr(2,6)-H), 7.81 (d, J = 8.5 Hz, 1H, Ar(5)-H); 13C NMR (CDCl3) δ 21.57
(q), 55.54 (q), 55.70 (q), 103.12 (d), 107.26 (d), 114.33 (d), 119.44 (d), 120.20 (s), 126.22 (d), 128.25 (s), 128.43 (d), 129.32 (d), 134.03 (s), 138.62 (s), 144.49 (s), 154.06 (s), 155.26 (s); exact mass calcd. for C₁₉H₁₉O₅S m/e 358.0874, found m/e 358.0874.

Anal. calcd. for C₁₉H₁₈O₅S: C, 63.68; H, 5.06; found C, 63.45; H, 5.07.

5-Hydroxy-4,8-dimethoxy-1-naphthaldehyde, p-toluenesulfonate (178). To a 0°C solution of 3.00 g (8.4 mmol) of tosylate 178 in 100 mL of dichloromethane was added 792 µL (958 mg, 8.4 mmol) of α,α-dichloromethyl methyl ether followed 5 min later by 2.3 mL (21 mmol) of titanium tetrachloride. The deep red solution was stirred for 1.5 h and then slowly poured into 300 mL of 5% aqueous hydrochloric acid. After stirring 10 min the layers were separated and the aqueous phase was extracted with two 100-mL portions of dichloromethane. The combined organic phases were washed with two 200-mL portions of brine, dried (MgSO₄), and concentrated in vacuo. The crude solid was recrystallized from petroleum ether-ethyl acetate (2:1) to afford 1.19 g (93%) of the aldehyde as red needles: mp 172-174°C, IR (neat) 3015, 2937, 1668 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.40 (s, 3H, ArCH₃), 3.88 (s, 3H, ArOCH₃), 3.94 (s, 3H, ArOCH₃), 6.75-6.89 (m, 3H, Ar(3,6,7)-H), 7.24-7.27 (m, 2H, Ar-H), 7.66-7.69 (m, 2H, Ar-H), 7.87 (d, J = 8.3, 1H, Ar(2)-H), 10.82 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ 21.53 (q), 55.75 (q), 55.89 (q), 106.06 (d), 106.26 (d), 120.37 (d), 120.54 (s), 126.34 (s), 127.74 (s), 128.28 (d), 129.44 (d), 129.86 (d), 133.63 (s), 139.31 (s), 144.80 (s), 154.91 (s), 159.21 (s), 193.58 (d); exact mass calcd. for C₂₀H₁₈O₆S m/e 386.0824, found m/e 386.0824.

Anal. calcd. for C₂₀H₁₈O₆S: C, 62.17; H, 4.69; found C, 62.09; H 4.72.
4,8-Dimethoxy-5-hydroxymethyl-1-naphthol, \( p \)-toluenesulfonate (179). To a slurry of 1.33 g (3.44 mmol) of aldehyde 178 in 43 mL of 5:1 tetrahydrofuran-water, was added 650 mg (10.3 mmol) of sodium cyanoborohydride, a spatula tip full of bromocresol green, and two drops of 5% aqueous hydrochloric acid such that the blue solution turned yellow. The resulting solution was stirred for 4 h with additional 5% HCl being added as needed to maintain the yellow color. The reaction mixture was diluted with 100 mL of dichloromethane, and washed with two 75-mL portions of water. The organic phase was dried (MgSO\(_4\)), and concentrated in vacuo to afford 1.53 g (98%) of crude product. This material was suitable for use in subsequent reactions without further purification. However, in a separate experiment, an analytical sample was prepared by chromatography over 50 g of silical gel (eluted with petroleum ether-ethyl acetate, 1:1) followed by recrystallization from ethanol to afford a cream colored solid: mp 129.5-130.5; IR (neat) 3416 (broad), 2990, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) 2.40 (s, 3H, Ar-H), 2.92 (bs, 1H, OH), 3.82 (s, 3H, ArOCH\(_3\)), 3.92 (s, 3H, ArOCH\(_3\)), 4.94 (bs, 2H, ArCH\(_2\)), 6.72-6.78 (m, 2H, Ar(3,7)-H), 6.82 (d, \( J = 8.5 \) Hz, 1H, Ar(2)-H), 7.24 (m, 2H, SAr(3,5)-H), 7.34 (d, \( J = 8.3 \) Hz, 1H, Ar(6)-H), 7.68 (m, 2H, SAr(2,6)-H); \(^13\)C NMR (CDCl\(_3\)) \( \delta \) 21.61 (q), 55.59 (q), 55.17 (q), 67.04 (t), 105.52 (d), 106.73 (d), 119.71 (d), 121.77 (s), 126.67 (s), 128.40 (d), 128.73 (s), 129.42 (d), 129.85 (d), 133.94 (s), 139.74 (s), 144.62 (s), 154.76 (s), 155.50 (s); exact mass calcd. for C\(_{20}\)H\(_{20}\)O\(_6\)S, 388.0981 m/e, found m/e 388.0992.

Anal. calcd. for C\(_{20}\)H\(_{20}\)O\(_6\)S: C, 61.84; H, 5.19; found C, 61.67; H, 5.18.
5-Bromomethyl-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (180). To a solution of 1.53 g (3.94 mmol) of alcohol 170 in 39 mL of benzene was added 2.13 mL (3.17 g, 11.8 mmol) of phosphorous tribromide in one portion. The resulting solution was stirred for 3h at room temperature, diluted with 100 mL of dichloromethane, washed with two 50-mL portions of water, and 100 mL of brine. The organic phase was dried (MgSO₄) and concentrated in vacuo to afford 1.51 g (85%) of bromide 180 as a gray solid which was suitable for use in subsequent reactions without further purification: mp 124-127°C (decomp); IR (neat) 3045, 2935, 2842, 1597, 1522 cm⁻¹; ¹H NMR (CDCl₃ 300 MHz) δ 2.41 (s, 3H, ArCH₃), 3.82 (s, 3H, ArOCH₃), 3.97 (s, 3H, ArOCH₃), 5.18 (s, 2H, BrCH₂), 6.72-6.86 (m, 3H, Ar-H), 7.26 (m, 2H, Ar-H), 7.35 (d, J = 8.1 Hz, 1H, Ar-H), 7.69 (m, 2H, Ar-H); ¹³C NMR (CDCl₃) δ 21.67 (q), 38.21 (t), 55.63 (q), 55.93 (q), 105.93 (d), 106.58 (d), 120.31 (d), 121.90 (s), 125.89 (s), 125.95 (s), 128.42 (d), 129.43 (d), 131.76 (d), 133.91 (s), 139.19 (s), 144.63 (s), 155.73 (s), 156.36 (s); exact mass calcd. for C₇₀H₅₃O₇S⁷⁹Br m/z 450.0137, found m/z 450.0165.

(±)-5-[[[2R*,3S*,4S*]-4-(tert-Butyldimethylsiloxy)-3-(methoxymethoxy)-2-methylpentyl]thio]methyl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (181). To a slurry
of 2.06 g of bromide 180 in 7 mL of degassed benzene was added 1.41 g (4.58 mmol) of thiol 110. To the resulting slurry was added 705 mg (4.58 mmol) of DBU dropwise over 2 min. The resulting thick slurry was stirred for 5 min, diluted with 4 mL of benzene, and filtered. The filter cake was rinsed with 5 mL of benzene and the combined filtrate and washings were concentrated in vacuo to afford 2.57 g (83%) of the sulfide as a red oil. Although this material was suitable for use in further reactions without purification, an analytical sample was prepared by chromatography of a 300 mg sample over 20 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1): IR (neat) 2930, 1598, 1521, cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.37 (s, 3H, SiCH₃), 0.46 (s, 3H, SiCH₃), 0.87 (s, 9H, CCH₃), 1.04 (d, J = 6.8 Hz, 3H, CH₃), 1.08 (d, J = 6.3 Hz, 3H, CH₃), 1.88-1.91 (m, 1H, C(2)-H), 2.27 (dd, J = 12.6, 9.3 Hz, 1H, C(1)-H), 2.42 (s, 3H, ArCH₃), 2.73 (dd, J = 12.6, 3.4 Hz, 1H, C(1)-H), 3.14 (t, J = 5.5 Hz, 1H, C(3)-H), 3.31 (s, 3H, OCH₃), 3.83 (s, 3H, ArOCH₃), 3.91 (s, 3H, ArOCH₃), 3.85-3.95 (m, 1H, C(4)-H), 4.12 (d, J = 13.3 Hz, 1H, ArCH₂), 4.34 (d, J = 13.3 Hz, 1H, ArCH₂), 4.55 (d, J = 6.7 Hz, 1H OCH₂), 4.65 (d, J = 6.5 Hz, 1H, OCH₂), 6.64 6.72 (m, 3H, Ar(2,3,7)-H), 7.1 (d, J = 8.5, 1H, Ar(6)-H), 7.23-7.27 (m, 2H, SAr(3,5)-H), 7.67-7.70 (d, J = 8.6, 2H, SAr(2,6)-H); ¹³C NMR (CDCl₃) δ -4.77 (q), -4.65 (q), 17.30 (q), 17.93 (s), 19.33 (q), 21.56 (q), 25.81 (q), 34.47 (t), 34.53 (d), 39.71 (t), 55.55 (q), 55.66 (q), 55.78 (q), 69.89 (d), 86.19 (d), 98.15 (t), 105.21 (d), 106.20 (d), 119.84 (d), 122.20 (s), 126.27 (s), 127.33 (s), 128.38 (d), 129.36 (d), 129.40 (d), 134.06 (s), 139.12 (s), 144.44 (s), 154.87 (s), 156.12 (s); exact mass calcd. for C₃₄H₅₀O₆S₂Si m/z 678.2716, found m/z 678.2744.

![Diagram of compound 182]
methylpentylsulfonylmethyl-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (181). To a solution of 2.54 g (3.75 mmol) of sulfide 180 at 0°C in 100 mL of dichloromethane was added 1.58 g (18.75 mmol) of sodium bicarbonate followed by 1.61 g (9.37 mmol) of 75% m-chloroperbenzoic acid (by iodometric titration) in one portion. The resulting slurry was stirred for 6h and then treated with 100 mL of saturated aqueous sodium thiosulfate. The mixture was vigorously stirred 45 min, the layers were separated, and the aqueous phase was extracted with three 200-mL portions of dichloromethane. The combined organic layers were washed with 200 mL of saturated aqueous sodium bicarbonate, 50 mL of brine, dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 75 g of silica gel (eluted with petroleum ether-ethyl acetate 3:1) to afford 2.52 g (94%) of the desired sulfone 181 as an oil: IR (neat) 2972, 1598, 1523 cm⁻¹; $^1$H NMR (CDCl₃ 300 MHz) δ -0.083 (s, 3H, SiCH₃), 0.0006 (s, 3H, SiCH₃), 0.85 (s, 9H, CCH₃), 1.04 (d, J = 6.3 Hz, 3H, CH₃), 1.24 (d, J = 6.7 Hz, 3H, CH₃), 2.43 (s, 3H, ArCH₃), 2.43-2.62 (m, 1H, C(2)-H), 2.61 (m, 1H, C(1)-H), 3.08-3.16 (m, 2H, C(1,3)-H), 3.73 (m, 1H, C(3)-H), 3.85 (s, 3H, ArOCH₃), 3.97 (s, 3H, ArOCH₃), 4.47 (d, J = 6.6 Hz, 1H, OCH₂), 4.63 (d, J = 6.6 Hz, 1H, OCH₂), 5.07 (m, 2H, ArCH₂), 6.72-6.86 (m, 3H, Ar(2,3,7)-H), 7.27 (d, J = 7.8 Hz, 2H, SAr(3,5)-H), 7.38 (d, J = 8.3 Hz, 1H, Ar(6)-H), 7.69 (m, 2H, SAr(2,6)-H); $^{13}$C NMR (CDCl₃) δ -4.80 (q), -4.68 (q), 17.89 (s), 19.09 (q, 2 carbons), 21.60 (q), 25.77 (q), 53.58 (l), 55.62 (q), 55.68 (q), 55.80 (q), 61.88 (l), 69.78 (d), 86.26 (d), 98.13 (l), 105.92 (d), 106.65 (d), 116.18 (s), 120.20 (d), 121.90 (s), 126.74 (s), 128.39 (d), 129.44 (d), 133.49 (d), 133.93 (s), 139.45 (s), 144 (s), 155.29 (s), 156.54 (s); A satisfactory high resolution mass spectrum was not obtained for this compound.
(±)-trans-5-[(2R*,3S*,4S*)-5-(tert-Butyldimethylsiloxy)-4-(methoxymethoxy)-3-methylhexen-1-yl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (183). To a solution of 2.52 g (3.54 mmol) of sulfone 182 in a mixture of 49 mL of tert-butanol and 120 mL of carbon tetrachloride was added 11.9 g (212 mmol) of freshly ground KOH. The resulting exothermic reaction attained a temperature of 38°C with SO₂ being evolved over a 5h period. The resulting dark brown solution was diluted with 600 mL of ether and washed with three 250-mL portions of water. The ether layer was washed with 200 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 75 g of silica gel (eluted with petroleum ether-ethyl acetate, 2:1) to afford 1.57 g (69%) of the E-alkene as a colorless oil: IR (neat) 2930, 1594, 1519 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.66 (s, 6H, SiCH₃), 0.90 (s, 9H, CCH₃), 1.19-1.24 (m, 6H, CH₃), 2.42 (s, 3H, ArCH₃), 2.65 (m, 1H, C(3)-H), 3.29 (dd, J = 3.8, 6.8, 1H, C(4)-H), 3.41 (s, 3H, OCH₃), 3.83 (s, 3H, ArOCH₃), 3.85 (s, 3H, ArOCH₃), 3.90-3.95 (m, 1H, C(5)-H), 4.67 (d, J = 6.7, 1H, OCH₂), 4.84 (d, J = 6.7, 1H, OCH₂), 5.74 (dd, J = 15.4, 8.7, 1H, C(2)-H), 6.63 (d, J = 8.6, 1H, Ar(3)-H), 6.77-6.81 (m, 2H, Ar(2,7)-H), 7.24-7.29 (m, 4H, C(1)-H, SAr(3,5)-H, Ar(6)-H), 7.69-7.72 (m, 2H, SAr(2,6)-H); ¹³C NMR (CDCl₃, 62.9 MHz) δ -4.64 (q, 2 carbons), 17.98 (s), 19.27 (q), 19.90 (q), 21.60 (q), 25.87 (q), 29.65 (s), 38.46 (d), 55.61 (q), 55.88 (q), 70.95 (d), 86.91 (d), 98.52 (t), 104.86 (d), 107.26 (d), 119.58 (d), 121.01 (s), 126.19 (s), 127.75 (d), 128.42 (d), 129.26 (s), 130.22 (d), 133.61 (d), 134.04 (s), 138.98 (s), 144.46 (s), 154.59 (s), 156.30 (s); exact mass calcd. for C₃₄H₄₈O₈SSi m/e 644.2839, found m/e 644.2834.

Anal. calcd. for C₃₄H₄₈O₈SSi C, 63.32; H, 7.50; found C, 63.12; H, 7.50.
(±)-5-[(3R*,4R*,5R*)-trans-5-Hydroxy-4-(methoxymethoxy)-3-methyl-2-hexen-1-yl]-
4,8-dimethoxy-1-naphthol, p-toluenesulfonate (184). To a solution of 100 mg (155 μmol) of
trans olefin 183 in 500 μL of tetrahydrofuran at room temperature was added 1.55 mL of a 1 M
solution (1.55 mmol) of tetra-n-butyl ammonium fluoride in tetrahydrofuran. The reaction mixture
was stirred for 24 h at room temperature, diluted with 25 mL of dichloromethane, and washed with
three 10-mL portions of water. The organic residue was dried (MgSO₄), and concentrated in
vacuo. The oily residue was chromatographed over 10 g of silica gel (eluted with petroleum
ether-ethyl acetate, 1:1) to afford 76 mg (92%) of the desired alcohol as an oil: IR (neat) 3452
(broad), 2964, 2842, 1593, 1519 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.19-2.25 (m, 6H, CH₂),
2.42 (s, 3H, ArCH₃), 2.61-2.67 (m, 1H, C(3)-H), 3.22 (dd, J = 7.1, 2.3 Hz, 1H, C(4)-H), 3.45 (s,
3H, OCH₂), 3.83 (s, 3H, ArOCH₃), 3.86 (s, 3H, ArOCH₃), 3.79-3.87 (m, 1H, C(5)-H), 4.71 (d, J =
6.6 Hz, 1H, OCH₂), 4.83 (d, J = 6.6 Hz, 1H, OCH₂), 5.66 (dd, J = 15.5, 8.7 Hz, 1H, C(2)-H), 6.63
(d, J = 8.5 Hz, 1H, Ar(3)-H), 6.76-6.80 (m, 2H, Ar(2,7)-H), 7.25-7.32 (m, 4H, C(1)-H, SAr(3,5)-H,
Ar(6)-H), 7.70 (d, J = 8.3 Hz, 2H, SAr(2,6)-H), the hydroxyl proton was not observed; ¹³C NMR
(CDCl₃) δ 18.32 (q), 18.91 (q), 21.49 (q), 39.28 (d), 55.53 (q, 2 carbons), 55.81 (q), 68.44 (d),
91.18 (d), 98.92 (l), 104.84 (d), 107.13 (d), 119.56 (d), 120.95 (s), 126.06 (s), 127.8 (d), 128.32
(d), 128.72 (d), 128.85 (s), 129.28 (d), 133.98 (s), 134.30 (d), 138.93 (s), 144.39 (s), 154.70 (s),
156.11 (s); exact mass calcd. for C₂₈H₃₄O₈S m/e 531.2053, found m/e 531.2021.
(±)-5-[(2R*,3R*,4S*,5R*,6S*)-Tetrahydro-3-(methoxymethoxy)-2,4-dimethyl-5-(phenylselenyl)-2H-pyran-2-yl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (185). To a -78°C solution of 890 mg (1.68 mmol) of enol 184 in 18 mL of dichloromethane was added 645 mg (3.36 mmol) of phenylselenenyl chloride in one portion. The resulting orange solution was stirred at -78°C for 2.5 h, diluted with 250 mL of dichloromethane, and washed with 100 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with two 100-mL portions of dichloromethane and the combined organic phases were washed with 100 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:2) to afford 920 mg (80%) of the selenide 185 as a colorless oil: IR (neat) 2934, 1599, 1523 cm⁻¹;¹H NMR (CDCl₃, 250 MHz) δ 1.25 (d, J = 6.5 Hz, 3H, CH₃), 1.38 (d, J = 6.7 Hz, 3H, CH₃), 1.98-2.07 (m, 1H, C(4)-H), 2.38 (s, 3H, ArCH₃), 3.28 (m, 1H, C(5)-H), 3.45-3.50 (m, 1H, C(3)-H), 3.47 (s, 3H, OCH₃), 3.76 (s, 3H, ArOCH₃), 3.72-3.83 (m, 1H, C(2)-H), 3.88 (s, 3H, ArOCH₃), 4.74 (d, J = 6.9 Hz, 1H, OCH₂), 4.78 (d, J = 6.9 Hz, 1H, OCH₂), 6.10 (d, J = 10.8 Hz, 1H, C(6)-H), 6.60 (d, J = 8.5 Hz, 1H, Ar(7)-H), 6.70 (d, J = 8.7 Hz, 1H, Ar(3)-H), 6.86-6.89 (m, 3H, SeAr-H, Ar(2)-H), 6.98-7.19 (m, 3H, SeAr-H), 7.23 (m, 2H, SAr(3,5)-H), 7.55 (d, J = 8.5 Hz, 1H, Ar(6)-H), 7.67 (m, 2H, SAr(2,6)-H);¹³C NMR (CDCl₃, 75.5 MHz) δ 18.03 (q), 18.17 (q), 21.48 (q), 42.60 (d), 54.33 (d), 55.36 (q), 55.42 (q), 56.33 (q), 76.48 (d), 79.95 (d), 80.92 (d), 98.76 (l), 105.34 (d), 106.75 (d), 119.01 (d), 120.84 (s), 126.95 (d), 127.17 (s), 127.58 (d), 128.29 (d), 128.37 (d), 129.21 (d), 129.70 (s), 133.89 (s), 134.97 (d), 139.29 (s), 144.29 (s), 155.01 (s), 155.98 (s), one aromatic singlet was not observed; exact mass calcd. for C₃₄H₃₈O₉Se m/z 686.1453, found m/z 686.1455; exact mass calcd.
for C\textsubscript{34}H\textsubscript{38}O\textsubscript{8}S\textsuperscript{78}Se m/e 684.1460, found m/e 684.1471.

(±)-5-[(2R*,5R*6R*)-5,6-Dihydro-5-(methoxymethoxy)-4,6-dimethyl-2H-pyran-2-yl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate. To a 0°C solution of 910 mg (1.32 mmol) of selenide 185 in 12 mL of tetrahydrofuran, was added 214 mg (2.69 mmol) of pyridine, followed 10 min later by 1.54 mL of 30% aqueous hydrogen peroxide. The resulting solution was stirred at ice bath temperature for 2 h, warmed to room temperature, and stirred 8 h. The reaction mixture was diluted with 150 mL of dichloromethane and washed with 75 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with two 150-mL portions of dichloromethane, and the combined organic phases were dried (MgSO\textsubscript{4}), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:2) to afford 539 mg (77%) of the glycal as a white solid: mp 155-157°C; IR (neat) 2990, 1598, 1499 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3} 300 MHz) \delta 1.39 (d, J = 6.5 Hz, 3H, CH\textsubscript{3}), 1.82 (t, J = 1.6 Hz, 3H, =CCH\textsubscript{3}), 2.42 (s, 3H, ArCH\textsubscript{3}), 3.46 (s, 3H, OCH\textsubscript{3}), 3.63 (s, 1H, C(5)-H), 3.78 (s, 3H, OCH\textsubscript{3}), 3.88 (s, 3H, ArOCH\textsubscript{3}), 3.8-4.0 (m, 1H, C(6)-H), 4.80 (d, J = 6.7 Hz, 1H, OCH\textsubscript{2}), 4.84 (d, J = 6.7 Hz, 1H, OCH\textsubscript{2}), 5.82 (t, J = 1.5 Hz, 1H, C(3)-H), 6.25 (s, 1H, C(2)-H), 6.67 (d, 1H, J = 8.6 Hz, Ar(3)-H), 6.8 (m, 2H, Ar(2,7)-H), 7.25 (apparent d, 2H, SAr(3,5)-H), 7.71 (d, J = 6.5 Hz, 2H, SAr(2,6)-H), 7.80 (d, J = 8.5 Hz, 1H, Ar(6)-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75.5 MHz) \delta 17.23 (q), 20.79 (q), 21.50 (q), 55.34 (q), 55.51 (q), 55.98 (q), 73.75 (d), 75.46 (d, 2 carbons), 96.77 (t), 104.84 (d), 107.42 (d), 119.25 (d), 121.77 (s), 125.81 (s), 126.40 (d), 128.34 (d), 129.25 (d), 129.82 (s), 130.14 (s), 130.82 (d), 134.01 (d), 139.28 (s), 144.35 (s), 154.55 (s), 155.49 (s); exact mass
calcd. for $C_{28}H_{32}O_8S$ $m/e$ 528.1818, found $m/e$ 528.1794.

Anal. calcd. for $C_{28}H_{32}O_8S$ C, 63.62; H, 6.10; found C, 63.45; H, 6.11.

(±)-4,8-Dimethoxy-5-[(2S*,3S*,4S*,5S*,6R*)-tetrahydro-3,4-dihydroxy-5-(methoxymethoxy)-6-dimethyl-2H-pyran-2-yl]-1-naphthol, p-toluenesulfonate (187). To a solution of 539 mg (1.02 mmol) of glycal 186 in 15 mL of acetone was added 144 mg (1.12 mmol) of N-methylmorpholine-N-oxide followed by 1.54 mL of a 2% by weight solution of osmium tetroxide in tert-butanol. The resulting solution was stirred at room temperature for 88h gradually becoming black. The resulting solution of osmate ester was diluted with 100 mL of dichloromethane and washed with 50 mL of water. The aqueous phase was extracted with three 100-mL portions of dichloromethane and the combined extracts were dried (MgSO$_4$) and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel to afford 555 mg (97%) of diol 187 as a white solid: mp 170-172°C; IR (neat) 3539 (broad), 3010, 2977, 1597, 1524 cm$^{-1}$; $^1$H NMR (CDCl$_3$ 300 MHz) δ 1.25 (d, $J$ = 6.5 Hz, 3H CH$_3$), 1.46 (s, 3H, CH$_3$), 2.08 (bs, 1H, OH), 2.43 (s, 3H, ArCH$_3$), 2.63 (bs, 1H, OH), 3.37 (s, 1H, C(5)-H), 3.49 (s, 3H, OCH$_3$), 3.68 (bd, $J$ = 9.6 Hz, 1H, C(3)-H), 3.82 (s, 3H, ArOCH$_3$), 3.95 (s, 3H, ArOCH$_3$), 4.27 (m, 1H, C(6)-H), 4.75 (d, $J$ = 6.8 Hz, 1H, OCH$_2$), 4.81 (d, $J$ = 6.8 Hz, 1H, OCH$_2$) 6.01 (d, $J$ = 9.5 Hz, 1H, C(2)-H), 6.70 (d, $J$ = 8.6 Hz, 1H, Ar(3)-H), 6.81 (d, $J$ = 8.6 Hz, 1H, Ar(2)-H), 6.90 (d, $J$ = 8.4 Hz, 1H, Ar(7)-H), 7.2 (apparent d, 2H, SAr(3,5)-H), 7.70 (d, $J$ = 8.2 Hz, 2H, SAr(2,6)-H), 7.87 (d, $J$ = 8.5 Hz, 1H, Ar(6)-H); $^{13}$C NMR (CDCl$_3$, 75.5 MHz ) δ 17.10 (q), 21.51 (q), 23.55 (q), 55.59 (q), 55.70 (q), 56.61 (q), 71.73 (d), 73.65 (s), 74.49 (d), 76.16 (d), 83.70 (d), 99.01 (t), 105.69 (d), 107.52 (d), 119.04 (d), 121.07 (s), 127.00 (s), 127.52 (d), 128.34 (d), 128.62 (s), 129.33 (d),
(±)-4,8-Dimethoxy-5-[(2R*3R*4S*5R*6S*)-tetrahydro-3,4,5-tris(methoxymethoxy)-4,6-dimethyl-2H-pyran-2-yl]-1-naphthol, p-toluensulfonate (188). To a solution of 555 mg (988 μmol) of C-aryl glycoside 187 in 2.4 mL of dichloromethane at 0°C was added 474 mg (5.9 mmol) of chloromethyl methyl ether followed by 752 mg (5.9 mmol) of ethyldiisopropylamine in single portions. The resulting solution was stirred for 1 h at 0°C then 2 h at room temperature, diluted with 100 mL of dichloromethane and washed with 50 mL of water. The aqueous phase was extracted with three 100-mL portions of dichloromethane, and the combined organic layers were washed with 50 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to afford 600 mg (94%) of the protected C-glycoside 187 as a colorless oil: IR (neat) 3054, 2985, 1654 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.27 (d, J = 6.6 Hz, 3H, CH₃), 1.47 (s, 3H, CH₃), 2.39 (s, 3H, OCH₃), 2.87 (s, 3H, OCH₃), 3.39-3.53 (m, 3H, C(3)-H, C(5)-H, OCH₂), 3.45 (s, 3H, OCH₃), 3.49 (s, 3H, OCH₃), 3.61 (d, J = 6.7 Hz, 1H, OCH₂), 3.79 (s, 3H, ArOCH₃), 3.92 (s, 3H, ArOCH₃), 4.39 (m, 1H, C(6)-H), 4.75 (m, 1H, C(6)-H), 5.16 (d, J = 6.9 Hz, 1H, OCH₂), 6.54 (d, J = 9.5 Hz, 1H, C(2)-H), 6.69 (d, J = 8.6 Hz, 1H, Ar(3)-H), 6.83 (d, J = 8.5 Hz, 1H, Ar(7)-H), 6.91 (d, J = 8.6 Hz, 1H, Ar(2)-H), 7.20 (m, 2H, SAr(3,5)-H), 7.63 (m, 2H, SAr(2,6)-H), 7.86 (d, J = 8.5 Hz, 1H, Ar(6)-H): ¹³C NMR (CDCl₃, 75.47 MHz) δ 17.20 (q), 18.59 (q), 21.46 (q), 55.49 (q, 2 carbons), 55.73 (q), 55.91 (q) 56.61 (q), 70.82 (d), 73.15 (d), 78.90 (s), 83.68 (d), 84.86 (d), 92.25 (l), 97.54
(±)-4,8-Dimethoxy-5-[(2R*3R*4S*5R*6S*)-tetrahydro-3,4,5-tri(methoxymethoxy)-4,6-dimethyl-2H-pyran-2-yl]-1-naphthol (189). To a solution of 275 mg (423 μmol) of the protected C-glycoside 188 in 7.5 mL of ice-cold degassed tetrahydrofuran-methanol (1:1) under argon was added 30 mg of disodium hydrogen phosphate in one portion. To the resulting buffered solution was added 3.09 g of 5.25% sodium amalgam in approximately 50-mg portions over a 2 h period. The reaction mixture was stirred an additional 1.5 h at 0°C and then diluted with 30 mL of chloroform and quenched with 25 mL of ice/water. The mixture was stirred for 20 min, the layers were separated, and the aqueous phase was extracted with one 25-mL portion of chloroform. The combined organic extracts were dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to afford 188 mg (90%) of naphthol 189 as a colorless oil: IR (neat) 3450 broad, 2957, 1631 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.24 (d, J = 6.6 Hz, 3H, CH₃), 1.44 (s, 3H, CH₃), 2.87 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 3.43 (m, 2H, C(3)-H, C(5)-H), 3.45 (s, 3H, OCH₃), 3.49 (d, J = 6.6 Hz, 1H, OCH₂), 3.64 (d, J = 6.6 Hz, 1H, OCH₂), 3.84 (s, 3H, ArOCH₃), 3.96 (s, 3H, ArOCH₃), 4.37 (m, 1H, C(6)-H), 4.73-4.79 (m, 3H, OCH₂), 5.14 (d, J = 7.1 Hz, 1H, OCH₂), 6.58 (d, J = 9.4 Hz, 1H, C(2)-H), 6.71 (d, J = 8.5 Hz, 1H, Ar(7)-H), 6.81 (d, J = 8.5 Hz, 2H, Ar(2,3)-H), 7.81 (d, J = 8.4 Hz, 1H, Ar(6)-H), 9.32 (s, 1H, OH); ¹³C NMR (CDCl₃, 75.47 MHz) δ 17.21 (q), 18.56 (q).
55.46 (q), 55.84 (q), 56.13 (q), 56.53 (q), 56.65 (q), 70.75 (d), 73.02 (d), 78.85 (s), 83.70 (d), 84.94 (d), 92.25 (l), 97.42 (l), 98.99 (l), 104.81 (d), 109.35 (d), 110.33 (d), 115.91 (s), 126.42 (d), 126.63 (s), 131.43 (s), 148.66 (s), 150.38 (s), 155.50 (s); exact mass calcd. for $C_{39}H_{37}O_{10}$ m/e 497.2288, found m/e 496.2337 exact mass calcd. for $C_{39}H_{36}O_{10}$ m/e 496.2294, found m/e 496.2301.

\[
\begin{align*}
\text{(±)-4,4,8-Trimethoxy-5-[(2R^*,3R^*,4S^*,5R^*,6S^*)-tetrahydropyran-2-yl]-1-(4H)-naphthalenone (190).} \\
\text{A solution of 188 mg (379 µmol) of naphthol 189 in 85 mL of 2% lithium perchlorate/methanol was electrochemically oxidized at a platinum gauze electrode for 20 min at 0.02 Amps, followed by 25 min at 0.1 Amp. The reaction mixture was diluted with 60 mL of dichloromethane and washed with 40 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with one 50-mL portion of dichloromethane and the combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of activity grade II neutral alumina (eluted with petroleum ether-ethyl acetate, 10:1, followed by 3:1) to afford 147 mg (74%) of the naphthoquinone monoacetal as a light green solid: mp 127-130°C; IR (CH$_2$Cl$_2$) 3010, 2938, 1673 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.11 (d, $J = 6.6$ Hz, 3H, CH$_3$), 1.47 (s, 3H, CH$_3$), 2.94 (s, 3H, OCH$_3$), 3.06 (s, 3H, OCH$_3$), 3.08 (s, 3H, OCH$_3$), 3.35 (s, 3H, OCH$_3$), 3.38 (m, 1H, C(5)-H), 3.41 (s, 3H, OCH$_3$), 3.83-3.87 (m, 1H, C(3)-H), 3.87 (s, 3H, OCH$_3$), 4.10 (d, $J = 6.6$ Hz, 1H, OCH$_2$), 4.18 (d, $J = 6.9$ Hz, 1H, OCH$_2$), 4.28 (m, 1H, C(6)-H), 4.66-4.75 (m, 3H, OCH$_2$), 5.15 (d, $J = 6.9$ Hz, 1H, OCH$_2$), 5.96 (d, $J = 10.0$ Hz, 1H, C(2)-H), 6.43 (d, $J = 10.3$ Hz, 1H, Ar(2)-H), 6.50 (d, $J = 10.3$ Hz, 1H, Ar(3)-H), 7.04 (d, $J = 8.9$ Hz, 1H, Ar(7)-H), 7.84 (d, $J = 8.9$ Hz, 1H, Ar(6)-).}
\end{align*}
\]
H); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ 17.17 (q), 18.99 (q), 51.10 (q), 51.51 (q), 55.33 (q), 56.09 (q), 56.15 (q), 56.63 (q), 70.73 (d), 71.39 (q), 78.46 (s), 80.82 (d), 84.26 (d), 92.09 (t), 97.48 (s), 97.81 (t), 99.08 (t), 112.99 (d), 121.45 (s), 132.16 (s), 133.55 (d), 135.87 (d), 140.15 (s), 142.12 (d), 159.83 (s), 184.23 (s); exact mass calcd. for C$_{26}$H$_{38}$O$_{11}$ m/e 526.2377, found m/e 526.2396.

(±)-3-[2-(4,5-Dihydro-4,4,8-trimethoxy)-5-methoxy-4-methylphenyl]-4,4,8-trimethoxy)-5-[(2R*,3R*,4S*,5R*,6S*)-tetrahydro-3,4,5-tris(methoxymethoxy)-4,6-dimethyl-2H-pyran-2-yl]-1(2H)-naphthalenone (191). A stock solution of MAD was prepared by adding 16 mL (32.0 mmol) of a 2 M solution of trimethylaluminum in toluene to a solution of 14.08 g (64.0 mmol) of 2,6-di-tert-butyl-4-methyl phenol in 184 mL of toluene. The resulting water-white solution was stirred for 2 h. In a separate reaction vessel, a stock solution of lithiated aryl oxazoline 60 was prepared by treating a solution of 219 mg (1.0 mmol) of oxazoline 60 in 5.4 mL of tetrahydrofuran at -45°C with 637 µL (1.02 mmol) of a 1.6 M solution of n-butyllithium dropwise over 10 min. The resulting orange-red oxazoline solution was stirred for 2 h at -45°- -50°C. Meanwhile a solution of 20 mg (38 µmol) of naphthaleneone 190 in 500 µL of toluene was cooled to -78°C and treated slowly with 590 µL (87.4 µmol) of the MAD stock solution. The dark brown solution was stirred for 25 min, before 611 µL (87.4 µmol) of the 0.143 M oxazoline stock solution was added dropwise. By the end of the addition, the solution had become reddish-brown. The reaction was stirred for 15 min at -78°C and then quenched with 1 mL of water. The resulting slurry was stirred for 30 min and the aqueous layer was extracted with
three 2-mL portions of dichloromethane. The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 750 mg of silica gel (eluted with petroleum ether-ethyl acetate, 1:2) to afford 8.0 mg (29%) of the conjugate addition product as a yellow oil: IR (neat) 2950, 1695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.08 (d, J = 6.6 Hz, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 2.31 (s, 3H, ArCH₃), 2.73 (dd, J = 17.1, 6.2 Hz, 1H, COCH₂), 2.74 (s, 3H, OCH₃), 2.93 (s, 3H, OCH₃), 3.05 (dd, J = 17.1, 11.4 Hz, 1H, COCH), 3.08 (s, 3H, OCH₃), 3.09 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.32 (s, 1H, C(5)-H), 3.78 (d, J = 10.6 Hz, 1H, C(3)-H), 3.44 (s, 3H, ArOCH₃), 3.84 (s, 3H, ArOCH₃), 3.95-4.15 (m, 5H, OCH₂, OCH₂, C(6)-H), 4.47 (dd, J = 11.4, 6.2 Hz, 1H, ArCH), 4.58 (d, J = 4.6 Hz, 1H, OCH₂), 4.65 (d, J = 5.3 Hz, 1H, OCH₂), 4.72 (d, J = 5.3 Hz, 1H, OCH₂), 5.03 (d, J = 4.6 Hz, 1H, OCH₂), 6.15 (d, J = 10.6 Hz 1H, C(2)-H), 6.55 (s, 1H, Ar-H), 6.98 (d, J = 7.5 Hz, Ar(7)-H), 7.02 (s, 1H, Ar-H), 7.73 (d, J = 7.5 Hz, 1H, Ar(6)-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 17.01 (q), 19.08 (q), 21.04 (q), 28.15 (q), 30.18 (q), 42.24 (d), 43.19 (l), 47.99 (q), 49.10 (q), 54.46 (q), 55.25 (q), 55.88 (q), 56.40 (q), 56.58 (q), 67.73 (s), 70.55 (d), 71.05 (d), 78.86 (s), 79.17 (l), 81.70 (d), 84.03 (d), 91.99 (l), 97.90 (l), 98.97 (l), 104.16 (s), 110.06 (d), 112.72 (d), 121.90 (d), 124.64 (s), 130.43 (s), 130.69 (s), 133.60 (d), 137.79 (s), 143.98 (s), 154.89 (s), 158.09 (s), 163.50 (s), 198.80 (s), one aromatic singlet was not observed; exact mass calcd. for C₃₉H₅₃NO₁₃ (M-1) m/e 743.3601, found m/e 743.3559.

![Image](image-url)

(+)-3,4-Dihydro-4,4,8-trimethoxy-3-phenyl-5-[(2R*,3R*,4S*,5R*,6S*)-tetrahydro-3,4,5-tris(methoxymethoxy)-4,6-dimethyl-2H-pyran-2-yl]-1(2H)-naphthalenone (192). To a -78°C
solution of 52.6 mg (100 μmol) of quinone monoketal 190 in 1.25 mL of degassed toluene under argon was added 1.25 mL of a 0.16 M stock solution of MAD (prepared by adding 16 mL of a 2 M solution (32 mmol) of trimethylaluminum in toluene to a degassed solution of 14.08 g (64 mmol) of 2,6-di-tert-butyl-4-methylphenol in 184 mL of toluene at room temperature) dropwise over a 2 min period. The black solution of MAD-ketone complex was stirred 20 min at -78°C, and then 130 μL of a 1.8 M solution of phenyllithium in cyclohexane-ether (70:30) was added dropwise over 5 min imparting a light yellow color to the reaction mixture. The reaction mixture was stirred 20 min, quenched with 1 mL of water, and stirred 1 h. The resulting slurry was filtered through 1 g of Celite, and the filter cake was rinsed with 100 mL of dichloromethane. The filtrate and washings were decanted from the aqueous phase and concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with petroleum ether-ethyl acetate, 1:1) to afford 25.4 mg (84%) of the conjugate adduct as a colorless oil: IR (neat) 2961, 1710, 1693, 1685 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 1.13 (d, J = 6.6 Hz, 3H, CH₃), 1.46 (s, 3H, CH₃), 2.90 (dd, J = 16.5, 4.7 Hz, 1H, COCH₂), 2.99 (s, 3H, OCH₃), 3.02 (s, 3H, OCH₃), 3.16 (dd, J = 17.8, 7.8 Hz, 1H, COCH₂), 3.30-3.40 (m, 1H, OCH), 3.33 (s, 3H, OCH₃), 3.39 (s, 3H, OCH₃), 3.46 (s, 3H, OCH₃), 3.59 (d, J = 7.0 Hz, 1H, OCH₂), 3.78 (d, J = 7.0 Hz, 1H, OCH₂), 3.80-3.88 (m, 2H, ArCH, OCH), 3.90 (s, 3H, ArOCH₃), 4.22 (m, 1H, C(6)-H), 4.61 (d, J = 6.8 Hz, 1H, OCH₂), 4.70 (d, J = 6.8 Hz, 1H, OCH₂), 4.75 (d, J = 6.8 Hz, 1H, OCH₂), 5.01 (d, J = 6.8 Hz, 1H, OCH₂), 6.0 (d, J = 9.8 Hz, 1H, C(2)-H), 7.08 (d, J = 9.0 Hz, 1H, Ar(7)-H), 7.12-7.16 (m, 5H, Ph-H), 7.76 (d, J = 9.0 Hz, 1H, Ar(6)-H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 17.12 (q), 18.76 (q), 43.62 (t), 45.00 (d), 48.70 (q), 50.02 (q), 55.31 (q), 55.89 (q), 56.10 (q), 56.59 (q), 70.68 (d), 71.63 (d), 78.54 (s), 80.50 (d), 83.89 (d), 92.12 (t), 96.85 (t), 98.99 (t), 104.07 (s), 112.60 (d), 123.70 (s), 126.50 (d), 127.90 (d), 129.21 (d), 131.72 (s), 134.85 (d), 140.34 (s), 140.68 (s), 157.73 (s), 196.97 (s); exact mass calcd. for C₃₂H₄₄O₁₁ m/z 604.2883, found m/z 604.2882.
4-Methoxy-8-(prop-2-ynyl-1-oxy)-1-naphthaldehyde (196). To a solution of 2.60 g (13.6 mmol) of 3-bromo-1-trimethylsilylpropyne in 30 mL of degassed acetone was added 4.68 g (33.9 mmol) of potassium carbonate. The resulting solution was heated to reflux and then a solution of 1.37 g (6.78 mmol) of naphthol 157 in 10 mL of acetone was added dropwise with stirring over a 1.5 h period. The reaction mixture was heated at reflux for an additional 4 h, and then filtered, washed with 50 mL of 10% citric acid, 50 mL of brine, dried (MgSO₄), and concentrated in vacuo. The crude trimethylsilylacetylene was dissolved in 33 mL of a 1:1 mixture of tetrahydrofuran-methanol and cooled with an ice bath. To the resulting solution was added a solution of 379 mg (6.78 mmol) of potassium hydroxide in 20 mL of methanol. The resulting solution was stirred for 20 min, diluted with 200 mL of dichloromethane, and washed with 100 mL of water. The aqueous phase was extracted with two 100-mL portions of dichloromethane and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The crude yellow solid was chromatographed over 75 g of silica gel (eluted with petroleum ether-chloroform, 1:1) to afford 1.40 g (84%) of the terminal acetylene as a yellow solid that was suitable for use in further reactions without additional purification. Recrystallization from ethyl acetate-hexanes (1:3) afforded 1.10 g (67%) of alkyne 196 as white needles: mp 161-162°C. IR (neat) 3016, 2968, 1671, 1513 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.56 (t, J = 2.4 Hz, 1H, CCH), 4.40 (s, 3H, OCH₃), 4.88 (d, J = 2.4 Hz, 2H, OCH₂), 6.88 (d, J = 8.2 Hz, 1H, Ar(7)-H), 7.15 (d, J = 7.7 Hz, 1H, Ar(3)-H), 7.43 (dd, J = 8.4, 7.9 Hz, 1H, Ar(6)-H), 8.00 (d, J = 8.5 Hz, 1H, Ar(2)-H), 8.08 (d, J = 8.3 Hz, 1H, Ar(5)-H), 11.06 (s, 1H, CHO); ¹³C NMR (CDCl₃, 62.9 MHz) δ 55.93 (q), 56.45 (t), 76.26 (d), 77.83 (s), 104.28 (d), 109.59 (d), 116.40 (d), 124.86 (d), 125.52 (d), 127.17 (s), 127.58 (s), 129.78 (d), 154.23 (s), 159.49 (s), 194.19 (d); exact mass calcd. for C₁₅H₁₂O₃ m/e 240.0792,
4-Methoxy-8-(prop-2-ynyl-1-oxy)-1-naphthol, formate (197). To a solution of 450 mg (2.5 mmol) of propargyl ether in dichloromethane at room temperature was added 2.58 g (7.5 mmol) of 50% m-CPBA in a single portion. The resulting solution was stirred for 1 h and poured into 75 mL of saturated aqueous sodium bisulfite. The biphasic mixture was stirred for 20 min and then diluted with 100 mL of dichloromethane. The layers were separated and the bisulfite layer was extracted with two 50-mL portions of dichloromethane. The organic phases were combined and washed with 50 mL of water, two 100-mL portions of saturated aqueous sodium bicarbonate, and 50 mL of saturated brine. The organic phase was dried (MgSO₄), and concentrated in vacuo. The residue was recrystallized from methanol to afford 325 mg (66%) of formate 197 as a colorless solid: IR (neat) 3052, 3009, 2962, 2940, 1761, 1739 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.55 (t, J = 2.4 Hz, 1H, CCH), 3.99 (s, 3H, OCH₃), 4.77 (d, J = 2.4 Hz, 2H, CH₂), 6.78 (d, J = 8.3 Hz, 1H, Ar(3)-H), 7.02 (m, 2H, Ar(2, 7)-H), 7.40 (m, 1H, Ar(6)-H), 7.96 (m, 1H, Ar(5)-H), 8.36 (s, 1H, CHO); ¹³C NMR (CDCl₃, 62.9 MHz) δ 55.77 (q), 56.79 (t), 75.80 (d), 77.94 (s), 103.77 (d), 109.16 (d), 116.13 (d), 119.14 (d), 119.23 (s), 125.81 (d), 128.32 (s), 138.57 (s), 152.74 (s), 153.68 (s), 160.82 (d); exact mass calcd. for C₁₅H₁₂O₄ m/e 256.0728, found m/e 256.0738.
4-Methoxy-8-(prop-2-ynyl-1-oxy)-1-naphthol (198). To a degassed solution of 86 mg (439 µmol) of formate 197 in 4 mL of tetrahydrofuran-methanol 1:1 was added an ice-cold degassed solution of 84 mg (1.5 µmol) of potassium hydroxide in 2 mL of methanol. The resulting solution was stirred 25 min and 4 mL of 5% aqueous HCl was added. The reaction mixture was diluted with 20 mL of dichloromethane and washed with 10 mL of water. The aqueous phase was extracted with two 10-mL portions of dichloromethane and the combined organic phases were concentrated to dryness. The resulting solid was chromatographed over 2 g of silica gel (eluted with petroleum ether-ethyl acetate, 2:1) to afford 59 mg (76%) of naphthol 198 as a blue-green solid. An analytical sample was obtained by recrystallization from ethanol affording white needles: mp 104-105°C; IR (neat) 3451 (broad), 3051, 3007, 2939, 1632 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.62 (t, J = 2.4 Hz, 1H, CCH), 3.93 (s, 3H, OCH₃), 4.88 (d, J = 2.4 Hz, 2H, CH₂), 6.76 (d, J = 8.4 Hz, 1H, Ar(2)-H), 6.82 (d, J = 8.4 Hz, 1H, Ar(3)-H), 6.90 (d, J = 7.7 Hz, 1H, Ar(7)-H), 7.31 (m, 1H, Ar(6)-H), 7.90 (d, J = 8.5 Hz, 1H, Ar(5)-H), 8.7 (s, 1H, OH); ¹³C NMR (CDCl₃, 62.9 MHz) δ 55.92 (q), 57.07 (t), 77.04 (d), 106.30 (d), 106.57 (d), 109.46 (d), 115.69 (s), 116.80 (d), 124.87 (d), 127.92 (s), 127.54 (s), 148.15 (s), 153.86 (s), the acetylenic singlet was not observed; exact mass calcld. for C₁₄H₁₂O₃ m/z 228.0774, found m/z 228.0780.

Anal. calcld. for C₁₄H₁₂O₃: C, 73.67; H, 5.30; found C, 73.55; H, 5.27.
4-Methoxy-8-(prop-2-ynyl-1-oxy)-1-naphthol, $p$-toluenesulfonate (199). To a solution of 29 mg (129 μmol) of naphthol 198 in 2 mL of degassed acetonitrile was added 5.5 mg (142 μmol) of sodium hydride and 25 μL of 15-crown-5. After $\text{H}_2$ evolution ceased, tosyl chloride (30 mg, 158 μmol) was added in one portion. The resulting solution was stirred for 3 h at room temperature, gradually becoming lighter in color. The reaction mixture was diluted with 10 mL of dichloromethane, washed with four 5-mL portions of water, and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel to afford 32 mg (65%) of the desired sulfonate ester 199 as an oil: IR (neat) 3058, 3052, 3007, 2961, 2908, 1595 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 2.43 (s, 3H, ArCH$_3$), 2.55 (t, $J = 2.4$ Hz, 1H, CCH), 3.96 (s, 3H, OCH$_3$), 4.73 (d, $J = 2.4$ Hz, 2H, CH$_2$), 6.64 (d, $J = 8.3$ Hz, 1H, Ar(3)-H), 6.93 (d, $J = 8.3$ Hz, 1H, Ar(2)-H), 7.08 (d, $J = 7.7$ Hz, 1H, Ar(7)-H), 7.28 (m, 2H, SAr(3,5)-H), 7.39 (m, 1H, Ar(6)-H), 7.75 (m, 2H, SAr(2,6)-H), 7.90 (d, $J = 7.7$ Hz, 1H, Ar(5)-H); $^{13}$C NMR (CDCl$_3$, 62.9 MHz) $\delta$ 21.62 (q), 55.74 (q), 56.65 (t), 75.79 (d), 78.64 (s), 103.14 (d), 110.01 (d), 115.58 (d), 119.75 (d), 120.44 (s), 125.94 (d), 128.33 (s), 128.56 (d), 129.39 (d), 133.68 (s), 138.29 (s), 144.57 (s), 153.02 (s), 154.07 (s); exact mass calcd. for C$_{21}$H$_{18}$O$_5$ m/e 382.0875, found m/e 382.0867.

Anal. calcd. for C$_{21}$H$_{18}$O$_5$: C, 65.95; H, 4.74; found C, 65.98; H, 4.80.
5-Hydroxy-8-methoxy-4-(prop-2-ynyl-1-oxy)-1-naphthaldehyde, p-toluenesulfonate (200). To a solution of 10 mg (26 pmol) of propargyl ether 199 in dichloromethane at 0°C was added 10 µL (92 µmol) of α,α-dichloromethyl methyl ether followed by 14 µL of (420 pmol) of titanium tetrachloride. The resulting deep red solution was stirred for 6 h at or below room temperature and was quenched with 2 mL of 5% aqueous HCl. The biphasic mixture was extracted with two 5-mL portions of dichloromethane and the combined extracts were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 1 g of silica gel (eluted with dichloromethane) to afford 10.5 mg (100%) of the aldehyde as a white solid: mp 142-144°C; IR (neat) 3058, 3048, 2987, 1674, 1591 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 2.42 (s, 3H, ArCH₃), 2.61 (t, J = 2.4 Hz, 1H, CCH), 3.88 (s, 3H, OCH₃), 4.82 (d, J = 2.4 Hz, 2H, CH₂), 6.80 (d, J = 7.7 Hz, 1H, Ar(7)-H), 6.93 (d, J = 7.7 Hz, 1H, Ar(6)-H), 7.12 (d, J = 8.5 Hz, 1H, Ar(3)-H), 7.28 (m, 2H, SAr(3,5)-H), 7.71 (m, 2H, SAr(2,6)-H), 7.88 (d, J = 8.5, 1H, Ar(2)-H), 10.85 (s, 1H, CHO); ¹³C NMR (CDCl₃, 62.9 MHz) δ 21.65 (q), 56.01 (q), 56.50 (l), 76.60 (d), 77.57 (s), 106.06 (d), 108.36 (d), 120.69 (d), 120.70 (s), 126.47 (s), 128.48 (d), 128.72 (s), 129.45 (d), 129.55 (d), 133.47 (s), 139.16 (s), 144.88 (s), 154.94 (s), 156.86 (s), 193.71 (d); exact mass calcd. for C₂₂H₁₈O₆S m/e 410.0824, found m/e 410.0828.
4,4-Dimethoxy-8-(prop-2-ynyl-1-oxy)naphthalene-1-one (210). A slurry of 200 mg (880 µmol) of naphthol 198 in 80 mL of 2% lithium perchlorate in methanol was electrochemically oxidized at 0.02 amps until all of the naphthol had dissolved. Further oxidation at 0.1 amp for 20 min resulted in the production of a blue-green solution that was diluted with 100 mL of dichloromethane and washed with 50 mL of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with 100-mL of dichloromethane and the organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was rapidly chromatographed over 30 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:2) to afford 170 mg (75%) of the desired quinone monoketal as a green oil: IR (neat) 3252, 2939, 2120, 1714 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) δ 2.54 (t, $J = 2.4$ Hz, 1H, CCH), 3.17 (s, 6H, OCH$_3$), 4.84 (d, $J = 2.4$ Hz, 2H, CH$_2$), 6.50 (d, $J = 10.4$ Hz, 1H, C(2)-H), 6.76 (d, $J = 10.4$ Hz, 1H, C(3)-H), 7.20 (d, $J = 8.4$ Hz, 1H, Ar(5)-H), 7.42 (d, $J = 7.8$ Hz, 1H, Ar(7)-H), 7.61 (m, 1H, Ar(6)-H) ; $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ 51.14 (q), 56.78 (t), 76.39 (d), 77.92 (s), 95.25 (s), 115.08 (d), 120.09 (d), 121.38 (s), 134.19 (d), 134.44 (d), 140.61 (d), 142.54 (s), 157.53 (s), 183.13 (s); exact mass calcd. for C$_{15}$H$_{14}$O$_4$ m/e 258.0902, found m/e 258.0897.
3-[(8-Formyl-5-methoxy-1-naphthyl)oxy]prop-1-ynyl trimethylsilane (203). To a solution of 2.54 g (11.8 mmol) of naphthol 157 in 60 mL of acetone was added 16.28 g of potassium carbonate followed by 2.91 g (15.3 mmol) of 3-bromo-(1-trimethylsilyl)-1-propyne.\textsuperscript{ref}

The resulting solution was heated under reflux for 6 h, cooled to room temperature and filtered. The filter cake was rinsed with 600 mL of dichloromethane and the combined filtrate and washings were washed with 100 mL of 10% citric acid, 100 mL of brine, dried (MgSO\textsubscript{4}), and concentrated in vacuo. The residue was purified by chromatography over 100 g of silica gel (eluted with petroleum ether-ethyl acetate, 10:1) to afford 3.25 g (84%) of the silyl acetylene: IR (neat) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 250 MHz) \delta 0.15 (s, 9H, Si(CH\textsubscript{3})\textsubscript{3}), 3.97 (s, 3H, OCH\textsubscript{3}), 4.83 (s, 2H, OCH\textsubscript{2}), 6.80 (d, J = 8.2 Hz, 1H, Ar(6)-H), 7.12 (d, J = 7.8 Hz, 1H, Ar(2)-H), 7.37 (t, J = 8.3 Hz, 1H, Ar(3)-H), 7.93 (d, J = 8.5 Hz, 1H, Ar(4)-H), 8.04 (d, J = 8.3 Hz, 1H, Ar(7)-H), 11.03 (s, 1H, CHO); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75.5 MHz) \delta -0.48 (q), 55.75 (q), 57.30 (l), 93.55 (s), 103.77 (d), 109.77 (d), 116.08 (d), 124.77 (s), 125.35 (d), 126.98 (s), 127.44 (s), 129.47 (d), 154.30 (s), 159.28 (s), 194.01 (d); exact mass calcd. for C\textsubscript{18}H\textsubscript{20}O\textsubscript{3}Si m/e 312.1143, found m/e 312.1163.
3[(8-Hydroxy-5-methoxy-1-naphthyl)oxy]-1-propynyl trimethylsilane (204). To a solution of 326 mg (1 mmol) of aldehyde 203 in 15 mL of dichloromethane was added 588 mg (7 mmol) of sodium bicarbonate followed by 645 mg (3 mmol) of 80% m-CPBA in one portion. The resulting solution was stirred for 3h, and quenched with 20 mL of 10% aqueous sodium thiosulfate. The mixture was vigorously stirred for 5 min, poured into 100 mL of 10% sodium thiosulfate, and extracted with three 50-mL portions of dichloromethane. The combined extracts were washed with two 50-mL portions of saturated aqueous sodium bicarbonate, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 10:1) to afford 131 mg of the crude formate as an oil. To a solution of 91 mg (266 pmol) of the resulting crude formate in 2 mL of tetrahydrofuran and 200 μL of methanol at -10°C was added 18 mg (461 pmol) of sodium borohydride in one portion. The reaction mixture was stirred for 1.5 h and an additional 9 mg (230 pmol) of sodium borohydride was added. After an additional 30 min of stirring, the mixture was partitioned between 2 mL of ether and 2 mL of water. The aqueous layer was extracted with three 2-mL portions of ether, and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. The resulting 73 mg (87%) of white solid was used in further reactions without purification: mp 0°C; IR (neat) cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.21 (s, 9H, SiCH₃), 3.93 (s, 3H, OCH₃), 4.88 (s, 2H, CH₂), 6.78 (d, J = 8.3 Hz, 1H, Ar(7)-H), 6.82 (d, J = 8.3 Hz, 1H, Ar(6)-H), 6.93 (d, J = 8.4 Hz, 1H, Ar(2)-H), 7.29 (m, 1H, Ar(3)-H), 7.89 (d, J = 8.5 Hz, 1H, Ar(4)-H), 8.80 (s, 1H, OH); ¹³C NMR (CDCl₃, 75.5 MHz) δ -0.53 (q), 55.88 (q), 57.97 (t), 94.53 (s), 98.26 (s), 106.23 (d), 106.62 (d), 109.23 (d), 115.70 (s), 116.53 (d), 124.80 (d), 127.85 (s), 147.59 (s), 148.07 (s), 154.05 (s); exact mass
calcd. for C_{17}H_{20}O_{3}Si m/e 300.1175, found m/e 300.1178.

\begin{align*}
&\text{4,4-dimethoxy-8-(3-trimethylsilylprop-2-yn-1-yloxy)naphthalene-1-one (205). A solution of 115 mg (366 \mu mol) of naphthol 204 in 80 mL of a 2\% solution of LiClO}_4 \text{ in methanol was electrochemically oxidized at 0.02 amps for 30 min, and then 0.1 amp for 20 min. The crude reaction mixture was diluted with 100 mL of dichloromethane and extracted with 50 mL of dichloromethane. The combined organic layers were dried (Na}_2\text{SO}_4 \) and concentrated in vacuo. The residue was flash chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:2) to afford 96 mg (80\%) of quinone monoketal 205 as a yellow oil: IR (neat) 3526, 3301, 1721, 2251 cm\(^{-1}\); } \\
&\text{\( ^{1}\)H NMR (CDCl}_3, 250 MHz) \delta 0.12 (s, 9H, SiCH}_3 \), 3.14 (s, 6H, OCH}_3 \), 4.80 (s, 2H, CH}_2 \), 6.46 (d, J = 10.5 Hz, 1H, =CH), 6.73 (d, J = 10.5 Hz, 1H, =CH), 7.19 (d, J = 8.3 Hz, 1H, Ar-H), 7.38 (d, J = 7.9 Hz, 1H, Ar-H), 7.57 (m, 1H, Ar-H); } \\
&\text{\( ^{13}\)C NMR (CDCl}_3, 75.0 MHz) \delta -0.484 (q), 51.11 (q), 57.75 (l), 93.59 (s), 95.27 (s), 99.40 (s), 115.50 (d), 119.95 (d), 121.42 (s), 134.06 (d), 134.46 (d), 140.51 (d), 142.39 (s), 157.76 (s), 183.17 (s): exact mass calcd. for C}_{18}H_{22}O_{4}Si m/e 330.1293, found m/e 330.1291.}
\end{align*}
8-(2-Butynyloxy)-4-methoxy-1-naphthol, \( p \)-toluenesulfonate (206). To a solution of 275 mg (720 \( \mu \)mol) of terminal acetylene 199 in 1.5 mL of tetrahydrofuran at -60\( ^\circ \)C was added 455 \( \mu \)L (756 \( \mu \)mol) of 1.6 M \( n \)-butyllithium in hexanes over a 2 min period. The resulting yellow solution was stirred at -60\( ^\circ \)C for 1 h and then 58 \( \mu \)L (936 \( \mu \)mol) of iodomethane was added in a single portion. The reaction was warmed to 0\( ^\circ \)C and stirred 5 h. The resulting solution was quenched with 10 mL of saturated aqueous ammonium chloride, and the aqueous layer was extracted with three 15-mL portions of dichloromethane. The combined organic phases were dried (\( \text{MgSO}_4 \)) and concentrated in vacuo to afford 255 mg (90\%) of the butynyl ether as a white solid mp 121-124\( ^\circ \)C. The resulting material was suitable for use in further reactions without purification, however, in a separate experiment, a sample was recrystallized from ethanol to afford a crystalline solid mp 126-127\( ^\circ \)C; IR (\( \text{CH}_2\text{Cl}_2 \)) 3063, 2923, 2358 cm\(^{-1}\); \(^1\)H NMR (\( \text{CDCl}_3 \), 300 MHz) \( \delta \) 1.86 (t, \( J = 2.3 \) Hz, 3H, Ar(3)-H), 2.37 (s, 3H, ArCH\(_3\)), 3.91 (s, 3H, ArOCH\(_3\)), 4.73 (m, 2H, ArOCH\(_2\)), 6.60 (d, \( J = 8.5 \) Hz, 1H, Ar(3)-H), 6.91 (d, \( J = 8.5 \) Hz, 1H, Ar(2)-H), 7.05 (d, 8.8 Hz, 1H, Ar(7)-H), 7.21 (m, 2H, SAr(3,5)-H), 7.34 (m, 1H, Ar(6)-H), 7.73 (m, 2H, SAr(2,6)-H), 7.84 (d, \( J = 8.4 \) Hz, 1H, Ar(5)-H); \(^{13}\)C NMR (\( \text{CDCl}_3 \), 75.7 MHz) \( \delta \) -1.28 (q), 16.57 (q), 50.70 (q), 52.16 (l), 69.16 (s), 78.92 (s), 98.09 (d), 104.58 (d), 110.04 (d), 114.62 (d), 115.35 (s), 121.03 (d), 123.29 (s), 123.56 (d), 124.32 (d), 128.69 (s), 133.39 (s), 139.54 (s), 148.36 (s), 149.02 (s); exact mass calcd. for \( \text{C}_{22}\text{H}_{20}\text{O}_5\text{S} \) \( \text{m/e} \) 396.1024, found \( \text{m/e} \) 396.1027.
4-(2-Butynyloxy)-5-hydroxy-8-methoxy-1-naphthaldehyde, p-toluenesulfonate (207).

To a solution of 245 mg (619 μmol) of butynyl ether 206 in 7 mL of dichloromethane at 0°C under argon was added (804 μmol) of α,α-dichloromethyl methyl ether followed by (1.61 mmol) of titanium tetrachloride in a single portion. The reaction mixture was stirred for 4 h and then poured into 100 mL of 1N hydrochloric acid. The resulting emulsion was stirred for 5 min, and then extracted with three 50-mL portions of dichloromethane. The combined extracts were washed with 25 mL of brine, dried (MgSO₄) and concentrated in vacuo. The crude yellow solid was chromatographed over 30 g of silica gel (eluted with petroleum ether-ethyl acetate-dichloromethane 5:1:1) to afford 215 mg (82%) of the aldehyde as a yellow solid: m.p. 142-143°C; IR (CH₂Cl₂) 2990, 2910, 1734, 1672 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.84 (t, J = 2.2 Hz, 3H, CCH₃), 2.38 (s, 3H, ArCH₃), 3.92 (s, 3H, ArOCH₃), 4.73 (m, 2H, ArOCH₂), 6.77 (d, J = 8.6 Hz, 1H, Ar(7)-H), 6.92 (d, J = 8.6 Hz, 1H, Ar(6)-H), 7.04 (d, J = 8.4 Hz, 1H, Ar(3)-H), 7.23 (m, 2H, SAr(3,5)-H), 7.70 (m, 2H, SAr(2,6)-H), 7.86 (d, J = 8.3 Hz, 1H, Ar(2)-H), 10.80 (s, 1H, CHO); ¹³C NMR (CDCl₃, 75.5 MHz) δ 3.58 (q), 21.50 (q), 55.89 (q), 57.09 (t), 73.10 (s), 84.76 (s), 105.99 (d), 108.12 (d), 120.47 (d), 120.66 (s), 126.35 (s), 128.16 (s), 128.40 (d), 129.38 (d), 129.47 (d), 133.41 (d), 139.14 (s), 144.73 (s), 154.82 (s), 157.81 (s), 193.56 (d); exact mass calcd. for C₂₃H₂₀O₆S m/e 424.0980, found m/e 424.0981.
Chapter III
X-Ray Crystallography of 1,8-Disubstituted Naphthalenes.

Aldehyde 75 presented a reactivity puzzle in the chrysomycin studies. It was speculated in Chapter I that at least four separate effects combined to reduce the reactivity of this compound toward nucleophiles. Solubility and deactivation via through resonance conjugation with three methoxy groups were issues discussed in Chapter I. Peri interactions with the C(4b) oxygen atom might also contribute as presented in Chapter II. This chapter describes X-ray studies which probe the possibility of a 1,8-disubstituted naphthalene nucleophile-electrophile interaction in aldehyde 75.

Steric Effects in 1,8-Disubstituted Naphthalenes.

The effects of peri interactions upon the reactivity of 1,8-disubstituted naphthalenes has been reviewed. The proximity of substituents in such compounds results in the production of ground state strain. This section evaluates the consequences of severe steric interactions upon the ground state conformations of such systems.

In contrast to the rigid planar structure of naphthalene, 1,3,6,8-tetra(tert)-butynaphthalene (207) is the most strained 1,8-disubstituted naphthalene yet studied. Its X-ray structure is presented in Figure 14. The distance between the C(1) and C(8) substituents in 219 is 3.86 Å, more than 1.5 times the distance of the peri hydrogens in naphthalene (2.45 Å). Thus one consequence of steric repulsion is that substituents are splayed in opposite directions. Naphthalene 219 shows another effect as the tert-butyl groups are twisted out of the naphthalene plane, one above and one below, such that a nearly 40° angle separates the two.
Figure 14. Stereoscopic View of 1,3,6,8-Tetra(tert)butyl-naphthalene 208.

1,2,3,4,5,6,7,8-Octamethyl naphthalene (209) reveals a second way in which crowded naphthalenes can reduce strain energy. In this molecule, the ring system buckles as shown in Figure 15).

Figure 15. 1,2,3,4,5,6,7,8-Octamethyl-naphthalene (209).

The crystal structure of 1-naphthoic acid (210) has also been reported. Steric effects of a peri hydrogen atom are enough to cause rotation of the carboxyl group out of the
naphthalene plane by 12°. To further relieve strain, the $C_{Ar}CO_2H$ carbon-carbon bond is in the naphthalene plane, but bent away from the hydrogen atom. Finally, the angle between oxygen atoms is only 110° (Figure 16).

![Figure 16. Naphthoic Acid (210).](image)

**Nucleophile-Electrophile Interactions in 1,8-Disubstituted Naphthalenes.**

Dunitz reported a different phenomenon in naphthalenes containing a heteroatom and carbonyl substituent at the 1,8-sites (Figure 17). The Dunitz group has devoted much effort to interpreting the crystal structures of such systems. The X-ray structure of methoxy-ketone 211 exemplifies the observations made in a series of seven structurally related naphthalenes. The acetyl group in 211 is splayed outward from the peri substituent. As shown in Figures 17 and 18, in contrast to the distortion pattern present in 1,8-dimethyl naphthalene (212), the methoxy group leans in the same direction as the acetyl group rather than the opposite.

In 211, it does not appear that substituents are attempting to avoid each other as in 212. In fact, it appears that the nucleophilic substituent is "chasing" the electrophilic one. This led to the proposal that an attraction, rather than a repulsion, exists between nucleophile-electrophile 1,8-substituted naphthalenes.

A feature in the X-ray of 211 consistent with nucleophilic addition of the heteroatomic moiety to the carbonyl center is depicted in Figure 19. As shown, a least squares plane passed through the carbonyl oxygen (O), the naphthalene carbon to which the ketone is attached ($R_n$), and the ketonic substituent ($R_k$), reveals that the carbonyl carbon is displaced from the plane by 0.044 Å in the direction of the peri substituent. Thus in Figure 19, $\Delta = 0.044$ Å. Thus "small but
significant" pyramidalization of the carbonyl group was observed.

Figure 17. Stereoview of 8-Methoxy-1-naphthyl Methyl Ketone 211.

Figure 18. Top View X-ray of 1,8-Dimethylnaphthalene 212.

Seven crystal structures were examined in the Dunitz work and data relevant to our
studies is compiled in Table I. Data for Δ suggests that amino derived nucleophiles coerce greater pyramidalization of the carbonyl group than corresponding hydroxy or methoxy substituents. This was ascribed to increased nucleophilicity of nitrogen. The pyramidalization results also depict a correlation between the electron withdrawing properties of a substituent and its respective degree of pyramidalization. Therefore CO-R > CO₂R ~ CO₂H > CONR₂. Hydroxy amides do not fit the pattern.

Data extracted from the crystallography studies were also used to examine the trajectory of nucophilic attack on carbonyl groups, and later triple bonds. In the oxo systems, the angle (a) formed by the "incoming nucleophile" (Nu), the carbonyl carbon (C), and oxygen (O), was between 93-107° (Figure 20). Thus, systems prepared by Dunitz support an attack angle of greater than 90°.67

Interatomic nucleus distances for the peri substituents, dᵢ, are in the range of 2.51-2.62 Å for the 7 compounds, while the distance between C(1) and C(8), dᵢᵣ, in the naphthalene core is consistently between 2.49 and 2.53 Å (Figure 21). This indicates that the distance between substituents is only slightly larger than the parent naphthalene carbons. Combining this data with the "leaning" effects supported an argument that the electrophilic center bent away from the peri substituent for the purpose of achieving an obtuse attack angle. As the electrophile bends away, however, internuclear distance is increased. To maintain the attraction, therefore, the nucleophile

![Figure 19. Depiction of Carbonyl Pyramidalization.](image)
follows the electrophile.

Figure 20. Angle of Nucleophilic Attack.

In all but one case (methoxy amide 214 being the exception), one substituent lies above the mean plane of the naphthalene and one below Figure 22. It should be noted that from crystal to crystal there is no distinction between up and down. For Table I, the electrophile is always designated as up $\delta E$ (a positive number) and the nucleophile $\delta Nu$.

Figure 21. Depiction of Internuclear Distances.

Figure 22. Displacement of Substituents from the Naphthalene Mean Plane.
Table 1. Data from Dunitz’s 1,8-Disubstituted Naphthalene X-ray Studies.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Nu</th>
<th>R</th>
<th>Δ*</th>
<th>a‡</th>
<th>d_i **</th>
<th>d_n **</th>
<th>δ (E)</th>
<th>δ (Nu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>OMe</td>
<td>Me</td>
<td>0.044</td>
<td>107.6</td>
<td>2.61</td>
<td>2.50</td>
<td>0.12</td>
<td>-0.08</td>
</tr>
<tr>
<td>213</td>
<td>OMe</td>
<td>OH</td>
<td>0.020</td>
<td>93.7</td>
<td>2.56</td>
<td>2.51</td>
<td>0.12</td>
<td>-0.04</td>
</tr>
<tr>
<td>214</td>
<td>OMe</td>
<td>N(Me)_2</td>
<td>0.039</td>
<td>103.3</td>
<td>2.60</td>
<td>2.53</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>215</td>
<td>OH</td>
<td>N(Me)_2</td>
<td>0.051</td>
<td>97.0</td>
<td>2.62</td>
<td>2.50</td>
<td>0.23</td>
<td>-0.09</td>
</tr>
<tr>
<td>216</td>
<td>N(Me)_2</td>
<td>Me</td>
<td>0.088</td>
<td>104.4</td>
<td>2.56</td>
<td>2.49</td>
<td>0.11</td>
<td>-0.10</td>
</tr>
<tr>
<td>217</td>
<td>N(Me)_2</td>
<td>OH</td>
<td>0.061</td>
<td>102.2</td>
<td>2.61</td>
<td>2.49</td>
<td>0.15</td>
<td>-0.17</td>
</tr>
<tr>
<td>218</td>
<td>N(Me)_2</td>
<td>OMe</td>
<td>0.062</td>
<td>98.6</td>
<td>2.59</td>
<td>2.51</td>
<td>0.24</td>
<td>-0.29</td>
</tr>
</tbody>
</table>

*See Figure 19. †See Figure 20. ‡See Figure 21.

Results and Discussion.

During the chrysomycin studies described in Chapter I, it was noted that the substitution pattern of the A and B rings in aldehyde 75 resembled the substitution pattern of the naphthalenes studied by Dunitz (Figure 23). Thus 75 appeared to be a “nucleophile-electrophile” 1,8-disubstituted naphthalene in which the electrophile was an aldehyde. An aldehyde would potentially be more electrophilic than any of the substituents examined by Dunitz. However, the nucleophilic component would be an electron deficient lactone ring-oxygen, which would likely be a weaker nucleophile than the hydroxyl, methoxyl, or amino groups examined by Dunitz.

It was thought that incipient nucleophilic addition to the aldehyde by the lactone oxygen would explain the lack of reactivity of 75. The hypothesis was that electrophilicity would be substantially decreased for a species undergoing nucleophilic attack in its ground state.
Presumably, the energy required to attain a transition state necessary for addition would require more energy than normal, and as a consequence it would be more difficult to add a nucleophile to such a species. Unfortunately, attempts to grow crystals of 75 always returned a powdery yellow solid exhibiting no crystalline qualities.

The MAD mediated conjugate addition-lactonization sequence to 75 developed by Merriman, however, provided a seemingly excellent intermediate for the preparation of derivatives of this aldehyde. Immediately following the addition-lactonization sequence, O(12)-naphthol 74 in equation 26 is obtained. One can imagine a variety of ways in which the O(12)-hydroxyl group could be elaborated, but unfortunately, the tosylation attempt described in equation 26 typifies the reactivity of this hydroxyl group. Thus, no sulfonate was formed after heating 74 in the presence of potassium carbonate and tosyl chloride for 3 days. Methylation of this position with dimethyl sulfate and potassium carbonate in refluxing acetone takes approximately one week to effect complete conversion.
The reluctance of 75 or a similar tetracycle to crystallize led to preparation of naphthaldehyde 156. It was hoped that the state of the formyl group in 75 could be inferred by extrapolation from an X-ray structure of this compound. Unfortunately, 156 crystallized as white plates unsuitable for X-ray analysis (Figure 24). This appears to be a characteristic of naphthaldehydes that are minimally functionalized. Throughout the course of our studies, the only naphthaldehydes which yielded X-ray quality crystals carried other functional groups around the ring. This may represent one reason why no aldehydes were studied in the Dunitz paper.

Figure 24. Aldehyde 156.

A breakthrough came during the synthesis of 1-O-methyl-chrysomycin B. Purification of the formylation product of tosylate 177 yielded poorly soluble, highly crystalline 178 (equation 27). Recrystallization of chromatographically purified 178 from dichloromethane-petroleum ether gave X-ray quality crystals.

Counter to our original intentions, the peri nucleophile in 178 was a methoxy unit. The
incorporation of a better nucleophile at C(8) suggested that X-ray data for 178 would likely overstate the interaction present in tetracycle 75. However, the edge on view ORTEP plot of 178 in Figure 25 indicated a contrasting situation. While the "angle of attack" in the compounds studied by Dunitz was consistently between 90-108°, aldehyde 178 exhibited an angle of 148°.

In addition, every compound in Dunitz's studies contained a carbonyl group more or less orthogonal to the naphthalene pi system. In aldehyde 178, this "twist angle" is 24°. According to these data, with an identical nucleophile, aldehyde 178 was encountering less of an interaction than 228. Since the greater electrophilicity of aldehydes is a well established principle in organic chemistry, it was difficult to rectify the crystal structure of 178 with the Dunitz attraction theory.

![Figure 25. ORTEP Plot of Edge On View of Aldehyde 178 Showing Aldehyde and Methoxy Groups.](image)

Some information from the crystal structure of 178, however, is consistent with an attractive interaction. X-ray parameters for 178 show the distance between the carbonyl and the methoxy centers to be separated by 2.63 Å. This places the electrophilic center of the formyl group just 0.02 Å further from the peri substituent than the corresponding groups in methoxy
ketone 211 (Figure 26). The approximately equal separation distances in 178 and 211 suggests that the substituents in 178 are within the range reported to facilitate an attractive interaction.

A least squares plane containing the aldehydic hydrogen, the carbonyl oxygen and C(1) of the naphthalene, shows that the carbonyl carbon in 178 is displaced by 0.088 Å and is directed towards the nucleophilic oxygen (Figure 26). This data is also consistent with incipient nucleophilic addition. However, a comparison of this data with data derived from ketone 211 indicates that even though the formyl group in 178 is slightly further from its peri substituent than the acetyl group in 211 is from the methoxy, pyramidalization of the aldehyde is twice that of the ketone. In fact, the degree of pyramidalization in aldehyde 178 is equal to or greater than the corresponding distance in every system studied by Dunitz. Remarkably this includes amino ketone 216 in which the substituents are actually 0.05 Å closer.

Figure 26. Distances of Separation and Pyramidalization in 178 and 221.

As shown in the top view ORTEP plot in Figure 27, the carbonyl-naphthalene bond in 178 is directed away from the peri substituent, generating a $115^\circ$ angle with the C(1)-C(2) naphthalene bond. The methoxy group is directed towards the aldehyde group making a similar angle with the naphthalene. Although difficult to discern from the view in Figure 27, the methoxy and aldehyde groups reside on the same face of the naphthalene.
This information raised a question with respect to the cause of conformational differences between aldehyde 178 and Dunitz's ketone (221). Were differences due to electronic effects, steric effects, or a combination of the two? Four hypotheses were generated that could potentially explain this dichotomy: 1) The C(4) and C(5) substituents in aldehyde 178 alter the electronic environment of the naphthalene such that the conformational preference of the
carbonyl group is also affected. 2) Less steric repulsion is involved in rotating a formyl group into conjugation with the aromatic pi framework than for a corresponding ketone. Thus a formyl group is more susceptible to conjugative interactions with C(4) and C(5) substituents. 3) No attraction between the C(1) and C(8) substituents exists, and therefore all observations are consistent with steric effects. 4) The approach trajectory of nucleophiles need not be 107°, thus steric effects govern the twist angle, angle of attack, and possibly pyramidalization, but electronic interactions could govern the leaning effect.

Methyl ketone 219 was prepared in an effort to clarify matters (equation 28). Friedel-Crafts acylation of 177 using acetyl chloride and titanium tetrachloride gave ketone 219 in 95% yield. Recrystallization from dichloromethane-petroleum ether gave large rectangular rods of X-ray quality. Previously, the formyl group in aldehyde 178 had twisted by 24°. Therefore if the carbonyl group in 219 rotated by approximately 24°, it could be concluded that the methoxy and tosylate groups at C(4) and C(5) played a role in determining the ground state structures of 178 and 219. However, this would also imply that to observe a true "degree of rotation" for the electrophilic substituent, another method of crystallizing naphthaldehydes would have to be found.

\[ \text{TiCl}_4, \text{CH}_2\text{Cl}_2 \]

\[ \text{MeCOCI} \quad 90\% \]

The edge on view ORTEP plot in Figure 28 shows, however, that the twist angle of ketone 219 more closely resembles the angle observed in Dunitz's studies (approximately 68°), and is approaching orthogonality with the naphthalene pi system. In ketone 219, the C(8)-methoxy is rotated 10° out of the naphthalene plane which allows for a nucleophilic attack angle
of $113^\circ$, in agreement with Dunitz's results. The methoxy and ketone functional groups lie on the same side of the naphthalene plane in 219, and the distance separating them is 2.58 Å. It is notable that the carbonyl carbon is displaced from the least squares plane involving the methyl, carbonyl oxygen, and C(1) naphthalene carbon by 0.07 Å. This is a bit higher than the 0.044 Å observed for ketone 211.

![ORTEP Plot of Edge On View of Ketone 219 Showing Methoxy and Ketone Groups.](image)

A top view of 219 is shown in the ORTEP plot in Figure 29. At $115^\circ$, the C(12)-C(6)-C(7) angle is $10^\circ$ less than the angle C(12)-C(6)-C(5). The complimentary O(4)-C(4)-C(5) angle is $114^\circ$, which is $10^\circ$ less than angle O(4)-C(4)-C(3). Thus, the leaning effect is present in ketone 219.

The similarity of ketone 219 to ketone 211 seemed to solidify Dunitz's findings for ketones, and showed that a significant difference in conformational preference existed for naphthaldehydes and naphthyl ketones. Furthermore, the crystal structure of 219 demonstrated that conjugating substituents on the aromatic ring played a lesser role in determining the twist.
angle and angle of attack in naphthyl ketones. These findings eliminated postulate 1 as a possible governing principle.

It was felt that postulate 2 could be examined by observing a system without a C(5) methoxy group. If the second proposal were true, then in the absence of a conjugating methoxy, the twist angle of the aldehyde group should expand to an angle more consistent with Dunitz’s compounds. Scheme LVI outlines the reaction sequence used to prepare such a substrate. 1,8-Naphthalic anhydride was ring contracted to lactam 221 in 77% yield using a known procedure.
Diazotization and degradation of 221 in the presence of 2 N H₂SO₄ afforded tricyclic lactone 222 in 75% yield. The furanone ring was opened with sodium methoxide and the resulting peri-alkoxide was alkylated with methyl iodide and potassium carbonate in refluxing acetone (82% for two steps). Formylation of the electron rich A ring in 223 gave naphthaldehyde 224 in 61% yield. Baeyer-Villiger oxidation produced an intermediate formate ester which was hydrolyzed with potassium hydroxide in methanol to give naphthol 225 in 71% yield. Preparation of the derived p-

**Scheme LV. Preparation of Aldehyde 228.**

- **220**
  - NH₂OHCl, pyridine;
  - TsCl; KOH, EtOH Δ
  - 75%

- **221**
  - NaOH;
  - NaNO₂, H⁺ 77%

- **222**
  - 82%
  - NaOMe, MeOH; MeI, K₂CO₃

- **223**
  - TiCl₄, C₂H₅CHO
  - 61%

- **224**
  - 1) m-CPBA, CH₂Cl₂;
  - 71%
  - 2) NaOH, MeOH

- **225**
  - 71%

- **226**
  - TsCl, K₂CO₃, Acetone
  - 73%

- **227**
  - DibalH, Toluene
  - 95%

- **228**
  - MnO₂, Benzene
  - 100%
Toluenesulfonate ester 226 was accomplished in 73% yield upon heating a mixture of 225 with tosyl chloride and potassium carbonate in acetone. The carbomethoxy group was reduced to the carbinol upon treatment with 2 M diisobutylaluminum hydride in toluene, thus affording 227 in 95% yield. The desired non-conjugated aldehyde was obtained by oxidation of alcohol 227 with activated manganese dioxide in benzene, thus delivering aldehyde 228 in quantitative yield.

As hoped, aldehyde 228 was a crystalline solid which yielded X-ray quality crystals from dichloromethane-petroleum ether. The X-ray electron density map of 228 showed the aldehyde was twisted out of the naphthalene plane by an angle of 34° (Figure 30). Comparison of this number to the twist angle in aldehyde 178 suggested that the presence of conjugating methoxy could be responsible for rotating the formyl group as much as 9° into the plane of the naphthalene. However, this still left a large difference in the rotation angles for aldehydes and ketones, and was a much smaller value than needed to justify postulate 2. Therefore, it was concluded that in the absence of extenuating circumstances, groups placed at C(4) and C(5) would have little consequence on conformational issues at C(1) and C(8).

![Figure 30. Edge on View of ORTEP Plot of Aldehyde 228 Showing Methoxy and Aldehyde Groups.](image-url)
As shown in Figure 31, the C(2)-C(1)-O(1) angle is 125° whereas the C(10)-C(1)-O(1) angle is 117°. Therefore, the tosylate is leaning towards the peri hydrogen atom, which is approximately at a normal angle. However, in the upper portion of the molecule, the O(4)-C(4)-C(3) angle is 8° greater than the O(4)-C(4)-C(5) angle, and the C(12)-C(6)-C(5) angle is 9°.

Figure 31. Top View of Aldehyde 228.
greater than the C(12)-C(6)-C(7) angle. Therefore the leaning effect is still present in the nucleophile-electrophile portion of aldehyde 228. Interestingly, the carbonyl carbon in aldehyde 228 is directed out of the least squares plane by 0.072 Å, which is slightly lesss than in aldehyde 178. This suggests that remote ring substituents may play a role in the degree of pyramidalization.

The differences in aldehydes and ketones observed to this point suggested that the twist angle (and therefore the angle of attack) was a steric artifact. Therefore it was projected that in 158 the carbonyl rotation angle would parallel earlier observations of 25-35°, and fluctuations in the leaning and pyramidalization effects could be correlated accordingly. Thus the X-ray structure of this single compound could allow assignment of every artifact as to steric or electronic in origin.

The difference between the remaining postulates was whether all, or some of the observations were due to steric effects. Postulate 3 could be eliminated if proof of a single electronic effect could be demonstrated. It was anticipated that the electron deficient nature of the peri oxygen in benzoate 158 would diminish its nucleophilic properties while retaining steric bulk equivalent to the methoxy containing substrates. Since 158 had already been prepared via the reaction shown in Equation 29, it was only necessary to crystallize this compound and obtain an X-ray.

The top view ORTEP plot of 158 in Figure 32 details a number of consequences encountered by changing from the electron rich methoxy nucleophile to the electron deficient
benzoate. The formyl group is splayed away from the peri substituent by $10^\circ$. The benzoate is splayed $1^\circ$ off the norm in the opposite direction. The leaning effect is absent in this compound and replaced by outwards splaying of the substituents which is consistent with repulsion. This data suggests that the leaning phenomenon is electronically derived, and that the presence of a good nucleophile is critical to maintaining an attractive interaction.

Figure 32. Top View ORTEP Plot of Aldehyde 158.
As shown in Figure 33, the twist angle associated with the aldehyde is only $12.6^\circ$. This value is $13^\circ$ less than in aldehyde 178, which had previously been most in plane with the naphthalene ring of all compounds studied. One must be cautious in invoking electronic arguments as the reason for this decrease, however. The only way to rationalize the small angle exhibited by 158 via electronic interactions is to assume that either aldehydes and ketones exhibit intrinsically different attack trajectories, or that aldehydes are less electrophilic than ketones. These explanations go against well established principles in organic chemistry. It is more likely that the decrease in this parameter is a function of an increase in separation distance between the peri substituents. This distance is 2.82 Å in compound 158. In fact, the twist angle in 158 is equal to the twist angle present in 1-naphthoic acid (221) which is twisted only as a function of steric consequences. Thus, as the distance separating the 1,8-substituents increases ($d_1$), more room is available for the aldehyde to rotate into the naphthalene plane. The small twist angle leads to a $151^\circ$ angle of attack for the benzoate-aldehyde.

Figure 33. Edge on View of ORTEP Plot of Aldehyde 158 Showing Aldehyde and Benzoate Groups.
At this point some trends in the aldehyde series could be noted. Bond lengths associated with the carbonyl group appear to be a function of the twist angle (A). As illustrated in Table 2, as the twist angle increases, the aldehyde C-H bond length increases (d_H), the aldehyde-naphthalene bond length increases (d_N), but the aldehyde C=O bond decreases (d_O). It is notable that the benzoate aldehyde C=O bond length is the longest in the three aldehydes. Based on the poor nucleophilicity of ester oxygens one might expect this bond to be the shortest.

Figure 34. Twist angle (A) and Bond Length Parameters for Aldehyde Series.

Also discernable from Table 2 is that the degree of pyramidalization Δ is independent of the twist angle. However, pyramidalization associated with formyl-benzoate 158 (0.057 Å) is greater than amounts reported for many of the Dunitz compounds. Since all other parameters in 158 appear to be derived from steric origin, either pyramidalization is the only electronically derived parameter in this system, or it is also sterically derived. It is tempting to conclude that this effect is also derived from steric, but from the available data, one can not rule out a possibility that aldehydes are simply more prone to pyramidalization due to their greater electrophilicity.

At this point, a case could be made for steric effects governing all artifacts in the crystal structures except for the leaning phenomenon. As a final proof for the involvement of steric rather than electronic media influencing the angle of attack, we attempted to prepare substrates containing similar degrees of steric bulk at the elecrophilic carbon but lacked electronic features. Olefins 238 and 239 were envisioned to be good steric mimics of the naphthyl ketones and aldehydes studied so far, and they presumably would not have nearly the same polarization
Table 2. Correlations to Twist Angle.

![Chemical structures]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$d_1^*$</th>
<th>$A^\dagger$</th>
<th>$d_H^\ddagger$</th>
<th>$d_N^\ddagger$</th>
<th>$d_O^\ddagger$</th>
<th>$\Delta^{**}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>228</td>
<td>2.64</td>
<td>32.9</td>
<td>1.03</td>
<td>1.491</td>
<td>1.173</td>
<td>0.072</td>
</tr>
<tr>
<td>178</td>
<td>2.63</td>
<td>23.9</td>
<td>1.00</td>
<td>1.479</td>
<td>1.177</td>
<td>0.088</td>
</tr>
<tr>
<td>158</td>
<td>2.82</td>
<td>12.6</td>
<td>0.98</td>
<td>1.477</td>
<td>1.190</td>
<td>0.057</td>
</tr>
</tbody>
</table>

* See Figure 21; † See Figure 33; ** See Figure 19.

Figure 35. Ketone and Aldehyde Analogs.

of the double bond (Figure 35).

The 2-propenyl naphthalene 230 had been prepared by Kirby, and was reported to be an oil. Therefore it seemed prudent to keep in line with our other compounds and install C(4) and
C(5) substituents including a tosylate. Unfortunately, our attempts to directly convert aldehyde 178 into an olefin were unsuccessful, similar to the problems encountered in the chrysomycin studies. Treatment of 178 with methyldene triphenylphosphorane led to the recovery of starting material. Attempted addition of methyllithium to the carbonyl led to tosyl group cleavage. Bromide 180 could not be alkylated by a sulfoxide since it decomposed.

\[
\begin{align*}
\text{OHC} & \quad \text{OH} \\
\text{MeO} & \quad \text{156} \\
\text{PhCOCl} & \quad \text{EtN(Pr)}_2 \\
\text{THF} & \quad 90\% \\
\text{OHC} & \quad \text{O} \\
\text{MeO} & \quad \text{158}
\end{align*}
\]

By this time, however, the extrusion technology presented in Chapter II was available. As shown in Scheme LVI, treatment of bromide 180 with sodium thiomethoxide in acetone delivered the corresponding methyl sulfide 231 in good yield. Oxidation with oxone afforded a quantitative yield of methyl sulfone 232. Exposure of sulfone 232 to potassium hydroxide, tert-butanol, and carbon tetrachloride gave olefin 229 in 60% yield. Unfortunately repeated attempts to crystallize this compound delivered white mica-like sheets which were simply too thin for X-ray analysis. It is tempting to attribute the absence of thickness in 229 to a very small rotation angle for both the olefin and tosylate groups. Unfortunately, without the proof of an X-ray, this may be science fiction.

As a final note, one might anticipate that spectral data could be used as evidence regarding this phenomenon. One would expect in a ketone like 221 for example, that if an electronic effect were present, the carbonyl group would absorb at lower energy in the IR spectrum since resonance should increase single bond character. Unfortunately, little spectral detail is described in the Dunitz work. In our own systems such a shift was not observed.
Conclusion:

The data collected here suggests, but does not prove, that data collected from 1,8-disubstituted naphthalenes as evidence for nucleophilic attack trajectory should be reevaluated since most of the evidence can be ascribed to steric effects. All evidence collected here suggests that the twist angle and angle of nucleophilic attack, strongly depend upon steric bulk at the carbonyl substituent, and the proximity of the nucleophilic center. Since the twist angle differs considerably for aldehydes and ketones, the only explanations that can be made based on electronic factors are that either aldehydes are less electrophilic than ketones, or they have different attack trajectories than ketones. Both of these arguments are counterintuitive. Proof of a steric origin would be provided by the X-ray structures of crystalline 229 and 230 or analogous systems.

Evidence further suggests that pyramidalization may also be an artifact of steric origin since instituting a poorly nucleophilic benzoate still incurred a fair degree of pyramidalization at
the carbonyl center. However, for this particular trait, it could be argued that aldehydes and ketones have different levels of sensitivity with respect to the presence of a nucleophile. In addition, the pyramidalization results in this work fit nicely into the trend described by Dunitz. Nevertheless, X-rays of aldehyde 233 and ketone 234 in Figure 35 would clarify this issue since no nucleophile is present at a peri site.

\[ \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \]
\[ \text{OTs} \]
\[ \text{OTs} \]

\[ 233 \quad 234 \]

Figure 36. Nonnucleophilic 1,8-Disubstituted Naphthalenes.

No arguments are made for steric origins of the splaying effect as this appears to have electronically related origins.

With respect to aldehyde 75, the compound which originated the research described in Chapter III, the crystal structures here do not make it clear whether a nucleophile-electrophile interaction or simply peri-strain is a greater source of the lack of reactivity. If one accepts benzoate 158 as a good "electronic model" for 75, then based on the divergent splaying of the 1 and 8 substituents in 158, it would appear that peri strain plays a greater role. However, the X-ray crystal structure of gilvocarcin M clearly shows the presence of a leaning effect in which the sugar is splayed away from the pyranone ring oxygen and the C(4b)-oxygen bond is buckled towards the sugar (Figures 33 and 34). No matter what the source of leaning is in this compound, it is highly unlikely that the steric bulk of the aldehyde in 75 would reverse the situation. Therefore, in aldehyde 75, the leaning phenomenon is most likely present.
Figure 37. Side and Top Stereoviews of Gilvocarcin M.
5-Hydroxy-4,8-dimethoxy-1-naphthyl methyl ketone, p-toluenesulfonate (219). To a solution of 358 mg (1.0 mmol) of tosylate 177 in 2.5 mL of dichloromethane at 0°C was added 94 mg (1.2 mmol) of acetyl chloride in one portion followed by one portion of 132 µL (3.0 mmol) of titanium tetrachloride. The dark red solution was stirred for 45 min and 20 µL (470 µmol) of additional acetyl chloride was added. The resulting solution was stirred 15 min, quenched with 3 mL of 5% aqueous HCl, diluted with 10 mL of dichloromethane, and washed with 20 mL of additional HCl. The aqueous layer was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were washed with 10 mL of brine, dried (MgSO₄), and concentrated in vacuo. The resulting foam was pure. Chromatography over silica gel (eluted with ethyl acetate-petroleum ether, 5:1) followed by recrystallization from dichloromethane, however, gave colorless crystals suitable for X-ray analysis: mp 148-150°C; IR (CH₂Cl₂) 2990, 1670 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.40 (s, 6H, CH₃), 3.84 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 6.69 (d, J = 8.5 Hz, 1H, Ar(3)-H), 6.78 (d, J = 8.1 Hz, 1H, Ar(7)-H), 6.88 (d, J = 8.5 Hz, 1H, Ar(6)-H), 7.17 (d, J = 8.1 Hz, 1H, Ar(2)-H), 7.27 (d, J = 8.5 Hz, 2H, SAr(3,5)-H), 7.69 (d, J = 8.5 Hz, 2H, SAr(2,6)-H); ¹³C NMR (62.9 MHz, CDCl₃) δ 21.62 (q), 31.91 (q), 55.70 (q), 55.76 (q), 105.15 (d), 106.23 (d), 120.49 (d), 124.44 (s), 124.63 (d), 128.39 (d), 129.48 (d), 131.84 (s), 133.74 (s), 139.77 (s), 144.77 (s), 153.24 (s), 156.16 (s) 204.89 (s), one aromatic singlet was not observed; exact mass calcd. for C₂₁H₂₀O₆S 400.1002 m/z; found 400.0992 m/z.

Anal. calcd. for C₂₁H₂₀O₆S: C, 62.99; H, 5.03. Found C, 63.06; H, 5.04.
Benz-[cd]indol-2-(1H)-one (221). To a solution of 13.0 g (65.6 mmol) of 1,8-naphthalic anhydride in 75 mL of pyridine was added 4.6 g (66.7 mmol) of hydroxylamine hydrochloride in one portion. The mixture was boiled under reflux for 1 h, cooled to room temperature, and 27.0 g (142 mmol) of p-toluenesulfonyl chloride was added in 3-4 g portions such that controlled boiling was maintained. Heating was resumed for 1 h and then the hot mixture was poured into 400 mL of water. The resulting yellow precipitate was filtered and then washed sequentially with 100 mL of 1N aqueous sodium hydroxide and 200 mL of water. The crude material was boiled in 200 mL of a 25% aqueous ethanol for 2 h and over the course of the second hour, ethanol was removed via distillation. The residue was acidified with 30 mL of concentrated hydrochloric acid such that a vigorously exothermic reaction ensued. The resulting solution was stirred for 4 h at room temperature, and the slurry thus produced was extracted with three 200-mL portions of dichloromethane. The combined organic layers were washed with four 200-mL portions of water and 200 mL of brine. The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 50 g of SiO₂ (eluted with benzene) to afford 8.30 g (75%) of the lactam 221 as a yellow solid: m.p. 168-173°C, lit 172-178°C.¹H NMR (300 MHz, CDCl₃) δ 7.00 (d, J = 8.8 Hz, 1H, Ar(7)-H), 7.46 (m, 1H, Ar(6)-H), 7.53 (d, J = 8.8 Hz, 1H, Ar(2)-H), 7.72 (m, 1H, Ar(3)-H), 8.55 (m, 2H, Ar(4,5)-H), 8.88 (bs, 1H, NH).
Naphtho-[1,8-bc]furan-2-one (222). A suspension of 2.00 g (11.8 mmol) of lactam 221 in 150 mL of 0.5 M aqueous NaOH was boiled for 2h. The reaction mixture was cooled to room temperature and mixed with 1.20 g (17.3 mmol) of solid sodium nitrite. The resulting solution was further cooled to 10 °C and then added dropwise to a 0°C solution of 2.3 N aqueous H₂SO₄ over a 25 min period such that the reaction temperature did not exceed 6 °C. At the end of the addition when the temperature reached 6 °C, the ice bath was removed and the mixture was subsequently heated with a bunsen burner until the temperature reached 85 °C. The reaction mixture was then cooled to room temperature and extracted with two 100-mL portions of benzene, and the combined benzene layers were dried (MgSO₄) and concentrated to afford 1.59 g (77%) of lactone 222 as a bright yellow solid: m.p. 108-109 °C; lit 108-110 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.07 (d, J = 8.8 Hz, 1H, Ar(7)-H), 7.50 (t, J = 8.4 Hz, 1H, Ar(6)-H), 7.62 (d, J = 8.8 Hz, 1H, Ar(2)-H), 7.71 (m, 1H, Ar(3)-H), 8.05 (m, 2H, Ar(4,5)-H).

Methyl 8-Methoxynaphthalene-1-carboxylate (223). To a slurry of 500 mg (2.94 mmol) of lactone 222 in 10 mL of ice-cold methanol was cautiously added 216 mg (5.40 mmol) of 60% sodium hydride dispersed in oil in 20 mg portions over a 25 min period. When vigorous
bubbling had subsided, the resulting solution was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and then carefully concentrated. To the resulting dark solution was added 10 mL of acetone, 834 mg (5.88 mmol) of methyl iodide, and 4.06 g (29.4 mmol) of potassium carbonate. The resulting slurry was heated at reflux for 4 h and then cooled to room temperature. The crude reaction mixture was filtered, washed with two 50-mL portions of 10% citric acid, two 50-mL portions of water, and 100 mL of brine. The organic phase was dried (MgSO₄) and concentrated in vacuo. Chromatography of the residue over 25 g of silica gel (eluted with petroleum ether-ethyl acetate, 4:1) afforded 520 mg (82%) of the methyl ether as an oil that crystallized upon standing: mp 49-51°C; ¹H NMR (300 MHz, CDCl₃) δ 3.88 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 6.80 (d, J = 8.1 Hz, 1H, Ar(7)-H), 7.35-7.45 (m, 4H, Ar(3,4,5,6)-H), 7.79 (m, 1H, Ar(2)-H).

**Methyl 4-methoxy-1-naphthaldehyde-5-carboxylate (224).** To a solution of 680 mg (3.14 mmol) of the ester 223 in 30 mL of dichloromethane at 0°C was added 426 µL (541 mg, 4.70 mmol) of α,α-dichloromethyl methyl ether, followed by 1.03 mL (9.42 mmol) of titanium tetrachloride. The resulting black solution was stirred for 2 h and then quenched by the addition of 3 mL of 5% aqueous HCl. The mixture was stirred 10 min at room temperature and further diluted with 50 mL of 5% aqueous HCl. The aqueous layer was extracted with two 50-mL portions of dichloromethane. The combined extracts were dried (MgSO₄) and concentrated in vacuo to afford 689 mg (90%) of the aldehyde as a cream colored solid that could be used without further purification. An analytical sample was prepared by chromatography over 25 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:1) followed by recrystallization from
dichloromethane-petroleum ether to afford 465 mg (61%) of the formylated naphthalene as white platelets: mp 135-136°C; IR (neat) 3054, 2985, 1730 1684 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.92 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.85 (d, J = 8.1 Hz, 1H, Ar(3)-H), 7.45 (d, J = 7.8 Hz, 1H, Ar(6)-H), 7.62 (m, 1H, Ar(7)-H), 7.81 (d, J = 7.8 Hz, 1H, Ar(2)-H), 9.37 (d, J = 8.8 Hz, 1H, Ar(8)-H), 10.1 (s, 1H, CHO); ¹³C NMR (75.0 MHz, CDCl₃) δ 52.29 (q), 56.36 (q), 104.46 (d), 121.22 (s), 124.84 (s), 125.67 (d), 126.41 (d), 128.32 (d), 129.91 (s), 132.07 (s), 139.81 (d), 159.56 (s), 171.19 (s), 191.93 (d); exact mass calcd. for C₁₄H₁₂O₄ m/e 244.0734, found m/e 244.0735.

Anal. calcd. for C₁₄H₁₂O₄: C, 68.85; H, 4.95. Found C, 68.70; H, 4.90.

Methyl 4-methoxy-1-naphthol-5-carboxylate (225). To a solution of 300 mg (1.23 mmol) of aldehyde 224 in 15 mL of dichloromethane was added 634 mg (3.70 mmol) of 99% m-CPBA in one portion. The resulting solution was stirred for 2.5 h and quenched with 15 mL of saturated aqueous sodium bisulfite. The resulting biphasic mixture was vigorously stirred for 25 min, and then poured into 25 mL of dichloromethane. The resulting solution was sequentially washed with 15 mL of saturated aqueous sodium bisulfite, 25 mL of saturated aqueous sodium bicarbonate, and 25 mL of brine. The combined organic layers were dried (MgSO₄) and concentrated in vacuo affording 303 mg of a white solid. To a degassed solution of the crude solid in 11 mL of methanol-tetrahydrofuran 1:1 was added a solution of 140 mg (3.51 mmol) of sodium hydroxide in 2 mL of methanol. The resulting green solution was stirred for 2 h and acidified to pH 1 by the addition of 5 mL of 5% HCl. The resulting mixture was extracted with two
25-mL portions of dichloromethane and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:1) to afford 193 mg (71%) of the desired naphthol as a white solid: mp 146-148°C; IR (neat) 3300, (broad) 3583, 3053, 1728 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 3.87 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 5.85 (bs, 1H, OH), 6.50 (ABq, J = 14.7, 8.8 Hz, 2H, Ar(2,3)-H), 7.45 (m, 2H, Ar(6,7)-H); ¹³C NMR (75.0 MHz, CDCl₃) δ 52.36 (q), 56.66 (q), 106.23 (d), 108.92 (d), 122.14 (s), 123.55 (d), 124.47 (d), 124.92 (d), 125.61 (s), 129.05 (s), 145.55 (s), 148.59 (s), 172.46 (s); exact mass calcd. for C₁₃H₁₂O₄ m/z 232.0747, found m/z 232.0742.

Methyl 8-methoxy-5-p-toluenesulfonate-1-carboxylate (226). To a solution of 150 mg (647 µmol) of naphthol 225 in 3 mL of acetone was added 897 mg (6.47 mmol) of potassium carbonate followed by 160 mg (841 µmol) of p-toluenesulfonyl chloride. The reaction mixture was heated under reflux for 12 h. After the first 2 h, an additional 80 mg (420 µmol) portion of p-toluenesulfonyl chloride was added. The reaction mixture was cooled to room temperature, filtered, and washed with 15 mL of 10% citric acid. The acid layer was extracted with 50 mL of dichloromethane, and the combined organic phases were washed with 15 mL of brine, dried (MgSO₄), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate, 3:1) to afford 183 mg (73%) of sulfonate 226 as a dark brown oil: IR (neat) 3085, 1732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.39 (s, 3H, CH₃), 3.95 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.74 (d, J = 7.9 Hz, 1H, Ar(7)-H), 7.17 (d, J = 7.9 Hz, 1H, Ar(6)-
5-Hydroxymethyl-4-methoxy-1-naphthol, p-toluenesulfonate (227). To a solution of 100 mg (259 mmol) of ester 226 in 500 µL of dichloromethane at -78°C was added 259 µL (259 µmol) of a solution of 1.0 M diisobutylaluminum hydride in toluene dropwise over 5 min. The resulting solution was stirred 2 h at -78°C, quenched with 5 mL of saturated aqueous ammonium chloride and warmed to room temperature. The aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with petroleum ether-ethyl acetate 5:1) to afford 88 mg (95%) of alcohol 227 as a yellow solid after recrystallization (CH₂Cl₂): mp 126-128°C; IR (neat) 3420 (broad), 3020, 1462 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.30 (bs, 1H, OH), 2.44 (s, 3H, ArCH₃), 4.03 (s, 3H, OCH₃), 5.06 (s, 2H, ArCH₂), 6.82 (d, J = 8.8 Hz, 1H, Ar(3)-H), 7.23 (d, J = 8.8 Hz, 1H, Ar(2)-H), 7.28 (m, 2H, SAr(3,5)-H), 7.39 (d, J = 8.1 Hz, 1H, Ar(6)-H), 7.48 (m, 1H, Ar(7)-H), 7.79 (m, 2H, SAr(2,6)-H), 7.83 (d, J = 8.1 Hz, 1H, Ar(8)-H); ¹³C NMR (CDCl₃, 75.47 MHz) δ 21.57 (q), 56.06 (q), 66.72 (t), 104.61 (d), 118.28 (d), 122.02 (d), 124.43 (s), 126.76 (d) 128.36 (d), 128.58 (d), 129.49 (s), 129.68 (d), 132.64 (s), 136.75 (s), 140.75 (s), 145.25 (s), 154.61 (s); exact mass calcld. for C₂₀H₁₈O₆S m/e 386.0834, found m/e 386.0829.
5-Hydroxy-8-Methoxy-1-naphthaldehyde, p-toluenesulfonate (228). To a solution of 77 mg (215 mmol) of alcohol 227 in 2.4 mL of benzene was added 120 mg of activated manganese dioxide. The resulting solution was stirred for 12 h at room temperature, filtered through celite, and the filter cake was rinsed with 50 mL of dichloromethane. The combined filtrate and washings were concentrated in vacuo to afford 76 mg (100%) of essentially pure aldehyde 228 as a white solid. Recrystallization from dichloromethane-petroleum ether afforded colorless prisms suitable for X-ray analysis: mp 145-146°C; IR (neat) 2995, 1677 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.40 (s, 3H, CH₃), 3.96 (s, 3H, OCH₃); 6.83 (d, J = 8.8 Hz, 1H, Ar(7)-H), 7.19 (d, J = 8.8 Hz, 1H, Ar(6)-H), 7.26 (m, 2H, SAr(3,5)-H), 7.46 (m, 1H, Ar(3)-H), 7.75 (m, 2H, Ar(2,6)-H), 7.84 (d, J = 8.6 Hz, 1H, Ar(2)-H), 8.02 (d, J = 8.8 Hz, 1H Ar(4)-H), 10.98 (s, 1H CHO); ¹³C NMR (62.9 MHz, CDCl₃) δ 21.67 (q), 55.97 (q), 105.24 (d), 119.32 (d), 123.83 (s), 126.51 (d), 127.86 (d), 128.29 (s), 128.43 (d), 128.73 (s), 129.84 (d), 132.34 (s), 135.06 (s), 139.65 (s), 145.61 (s), 154.85 (s), 194.85; exact mass calcd. for C₁₉H₁₆O₅S m/e 356.0728, found m/e 356.0723.

Anal. calcd. for C₁₉H₁₆O₅S: C, 64.03; H, 4.52; found C, 64.06; H, 4.58.
5-[[((Methyl)thio)methyl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (231). To a slurry of 640 mg (1.42 mmol) of bromide 180 in 3 mL of acetone was added 99 mg (1.42 mmol) of sodium thiomethoxide in one portion at room temperature. The resulting slurry was stirred for 8 h, filtered through a 50 mg plug of celite, and concentrated in vacuo thus affording 511 mg (86%) of the sulfide 231 as an orange solid. The residue was recrystallized from acetone to afford an analytical sample: mp 106-108°C; IR (neat) 3098, 1598 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.98 (s, 3H, SCH₃), 2.43 (s, 3H, ArCH₃), 3.85 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 4.24 (s, 2H, ArCH₂), 6.68 (d, J = 8.8 Hz, 1H, Ar(3)-H), 6.73 (d, J = 8.6 Hz, 1H Ar(7)-H), 6.80 (d, J = 8.8 Hz, 1H, Ar(6)-H), 7.09 (d, J = 8.8 Hz, 1H, Ar(2)-H), 7.26 (m, 2H, SAr(3,5)-H), 7.71 (m, 2H, SAr(2,6)-H); ¹³C NMR (74.5 MHz, CDCl₃) δ 14.54 (q), 21.50 (q), 41.28 (l), 55.50 (q), 55.60 (q), 105.26 (d), 106.07 (d), 119.86 (d), 122.25 (s), 126.13 (s), 126.61 (s), 128.35 (d), 129.27 (d), 129.37 (d), 133.97 (s), 139.11 (s), 144.40 (s), 154.87 (s), 156.05 (s); exact mass calcd. for C₂₁H₂₂O₅S₂ m/e 418.0911, found m/e 418.0910.

Anal. calcd. for C₂₁H₂₂O₅S₂: C, 60.27; H, 5.30. Found C, 60.35; H, 5.35.
5-[(Methyl)sulfonyl]methyl]-4,8-dimethoxy-1-naphthol, p-toluenesulfonate (232).

To 133 mg (536 mmol) of methyl sulfide 231 dissolved in a solution of 14 mL of methanol and 1.1 mL of dichloromethane was added a solution of 460 mg of "oxone" in 2.7 mL of water such that the temperature of the resulting solution did not exceed 5°C. The resulting slurry was stirred for 1.5 h, diluted with 25 mL of dichloromethane, and washed with 15 mL of water. The aqueous phase was extracted with two 20-mL portions of dichloromethane, and the combined organics were washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was recrystallized from methanol to afford dark red prisms: mp 182.5-183.5; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 2.45 (s, 3H, ArCH₃), 2.65 (s, 3H, SCH₃), 3.88 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 5.08 (s, 2H, ArCH₂), 6.77 (d, \(J = 8.1\) Hz, 1H, Ar(3)-H), 6.84 (m, 2H, Ar(6,7)-H), 7.29 (m, 2H, SA(S,5)-H), 7.43 (d, \(J = 8.1\) Hz, 1H, Ar(2)-H), 7.71 (m, 2H, SA(S,6)-H); \(^1\)C NMR (75.0 MHz, CDCl₃) \(\delta\) 21.52 (q), 38.86 (q), 55.57 (q, 2 carbons), 61.94 (t), 105.94 (d), 106.73 (d), 116.05 (s), 120.16 (d), 121.84 (s), 126.30 (s), 128.31 (d), 129.36 (d), 133.68 (s), 139.50 (s), 144.65 (s), 154.84 (s), 156.61 (q); exact mass calcd. for \(\text{C}_{21}\text{H}_{22}\text{O}_{7}\text{S}_{2}\) \(m/e\) 450.0802, found \(m/e\) 450.0804.

Anal calcd. for \(\text{C}_{21}\text{H}_{22}\text{O}_{7}\text{S}_{2}\): C, 55.99; H, 4.92. Found C, 56.01; H, 4.97.
(5-hydroxy-4,8-dimethoxy-1-naphthyl)ethene, p-toluenesulfonate (229). To a solution of 71 mg (154 mmol) of sulfone 232 in 2.1 mL of tert-butanol was added 518 mg (9.26 mmol) of freshly ground KOH followed by 5.2 mL of carbon tetrachloride. The resulting solution was stirred for 1.5 h while a gas evolved. The resulting dark solution was diluted with 25 mL of ether, and washed with three 10-mL portions of water. The organic phase was dried (MgSO\(_4\)) and concentrated. The residue was chromatographed over 10 g of silica gel (eluted with dichloroethane-benzene, 12:1) to afford a white solid. The solid was recrystallized from ethanol to afford white plates: m.p. 122-124°C; IR (CH\(_2\)Cl\(_2\)) 3054, 2980, 1594 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 2.43 (s, 3H, ArCH\(_2\)), 3.85 (s, 3H, OCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 5.09 (dd, \(J = 10.4, 2.1\) Hz, 1H, \(=CH_2\) (cis)), 5.25 (dd, \(J = 17.1, 2.0\) Hz, 1H, \(=CH_2\) (trans)), 6.65 (d, \(J = 8.6\) Hz, 1H Ar(7)-H), 6.81 (m, 2H, Ar(2,3)-H), 7.26 (m, 2H SAr(3,5)-H), 7.35 (d, \(J = 8.2\) Hz, 1H, Ar(6)-H), 7.68 (dd, \(J = 17.1, 10.4\) Hz, 1H, ArCH), 7.71 (m, 2H, SAr(2,6)-H); \(^{13}\)C NMR (MHz, CDCl\(_3\)) \(\delta\) 21.52 (q), 55.52 (q), 55.68 (q), 105.10 (d), 107.10 (d), 111.80 (d), 119.65 (d), 120.93 (d), 126.05 (s), 127.69 (d), 128.35 (d), 129.29 (d), 133.93 (s), 138.95 (s), 140.97 (d), 144.42 (s), 155.02 (s), 156.08 (s); exact mass calcd. for C\(_{21}\)H\(_{20}\)O\(_5\)S \(m/e\) 384.1055, found \(m/e\) 384.1044.
LIST OF REFERENCES

12 No explanation for regiospecific delivery is offered by the biosynthesis investigators.
16 The LD$_{50}$ value of Gilvocarcin V in mice is 300 mg/kg when administered orally, see: Ito, K.; Ohkubo, S.; Morimoto, M.; Tomita, F.; Matsuda, Y.; Nakano, H.; J. Antibiotics 1981, 34, 1544.
24 A review on C-Aryl glycoside synthesis has appeared: see: Jaramillo, C.; Knapp, S. Synthesis, 1994, 1, 1.


40 For a review on the use of aryl oxazolines in organic synthesis see: Reuman, M.; Meyers, A. I.; Tetrahedron, 1985, 41, 837.


42 Merriman, G. H., PhD Thesis The Ohio State University, 1990.

43 (a) Merriman, G. H., PhD Thesis The Ohio State University, 1990. (b), and (b) Young, D. G. J., M.S. Thesis, The Ohio State University, 1991.


45 (a) For a review on the Julia method of olefination see Kocienski, P. Phosphorus and Sulfur, 1985, 24, 97. (b) For a related example in which a sultone served nicely as an alternative to the Wittig reaction see: Kocienski, P.; Lythgoe, B.; Roberts, D. J. C. S. Perkins Trans I. 1978, 834.
For preparation of aldehyde 99 see ref 43 (b).

The elimination problem is examined in ref 43 (b).


The peri interaction has been reviewed. Balasubramaniam, V. *Chem. Rev.* 1966, 66, 567.


Dunitz has examined the extremely electron withdrawing diazonium group, however, this

69 No specific twist angles are quoted by Dunitz in ref 68, however he states that “in all cases the mean plane of the electrophilic COR-substituents are nearly perpendicular to the naphthalene plane.” Some crude sketches are provided.

70 Birch, A. J.; Salahud-Din; Smith, D. C. C. J. Chem. Soc. (Q) 1966, 523.
Appendix A

$^1$H NMR and $^{13}$C NMR of Selected Compounds
**89**

\[
\text{HO} \quad \text{OTs} \\
\text{Me} \quad \text{MOMO} \quad \text{Me}
\]

* = impurity
* = tetrahydrofuran
* = tetrahydrofuran
126
Machine artifact

= impurity

160
INTEGRAL

MeO

OMe

164

* = impurity

\[ \text{U} \]

4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 .2 0

248

\[ \text{ppm} \]
* = impurity

MOMO
Me
Me
O
Hb
PhSe
H2OMe
MeO
MeO

171

o machine artifact
* = impurity
Me, MOMO MeO OTs

= impurity

* = impurity
o machine artifact

188
o machine artifact
O MOM
MOMO
MOMO OOMe
Me
MOM
MOM
\[\text{MeO} \quad \text{K} \]
190

\text{o machine artifact}
* = impurity
191

* = impurity
= impurity
 o machine artifact
MeO OMe
201 = EtOAc

* = EtOAc
204 = impurity

* = impurity

TMS

OMe

204
Me

OMe

OTs

206

o machine artifact
* = impurity
MeO

TsO

* = impurity
MeO
TsO

227

MeO CH₂OH

TsO