SYNTHESIS OF TRICHOVERROL B AND STUDIES TOWARDS THE SYNTHESIS OF THE RORIDINS

by

ALFRED PAUL SPADA

B.S., Worcester Polytechnic Institute (1979)

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SYNTHESIS OF TRICHOVERROL B AND STUDIES
TOWARDS THE SYNTHESIS OF THE RORIDINS

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ALFRED PAUL SPADA

Submitted to the Department of Chemistry on
April 30, 1984 in partial fulfillment of the Degree
of Doctor of Philosophy.

ABSTRACT

The synthesis of trichoverrol B (31) from verrucarol and
diene acid 54 is discussed. Studies directed toward the develop-
ment of a general method for the preparation of the roridins
are also presented.

A general method for the synthesis of the four possible
isomers of \((Z,E)\)-diene acid 79 in optically pure form is
described. Application of this methodology to prepare optically
pure erythro-diene acid 54 and threeo-diene acid 194 necessary
for the synthesis of the trichoverrins and roridins, respect-
ively is discussed in detail.

Methodology for the acylation of the C(4)-OH of the tri-
chothecene nucleus with either erythro-(Z,E)-diene mixed anhydride
158 or threeo-(Z,E)-diene mixed anhydride 168 to yield isomerically
pure \((Z,E)\)-diene esters is described.

These methods are used to synthesize the trichoverrol B (31)
from 158 and trichothecene derivative 155. Studies directed
toward the development of a general method for the synthesis
of the roridins is described.

Thesis Supervisor: Dr. William R. Roush
Title: Roger and Georges Firmenich Career
Development Associate Professor of Natural Products Chemistry
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tr>
<td>BOP-Cl</td>
<td>N,N'-bis[2-oxo-2-oxazolidinyl]-phosphorodiamidic chloride</td>
</tr>
<tr>
<td>CDI</td>
<td>N,N'-carbonyldiimidazole</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
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<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DHP</td>
<td>dihydropyran</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>disobutylaluminum hydride</td>
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<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>4-DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>HMPT</td>
<td>hexamethylphosphororictriamide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>4-PP</td>
<td>4-pyrrolidinopyridine</td>
</tr>
<tr>
<td>SEM</td>
<td>2-trimethylsilylethoxymethyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TBMDMS</td>
<td>tert-butyltrimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
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<td>Full Name</td>
</tr>
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<td>--------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butylhydroperoxide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>pTsCl</td>
<td>p-toluenesulfonylchloride</td>
</tr>
<tr>
<td>pTsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

First, I would like to express my gratitude to Professor William R. Roush for his support, understanding and advice throughout the course of this work. His seemingly limitless enthusiasm for chemistry as well as high standards for research have been inspirational.

I would also like to thank Professor James W. Pavlik of Worcester Polytechnic Institute for nurturing my appreciation of scientific investigation.

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I would like to thank the Department of Chemistry for a teaching assistantship during my first year and Professor Roush for research assistantships from June 1980 to February 1983 and February 1984 to April 1984. Financial support from February 1983 through February 1984 was provided by a Traineeship from the National Cancer Institute (Grant No. T32-CA-09112).

In consideration of the support received from the National Institute of Health, the author hereby grants to the United States Government an irrevocable, non-exclusive, royalty-free license to reproduce, translate, publish, use and dispose of copies of this work for Government purposes.
To members of the Roush group past and present, it has been a pleasure to work with you and I am honored to have you as friends as well as colleagues. Special thanks go to Drs. Wesley Chong and Thomas Caggiano for proofreading this thesis in addition to offering many helpful suggestions over the past year.

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Lastly, I would like to thank the members of the Chemistry Department as a whole for providing a most stimulating environment in which to cultivate my interest in chemistry.
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To Barbara
CHAPTER I

INTRODUCTION
The trichothecenes are a class of terpenoids produced by various fungi of the Trichothecium, Trichoderma, Myrothecium, Cephalosporium, Fusarium, Stachybotrys, Verticimonosporium, and Culindocapron genera.\textsuperscript{1} These fungi grow, particularly in the temperate regions of the world, on agricultural grain products such as corn and wheat.\textsuperscript{1,2} Many, especially members of the Mycothecium, Trichoderma, and Cephalosporium families, are also found in soils rich in decomposing plant tissue.\textsuperscript{1f}

The trichothecenes possess common structural features based on the trichothecane skeleton illustrated in Figure 1.\textsuperscript{3}

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{figure1.png}
\caption{Figure 1}
\end{figure}

With very few exceptions, the naturally occurring trichothecenes contain an epoxide at C(12)-C(13) and an olefin at C(9)-C(10) (c.f., structure 2).
In addition, various levels of oxygenation are found at carbons 3, 4, 7, 8 and/or 15. Representative examples of the so-called simple trichothecenes are listed in Table I. Other trichothecenes contain macrocyclic ring systems. Representative examples of these compounds are listed in Tables III, IV and V.

Although the position and degree of hydroxylation of the trichothecene nucleus varies, it has been demonstrated that the presence of the 12,13-epoxide is essential for biological activity. Thus, reduction of diacetoxyverrucarol (3) with lithium aluminum hydride followed by acylation affords the tertiary alcohol 4, which is completely devoid of biological activity. Similarly, acid-induced rearrangement of the

12,13-epoxy trichothecene nucleus affords the apotrichothecene

skeleton 15, which also lacks biological activity. In addition, catalytic hydrogenation of the C.9,10 olefin affords products
Table I

Structures of Selected Trichothecenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichothecin 5</td>
<td>0</td>
<td>0</td>
<td>H</td>
<td>H</td>
<td>COOCH=CHCH₃</td>
<td>H</td>
</tr>
<tr>
<td>Trichotheclone 6</td>
<td>0</td>
<td>0</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Diacetoxyscirpenol (anguidine) 7</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OAc</td>
<td>OAc</td>
<td>OH</td>
</tr>
<tr>
<td>Verrucarol 8</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>T-2 Toxin 9</td>
<td>H</td>
<td>OOCOCH₂CH(CH₃)₂</td>
<td>H</td>
<td>OAc</td>
<td>OAc</td>
<td>OH</td>
</tr>
<tr>
<td>Calonectrin 10</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OAc</td>
<td>H</td>
<td>OAc</td>
</tr>
<tr>
<td>Trichodermol 11</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Trichodermin 12</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OAc</td>
<td>H</td>
</tr>
<tr>
<td>Deoxynivalenol 13 (vomitoxin)</td>
<td>0</td>
<td>0</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>OH</td>
</tr>
</tbody>
</table>
with greatly diminished activity.\textsuperscript{5}

The isolation of the first trichothecone, glutinosin, from \textit{M. glutinosium}, was accomplished by Brian and McGowan in 1946.\textsuperscript{6} This was the result of an extensive search for new antibiotics from various fungal sources. Glutinosin, a highly fungistatic material, was later shown to be a mixture of verrucarins A (25) and B (26).\textsuperscript{7} Two additional trichothecenes, trichothecin (5)\textsuperscript{8} and trichothecolone (6)\textsuperscript{9} were isolated in 1947 and 1948, respectively. No new trichothecenes were reported until the mid-1960's when thirteen new compounds were discovered as the result of systematic screening of various molds for antifungal and cytostatic agents.\textsuperscript{14} Continued interest in the biological properties of the trichothecenes has led to the isolation and characterization of approximately eighty members of this family, most of which were discovered in the past decade.

Although the first reported isolation of a trichothecone was in 1946, it was not until 1964 that the structures of these sesquiterpenes were established through detailed chemical and spectroscopic studies of trichodermol (11), trichothecolone (6) and verrucarol (8).\textsuperscript{10} The absolute stereochemistry of the trichothecone nucleus was determined through an X-ray analysis of the p-bromobenzoate derivative of trichodermol.\textsuperscript{11} The structures of the trichothecenes subsequently isolated were correlated with these compounds.

The trichothecenes possess an exceptionally broad spectrum of biological activity including antifungal, antiviral, anti-
bacterial, and insecticidal activities as well as phytotoxicity, and cytotoxicity.\textsuperscript{1h} This range of biological activity is probably related to the ability of the trichothecenes to inhibit protein synthesis in most eukaryotic cells.\textsuperscript{1a} Although the details of the mechanism of action of the trichothecenes on a molecular level are not known, it has been shown that these compounds bind to the ribosomal protein L2, located on the 60S ribosomal subunit.\textsuperscript{12}

In general, substances that inhibit protein synthesis do so by specifically inhibiting one of the three phases of protein synthesis, i.e., initiation, elongation, or termination. The trichothecenes as a class of protein synthesis inhibitors are atypical, however, in that different members are able to act upon any of these three specific steps. The entries listed in Table II serve to illustrate this point.\textsuperscript{1j}

Trichothecenes which inhibit the initiation step are invariably more toxic than those which inhibit the elongation and/or termination processes.\textsuperscript{1e} Nonetheless, the majority of the trichothecenes are fatally toxic to most plants and animals at very low dose levels, usually less than 10 mg/kg.\textsuperscript{1a,f}

The ubiquitous nature of the trichothecene-producing fungi and their tendency to grow on cereal grains has captured the attention of health and agricultural organizations worldwide.\textsuperscript{13} Many nations, including the United States and Canada, have established active research and screening programs for the detection of trichothecenes in grain products.\textsuperscript{14} The scope of
## Table II^le

### Modes of Inhibition of Selected Trichothecenes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type of Inhibition</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; values (mg/kg) (mouse i.p.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roridin A 16</td>
<td>Initiation</td>
<td>0.5</td>
</tr>
<tr>
<td>Verrucarin A 25</td>
<td>Initiation</td>
<td>0.5</td>
</tr>
<tr>
<td>Verrucarin J 27</td>
<td>Initiation</td>
<td>0.5</td>
</tr>
<tr>
<td>T-2 Toxin 9</td>
<td>Initiation</td>
<td>5.2</td>
</tr>
<tr>
<td>Trichodermin 12</td>
<td>Elongation</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Trichothecin 5</td>
<td>Elongation</td>
<td>&lt;250</td>
</tr>
<tr>
<td>Trichodermol 11</td>
<td>Termination</td>
<td>500-1000</td>
</tr>
</tbody>
</table>
the problem is dramatically illustrated by the finding of the Canadian government that 100% of the samples collected from Quebec's 1980 crop of red spring wheat were contaminated with varying levels of vomitoxin (deoxynivalenol). Similarly, 99% of the samples of Ontario's 1980 crop of white winter wheat were also contaminated with this toxin. Little difference was noted in the levels of vomitoxin in grain samples taken from fields designated for human consumption (0.09 to 1.1 µg) and those designated for animal consumption (0.06 to 7.0 µg).

Trichothecenes, like other mycotoxins, have been shown to induce feed refusal in swine and other farm animals, wherein the animal will not eat the contaminated food source. It has been shown that 40 µg of vomitoxin/g of feed corn will induce this response. The resulting loss of weight will generally make the animal unmarketable and in prolonged cases the animal will die. A financially disastrous episode of feed refusal by swine occurred in northwestern Ohio in 1975. In the aftermath of this outbreak, it was shown that the feed corn was in fact contaminated with vomitoxin. Incidents such as this have served to heighten the awareness of farmers to the potential problems associated with feedstock contaminated with various trichothecene-producing fungi. Many farmers now visually inspect their feed for the presence of toxin-producing fungi in order to avoid such problems.

In retrospect, outbreaks of various human toxicosis have been attributed to the consumption of grains contaminated with trichothecene-producing molds. Perhaps the most tragic
## Structures of Selected Roridins

### Table III

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Roridin A</td>
<td><img src="image" alt="Structure" /></td>
<td>18</td>
</tr>
<tr>
<td>2. Roridin D</td>
<td><img src="image" alt="Structure" /></td>
<td>18, 21</td>
</tr>
<tr>
<td>3. Roridin E</td>
<td><img src="image" alt="Structure" /></td>
<td>19, 21, 22</td>
</tr>
<tr>
<td>4. Isororidin E</td>
<td><img src="image" alt="Structure" /></td>
<td>18</td>
</tr>
<tr>
<td>5. Isororidin A</td>
<td><img src="image" alt="Structure" /></td>
<td>18</td>
</tr>
</tbody>
</table>
incident occurred during the winter of 1943-4 in the Orenberg region of the Soviet Union.\textsuperscript{16} The lack of available food forced both men and animals to forage the fields for unpicked wheat and millet. Unfortunately, the over-wintered grain had acquired substantial amounts of trichothecene-producing \textit{Fusarium} fungi. The ingestion of the moldy grain was believed to be the cause of an epidemic of alimentary toxic aleukia (ATA), the symptoms of which include internal hemorrhaging, loss of muscle coordination, vomiting, and depletion of bone marrow.\textsuperscript{16} Joffe reported that more than 10% of the population of this region contracted this disease, which has a mortality rate of 60%.\textsuperscript{16} Thirty years after the epidemic, a sample of the wheat, supplied by the Soviet Union, was shown by Mirocha and coworkers to contain high levels of T-2 toxin (9).\textsuperscript{17}

One major subgroup of the epoxytrichothecene mycotoxins contain macrocyclic rings.\textsuperscript{1h} Representative samples of these macrocycles are presented in Tables III, IV, and V. Table III contains examples of the class of trichothecenes known as the roridins. One characteristic of these compounds is the Z,\textit{E}-dienoic acid unit which is esterified to the \textit{C}(4)-OH position of the trichothecene nucleus. The stereochemistry of \textit{C}(6') has been shown to be \textit{(R)} in roridins \textit{A} (16)\textsuperscript{18} and \textit{E} (18)\textsuperscript{19} and it has been predicted that other members of this family will also have the \textit{(R)} configuration at this center.\textsuperscript{18,20} Isororidin \textit{E} (19), however, is \textit{(S)} at \textit{C}(6'). Interestingly, both \textit{(R)} and \textit{(S)} isomers at \textit{C}(13') are known to occur in nature.\textsuperscript{18} Considerable
variation exists in the C(1') to C(5') unit which is esterified to C(15). Variable C(1')-C(5') acyl fragments are also a distinguishing characteristic among members of the baccharins (Table IV) and verrucarins (Table V).

The baccharins and baccharinols (Table IV) are structurally similar to the roridins; like the roridins, the baccharinoids exist naturally as epimers at C(13')\(^\text{23}\). They differ from the roridins, however, in that the nucleus contains a \(\beta\)-epoxide at the 9,10 positions in the case of the baccharins, and a C(8)-\(\beta\)-hydroxyl group in the case of the baccharinols. Recently, Jarvis and coworkers have presented evidence which indicates that the baccharinoids, which were isolated from the Brazilian shrub *Baccharis megapotamica* by Kupchan in 1975, are plant-modified roridins.\(^\text{25}\) Specifically, Jarvis has shown that this shrub rapidly absorbs roridins, despite their usual phytotoxicity, and transforms them into baccharinoids via oxidation of the A ring of the trichothecene nucleus.\(^\text{25}\) Since *B. megapotamica* is incapable of de novo trichothecene biosynthesis, Jarvis has speculated that the source of roridins for the plant is *M. verrucaria*, which may grow in the surrounding area.

The baccharinoids are generally more phytotoxic than the precursor roridins. However, the interesting question of how *B. megapotamica* remains immune to the effects of these compounds remains unanswered. Jarvis has suggested that *B. megapotamica*'s insensitivity to the trichothecenes may derive from the inability of baccharinoids to bind to the plant's 60S ribosomal subunit.\(^\text{24}\)
That is, this shrub may have a mutant form of the appropriate ribosomal protein. This phenomenon has been observed in the

Table IV\(^{18,23,24}\)

The Baccharinoids

Baccharin B5 \(^{21}\)  

Baccharinols B4 and B6 \(^{23}\)

Baccharin B8 \(^{22}\)  

Baccharinols B3 and B7 \(^{24}\)

case of the fungus \textit{M. verrucaria}\(^{26}\) and probably explains why these fungi are resistant to the toxins they produce.

The third major class of trichothecene macrocycles are the verrucarins (Table V), which are macrocyclic triesters incorporating a (E,Z)-muconic acid unit. It is this characteristic muconic acid unit which distinguishes the verrucarins from the roridins.

A recently discovered group of trichothecenes are the trichoverroids (Table VI)\(^{20,27}\), which bridge the biosynthetic gap between the simple trichothecene (e.g., verrucarol) and
the macrocyclic groups. It is interesting to note that the trichoverroids are less potent biologically than the roridins or

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verrucarin A 25</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Verrucarin B 26</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Verrucarin J 27</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
</tbody>
</table>

The Verrucarins

Verrucarins. Thus, whereas trichoverrin A (28) shows no activity at dose levels below 32 mg/kg, isororidin E (19) is active at ca. 5 mg/kg.\textsuperscript{1h,20,27} This diminished activity may reflect the difficulty which these relatively polar compounds experience in crossing cell membranes.

Jarvis and coworkers have conducted a series of experiments which suggest that the trichoverrins are biogenetic precursors
Table VI 20, 27, 28

The Trichoverroids

![Chemical structure of Trichoverroids]

Trichoverrins

28 A: \( R_1 = H \); \( R_2 = OH \)
29 B: \( R_1 = OH \); \( R_2 = H \)

Trichoverrols

30 A: \( R_1 = H \); \( R_2 = OH \)
31 B: \( R_1 = OH \); \( R_2 = H \)

Trichodermadiene 32 H
to the macrocyclic trichothecenes (Scheme II). \(^{20,27}\)

**Scheme II**

\[
\begin{align*}
\text{Trichoverrinn B} & \quad 29 \\
\text{M. verrucaria} & \quad \rightarrow \\
\text{Roridin E} & \quad 18 \\
\text{Roridin A} & \quad 16 \\
& \quad + \quad \text{and Verrucarins} \\
\text{A}(25), \text{B}(26), \text{and J}(27)
\end{align*}
\]

Thus, trichoverrins A (100 mg) and B (100 mg) were fed to separate resting cultures of *M. verrucaria*. The mixture of trichothecenes recovered from each experiment contained approximately 50 mg of unchanged trichoverrin along with roridins A (16; 1-2 mg), roridin E (18; 1-2 mg) and isororidin E (19; 1-2 mg). The major products from these fermentations were verrucarins A (25; 10-13 mg), B (26; 4-6 mg), and J (27; ca. 4-5 mg). The timing of the oxidative cleavage of the
hydroxyethyl side chain leading to the verrucarins, is not yet known. It is certain, however, that roridins A (16) and E (18), the stereochemistry of which are firmly established,\textsuperscript{18,19} must arise from the trichoverrrin precursors by inversion of configuration at C(6'). One puzzling result, though, is that isororidin E (20) is produced with retention of the (S) configuration at C(6') in the ring-closure step.\textsuperscript{18} It may be that a species related to trichodermadiene (32) may be involved here.

The toxic nature of the trichotheccenes nonwithstanding, interest in the potential use of members of this class as chemotherapeutic agents for the treatment of a variety of carcinomas is very great.\textsuperscript{1a,g,h} In particular, the baccharinoids and related trichotheccenes have proven to be very active in the \textit{in vivo} P388 mouse leukemia assay (Table VII).\textsuperscript{23} This observation has stimulated general interest in the trichotheccenes as possible models for the design of effective antileukemic agents.\textsuperscript{1a,24}

As a result of this research, several qualitative structure-activity relationships have been observed (see Table VII).\textsuperscript{1a} For example, oxidation of C(8) of the cyclohexenyl A ring of the macrocyclic trichotheccenes to give a β-hydroxyl group (entry 5) or oxidation of the 9,10 double bond to the corresponding β-epoxide (entry 3) greatly enhances \textit{in vivo} P388 activity. Jarvis and coworkers have found greatest P388 activity when both of these positions are oxidized and are currently studying additional modifications of naturally occurring trichotheccenes by microbial and chemical means.\textsuperscript{24} It is hoped that further exploration of the


**Table VII**

**Activity of Selected Trichothecenes for P388 Carcinoma**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>dose (mg/kg)</th>
<th>T/C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Baccharin</td>
<td>7.5</td>
<td>246</td>
<td>1a</td>
</tr>
<tr>
<td>2.</td>
<td>Baccharininol</td>
<td>2.5</td>
<td>185</td>
<td>1a</td>
</tr>
<tr>
<td>3.</td>
<td>9,10-Epoxyverrucarin A</td>
<td>8.0</td>
<td>210</td>
<td>1a</td>
</tr>
<tr>
<td>4.</td>
<td>Verrucarin A 25</td>
<td>2.0</td>
<td>127</td>
<td>1a</td>
</tr>
<tr>
<td>5.</td>
<td>8-β-Hydroxyroridin A</td>
<td>3.75</td>
<td>205</td>
<td>1a</td>
</tr>
<tr>
<td>6.</td>
<td>Roridin A 16</td>
<td>.08</td>
<td>128</td>
<td>1a</td>
</tr>
<tr>
<td>7.</td>
<td>Roridin D 17</td>
<td>Inactive</td>
<td></td>
<td>1a</td>
</tr>
<tr>
<td>8.</td>
<td>Trichoverrinn A 28</td>
<td>Inactive</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>9.</td>
<td>Trichoverrinn B 29</td>
<td>Inactive</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>10.</td>
<td>Roridin E 18</td>
<td>ca. 5</td>
<td>~160</td>
<td>1h</td>
</tr>
<tr>
<td>11.</td>
<td>Iso Roridin E 19</td>
<td>ca. 5</td>
<td>~160</td>
<td>1h</td>
</tr>
</tbody>
</table>

---

*a) The activity is expressed as T/C values, which is defined as the number of days the test animals live, divided by the number of days the control animal lives, multiplied by 100. Compounds with T/C values >120 are considered active; those with T/C > 180 are considered very active.*
structure-function relationships of the trichothecenes will lead to a series of effective chemotherapeutic agents. In addition, it is probable that such studies will afford new insights into the mechanism of action of the epoxytrichothecenes at the molecular level.

Early synthetic efforts toward this class of sesquiterpenes focused on the preparation of the trichothecene nucleus. Colvin reported in 1971 the first synthesis of a naturally occurring epoxytrichothecene, trichodermin (12).\(^{30}\) Attempts to apply the trichodermin strategy towards the synthesis of verrucarol, however, was unsuccessful.\(^{30c}\)

Of all the simple trichothecenes, verrucarol has received the most attention as a synthetic target, since this is the nucleus common to all of the macrocyclic epoxytrichothecenes. However, it was not until twelve years after Colvin's initial attempt that a successful verrucarol synthesis was reported by Schlessinger and coworkers.\(^ {31}\) Shortly thereafter, both Trost\(^ {32}\) and Roush\(^ {33}\) reported total synthesizes of verrucarol (8). At present, a significant amount of interest remains in the synthesis of the simple trichothecenes.\(^ {34}\) However, the synthesis of the macrocyclic trichothecenes, which received little attention until the late 1970's, have now become a major objective of several research groups worldwide.

The first synthesis of a naturally occurring macrocyclic trichothecene, verrucarin A (25), was reported by Still and Ohmizu in 1981.\(^ {35}\) This synthesis is outlined in Scheme III.
Scheme III

\[ \text{HO} \quad \xrightarrow{\text{a,b,c,d,e}} \quad \text{HO} \quad \xrightarrow{\text{OTBDPS}} \quad 33 \quad \xrightarrow{\text{f,g}} \quad \text{OR} \quad \xrightarrow{\text{h,i}} \quad \text{AcO} \quad \text{CH}_3 \quad 35 \]

\[ \text{CHO} \quad \xrightarrow{\text{j}} \quad \text{MeO} \quad \xrightarrow{\text{CO}_2\text{Me}} \quad 37 \quad \xrightarrow{\text{k}} \quad \text{38} \quad \xrightarrow{\text{l,m,n}} \quad \text{40} \]

\[ \text{8} \quad \xrightarrow{\text{m}} \quad 39 \quad \xrightarrow{\text{n}} \quad 41 \quad \xrightarrow{\text{o,p,q}} \quad 42 \]

28
Key to Scheme III:

a) EtOCH=CH₂, p-TsOH; b) iPrMgBr, THF, ethylene oxide; c) TBDPS-Cl, imidazole, DMF; d) AcOH, H₂O; e) H₂, Lindlar catalyst, MeOH;
f) t-BuOOH, (iPrO)₄Ti, CH₂Cl₂, -20°C; g) 2% RuCl₃, NaIO₄, CCl₄-CH₃CN-H₂O; h) Al(Me)₃, petroleum ether, 25°C, 40h; i) Ac₂O, pyridine; j) Pt electrodes, MeOH, Et₄NClO₄, 1.5 amps, 18h;
k) 1 N H₂SO₄, 25°C, 18h; l) (Ph)₃P=CHCO₂CH₂CH₂SiMe₃, 39; m) 38, DCC, 4-pyrrolidinopyridine, CH₂Cl₂, 25°C, 5h; n) 40, DCC, 4-pyrrolidinopyridine, CH₂Cl₂, 25°C, 5h; o) (nBu)₄NF, THF, 25°C, 3h; p) (Ph)₃P, EtO₂CN=NCO₂Et, 25°C, 20h, 52%; q) NaOMe, MeOH, 0°C, 2h, 70%.
Carboxylic acid 35 was prepared in 28% overall yield from 4-butyn-1-ol. Key steps of this sequence included the enantioselective epoxidation of (Z)-allylic alcohol 33 followed by RuCl₃ catalyzed oxidation, which afforded epoxy acid 34. Introduction of the β-methyl group at C(3') was accomplished with trimethylaluminum. Subsequent acylation afforded the C(15) acyl synthon 35. Mono-protected (Z,E) muconic acid 40 was prepared from furfural in three steps in 42% overall yield. Interestingly, the Wittig olefination of pseudoacid 38 with ylid 39 afforded only the desired (E,Z) muconate derivative.

Selective esterification of acid 38 with C(15)-OH of verrucarol (8), which was prepared from readily available anguidine (7) by using a method reported by Fraser-Reid and coworkers was accomplished in 95% yield by using dicyclohexyl-carbodiimide (DCC) and 4-pyrrolidinopyridine (4PP) as the acylation catalyst. 36 Acylation of the C(4) position with acid 40 was accomplished under the same conditions to afford diester 42 in 86% yield. It is interesting to note that no isomerization of the muconate unit to the (E,E) isomer was observed. As will be shown subsequently, and has been observed by Blizzard in these laboratories, 41a olefin isomerization is often a serious problem when attempting to acylate C(4)-OH with (Z)-α,β-unsaturated acid derivatives. Still, too, found that (E,E)-42 was produced when the CDI method 37 was used in the coupling of 40 and 41. Removal of the silyl protecting groups followed by macro-
lactonization by using the Mitsunobu procedure\textsuperscript{38} afforded verrucarin A acetate in 52\% yield from diester \textsuperscript{42}, deprotection of which provided the natural product. Interestingly, the corresponding (E,E)-secoacid did not cyclize under these conditions.

Tamm and coworkers have also reported a synthesis of verrucarin A (\textsuperscript{25}), which is outlined in Scheme IV.\textsuperscript{39} Thus,

\textbf{Scheme IV}\textsuperscript{39}

\begin{center}
\begin{tikzpicture}

\begin{scope}[yscale=0.7, xscale=0.7]

\node at (0,0) {43};
\node at (2,0) {\textbullet \textsuperscript{55}\% \rightarrow \textbullet \textsuperscript{95}\% \rightarrow \textbullet 44};
\node at (4,0) {40};
\node at (6,0) {\textbullet \textsuperscript{95}\% \rightarrow \textbullet \textsuperscript{95}\% \rightarrow \textbullet \textsuperscript{E,E} 45};
\node at (8,0) {46 \textsuperscript{(E,2)} \rightarrow \textbullet \textsuperscript{E,E} 47};
\node at (10,0) {\textbullet \textsuperscript{(E,2)} \rightarrow \textbullet \textsuperscript{E,E} 25};
\node at (11.5,0) {R\textsubscript{1}: THP};
\node at (12,0) {R\textsubscript{2}: TBDMS};
\end{scope}

\draw[->] (0,0) -- (2,0);
\draw[->] (2,0) -- (4,0);
\draw[->] (4,0) -- (6,0);
\draw[->] (6,0) -- (8,0);
\draw[->] (8,0) -- (10,0);
\draw[->] (10,0) -- (12,0);
\end{tikzpicture}
\end{center}

a) \textsuperscript{8}, DCC, 4-pyrrolidinopyridine; b) \textsuperscript{40}, DCC, 4-pyrrolidinopyridine; c) separation; d) (nBu)\textsubscript{4}NF, THF; e) 2,4,6-trichlorobenzoylchloride; f) 4-dimethylaminopyridine, toluene, 110\°; g) pyridinium p-toluenesulfonate, MeOH, 50\°C.
acylation of the C(15) position of verrucarol 8 with acid 43 in the presence of DCC and 4-PP afforded monoester 44 in 55% yield. Acylation of C(4) with the monoprotected muconic acid 40 under similar conditions afforded diester 46 in 95% yield as a 3:1 mixture of (Z,E) and (E,E)-products. These isomers were separated by silica gel chromatography at this stage. Removal of the silyl groups followed by macrolactonization and THF ether hydrolysis proceeded in 50% overall yield to provide verrucarin A (25). Two additional verrucarins have been synthesized: verrucarin J (27) by both Fraser-Reid40 and Roush,41b,c and verrucarin B (26) by Roush.42 The synthesis of verrucarins J and B by Roush and Blizzard will not be described here as they are the subject of a recent Ph.D. thesis41a from these laboratories. The synthesis of verrucarin J by Fraser-Reid was accomplished in connection with work on the synthesis of trichoverrinn B which is outlined below.

Fraser-Reid and coworkers in 1982 published the synthesis of trichoverrinn B (29) and its conversion to verrucarin J (27) (see Scheme V).40 The synthesis of the octadienoate fragment was first developed in order to determine the absolute stereochemistry of C(6') and C(13') of the trichoverrins.28,43 This synthesis starts from commercially available triacetyl glucal 48. Reduction of the C(6) to a methyl group was accomplished in five steps in 51% overall yield. Compound 50 was then transformed to the α,β-unsaturated aldehyde 51 using the method reported by Perlin (H₂SO₄, H₂O, dioxane) in 95% yield. Final
Scheme V

a) NaOMe, MeOH; b) TsCl, pyridine, 0°, 48h; c) Ac₂O, pyridine; NaI; e) n(Bu)₃SnH; f) HgSO₄, H₃O⁺, dioxane; g) LDA, Me₃SiCH₂CO₂Et, THF, -78°; h) NaOMe, MeOH; i) TBDMSCl, DMF, imidazole; j) chromatography; k) LiOH, DME, H₂O; l) 2-methoxypropene, TsOH; m) methyl trimethylphosphono acetate, NaH, DME; n) H₃O⁺; o) NaOH, followed by H₃O⁺; p) TBDPS-Cl, imidazole, DMF; q) LiOH, DME, H₂O.
elaboration to diene acid 54 was accomplished in four steps. First aldehyde 51 was homologated to diene esters 52 as a (2:1) mixture of (Z,E) and (E,E)-isomers via a Peterson olefination with ethyl trimethylsilylaceta te. These isomers were separated and the major compound was elaborated to 54 by a straightforward sequence.

The synthesis of the acrylic acid side chain was accomplished in five steps from β-hydroxyketone 55 (Scheme V). Protection of the free hydroxyl group of the 55 as a mixed ketal followed by olefination with trimethyl phosphonoacetate (NaH, DME) and hydrolysis of the protecting group gave hydroxy ester 56 as a 5:1 mixture of E:Z olefin isomers in 65% overall yield. Saponification of the methyl ester (NaOH, H2O) gave the corresponding hydroxy acid in 75% yield. Treatment of this material with tert-butyldiphenylsilyl chloride followed by hydrolysis of the silyl ester (LiOH, DME:H2O) gave, after chromatographic separation of the isomeric acids, pure E-acid 57 in 81% yield.

Coupling of these two fragments to the trichothecene nucleus is outlined in Scheme VI. Selective acetylation of verrucarol 8 (Ac2O, py, CH2Cl2) gave the C(15) monoacetate 58. Acylation of 58 with diene acid 54 proved to be somewhat problematic. However, treatment of the C(4) sodium alcohololate (THF, 1% HMPT, -10°C) with the acylimidazolide 54b afforded diester 59 in 50% yield as a 1:1 mixture of (E,E) and (Z,E) isomers, which were separated by HPLC. Selective hydrolysis (LiOH, DME, H2O) of the C(15) acetate of 59 afforded the
corresponding C(4) monoester in 91% yield.

Acylation of the C(15) portion with acrylic acid 57 required somewhat different conditions than those used for the acylation of C(4)-OH. Thus, treatment of the C(15) sodium alcoholate in THF with the acylimidazolide 54b and tetra n-butylammonium iodide with 57b gave diester 60 in 60% yield. Desilylation with (nBu)$_4$NF in THF then afforded trichoverrinv B (29) in 60% yield. Exposure of trichoverrinv B to pyridinium dichromate in DMF for 13 days effected oxidative ring closure and gave verrucarin J (27) in 50% yield.
Still and coworkers have recently completed syntheses of roridin E (19) and baccharin B5 (21). These represent the first syntheses of members of the roridin/baccharinoid classes of trichotheccenes (see Scheme VII).¹⁹ The side chain synthon 68 was prepared in a straightforward manner from D-xylose (61) and 3-butyne-1-ol (63). Acylation of verrucarol with 68 proceeded in high yield at moderate conversion to afford monoester 69 which was subsequently acylated with dimethylphosphonoacetic acid to afford diester 70. Through a series of standard transformations the furanose moiety was converted to the desired unsaturated aldehyde 71, which served as the precursor for the macrocyclization step. Still had hoped that the intramolecular Horner-Emmons olefination reaction would afford only the desired (Z,E) diene 72a.¹⁹ The cyclization of 71, however, afforded both possible isomers 72a and 72b in a ratio of 1.5:1.⁴⁴ Macrocycle 72a was obtained in 45% yield from 71 after chromatographic removal of 72b. Treatment of 72a with potassium tert-butoxide effected stereoselective olefin conjugation and completed the synthesis of roridin E. This synthesis is also important in that it established the (R)-stereochemistry at C(6') and C(13'), which had not been known with certainty prior to this work.

Macrocycle 72a also served as an intermediate in the synthesis of baccharin B5 (see Scheme VIII). Thus, protection of the C(13') hydroxyl group as a tert-butyldimethylsilyl ether, followed by epoxidation of the C(9,10) and C(3',4') double bonds afforded bis epoxide 73. The stereoselectivity for this
Scheme VII

61 \( \xrightarrow{a,b,c,d} \) 62

63 \( \xrightarrow{e,f,g,h} \) OTBDMS 64 \( \xrightarrow{i} \) OTBDMS 65

66 \( \xrightarrow{j} \) 67 \( \xrightarrow{k,l} \) OTBDMS 68

69 \( \xrightarrow{m} \) 95% at 55% conversion

69 \( \xrightarrow{n} \) quanitative

71 \( \xrightarrow{o,p,q,r} \) 60-65%

71 \( \xrightarrow{s} \) 75%

72a (E,\( \varepsilon \))
72b (E,\( \varepsilon \))

72a, t \( \xrightarrow{72a, t} \) roridin E(19)
a) cyclopentanone, CuSO₄, cat. H₂SO₄; b) 0.2% HCl, THF, H₂O; c) p-TsCl, pyridine; d) LiAlH₄; e) TBDMS-Cl, imidazole, DMF; f) i. n-BuLi, ii. ClCO₂Et; g) (Me)₂CuLi, Et₂O; h) LiAlH₄; i) NCS, Me₂S; j) 65, NaH, THF, HMPT, cat. n-Bu₄NI; k) (nBu)₄F THF; l) Jones oxidation; m) 8, 68, DCC, 4-pyrrolidinopyridine; n) (MeO)₂POCH₂CO₂H, DCC, 4-pyrrolidinopyridine; o) 0.1 M p-TsOH, 1:3 H₂O:AcOH; p) NaIO₄, THF, H₂O; q) Et₃N, MeOH; r) (Ph)₃P=CHCHO, toluene, 25°, 40h; s) K₂CO₃, 18-crown-6, toluene, -20° to 0°C; t) K⁺OBu, isopropanol
Scheme VIII

a) TBDMSOTf, lutidine; b) mCPBA benzene, 25°C, 4h; c) K^t-OBu, isopropanol, -25°C, 2h; d) tBuOOH,VO(acac)₂, CH₂Cl₂, 25°C; e) Ph₃P, EtO₂CN=NCO₂Et, formic acid, benzene; f) (nBu)₄NF, THF.

epoxidation was greater than 15:1 at both positions. Treatment of 73 with potassium tert-butoxide afforded (E)-unsaturated ester 74 as the sole product. Transition metal-mediated epoxidation of the C(2',3') olefin afforded a single epoxide 75. This product proved to have the natural stereochemistry at
C(2') and C(3'), but incorrect stereochemistry at C(4'). Mitsunobu inversion of the C(4') hydroxyl group followed by fluoride ion promoted cleavage of the tert-butyldimethylsilyl group completed the synthesis of baccharin B5 (21). The absolute stereochemistry of baccharin B5 had previously been established by single crystal X-ray analysis, carried out by Kupchan and coworkers.23b All of the work described above concerning synthetic efforts toward the macrocyclic trichothecenes, had not yet been published when we began our research program in 1980. Thus, the retrosynthetic analysis presented below represents our initial dissection of this synthetic problem.

One characteristic feature of the roridins, as discussed earlier in this chapter, is the presence of the octadieneoate fragment attached to the C(4) position of the trichothecene nucleus. This observation suggested to us a simple retro-synthetic plan (Scheme IX) which would be applicable to the synthesis of all of the members of the roridin/baccharin class.

Scheme IX

\[ \text{Scheme IX} \]
Thus, selective acylation of C(15)-OH of verrucarol 8 with the requisite acid would afford monoester 76. Subsequent acylation of 76 with a differentially protected diene acid would yield the key intermediate 77. Macro cyclic etherification of this diester followed by removal of any protecting groups would afford the desired roridin/baccharin 78.

We envisaged that three major problems would need to be solved for successful execution of this plan. First, an efficient and enantioselective synthesis of diene acid 79 would be required. Our solution to this problem is discussed in Chapter 2.

Second, the problem of olefin isomerization during esterification reactions of α,β-unsaturated acids, which had plagued all previous synthetic efforts in this area, would have to be addressed. A solution to this problem was found during our synthesis of trichoverrol B (31), the details of which are discussed in Chapter 3.

Finally, development of a method for effecting the macro-etherification reaction of diester 77 would be necessary. We selected roridin D (17) as a target for the initial phase of this study (Scheme X). Efforts directed toward accomplishing
Scheme X

17 → 80

The synthesis of roridin D are discussed in Chapter 4.
CHAPTER II

SYNTHESIS OF THE OCTADIENOATE FRAGMENT
OF THE RORIDINS AND TRICHOVERRINS
Our objective was to develop a general synthetic strategy for the synthesis of the roridin and baccharin classes of macrocyclic epoxy trichothecenes. One potentially versatile method would involve diesters of the general structure 77, which would be cyclized to yield roridins of the general structure 78.

Scheme XI

An appealing aspect of this strategy is that 77 would be constructed by the sequential coupling of verrucarol (8) and the C(4)- and C(15)-ester units. Preparation of 77 would take advantage of the greater reactivity of the C(15)-hydroxyl group under a range of acylation conditions. 35, 36, 40 Thus, we envisaged that the requisite C(15)-acyl fragment could be coupled to verrucarol to give monoester 76 which would then be converted to 77 by coupling with the necessary dihydroxy-octadienoic acid unit. Access to any roridin, in principle, would be possible by selecting the appropriate C(15)-acyl fragment
We envisaged that these relatively simple C(15) acyl units could be constructed with little difficulty. On the other hand, the octadienoic acid fragment (e.g. 79) necessary for esterification to the C(4) hydroxyl is a much more challenging target. Clearly, a satisfactory synthesis of 79 must achieve high optical and diastereomeric purity of the three di-alkoxy unit as well as permit the introduction of the (E,Z)-diene in a highly stereocontrolled manner. Our research thus began with an examination of strategies for the preparation of the differentially protected dihydroxy octadienoic acid 79.

Base-promoted rearrangements of α,β-unsaturated δ-lactones have long been known to afford (Z,E)-diene acids stereospecifically. Eisner, for example, reported in 1953 that unsaturated lactone 81 gave diene acid 82. More recently, Corey et al

\[
\text{NaOH, MeOH} \rightarrow \text{CO}_2H
\]
have used this rearrangement to prepare the dienoic acid portion of the ansa bridge of riframycin S.\(^{48}\) An example of this rearrangement also appears as the last step of their bongkreic acid synthesis.\(^{49}\) On the basis of this precedent we believe that 83 would serve as a suitable precursor to 79. Although

\[
\begin{align*}
83 & \rightarrow 79 \\
\end{align*}
\]

the stereocenter at C(5) in 83 would appear to be inconsequential, the selection of 83 as a key intermediate required that we design a synthesis which would control three contiguous stereo-centers so as to avoid diastereomeric mixtures at earlier stages in the synthesis.

Our initial route toward the synthesis of 79 originated from xylose derivative 85 (Scheme XII). We imagined that

**Scheme XII**

\[
\begin{align*}
79 & \rightarrow 83 \rightarrow 84 \rightarrow 85 \\
\end{align*}
\]
epoxide $84$ could be converted to lactone $83$ by a three-step sequence. For example, alkylation of $84$ with LiC≡C-CO$_2$Me would afford acetylenic hydroxy ester $86$, catalytic hydrogenation, and lactonization of which could lead to unsaturated lactone $83$, (Scheme XIII).

**Scheme XIII**

\[ R_O \rightarrow R_O \rightarrow R_O \]

Preparation of the first key intermediate, epoxide $84$, is outlined in Scheme XIV. D-xylose was treated with catalytic FeCl$_3$ in acetone at reflux (30 min) to afford the 1,2,3,5-bisacetonide derivative in 96% yield.$^{50}$ Selective hydrolysis of the 3,5-acetonide$^{51}$ (0.2% HCl, H$_2$O) gave 1,2-isopropylidine D-xylose ($88,82\%$) which was selectively tosylated (pTsCl, pyridine, CH$_2$Cl$_2$)$^{51}$ and subsequently reduced with lithium aluminum hydride to afford the 5-deoxy sugar $89$ in 43% yield from $88$. Protection of the free hydroxyl group as either a benzyl ether ($85a$) (benzyl bromide, NaH, DME) or a pivaloyl ester ($85b$), (n-BuLi, pivaloyl chloride, THF) followed by hydrolysis of the 1,2 acetonide (50% aqueous trifluoroacetic acid)$^{52}$ cleanly afforded hemiacetals $90a,b$. Unfortunately, repeated attempts to reduce hemiacetal $90a$ to triol $91$ met with only limited success. Seven different reducing agents were tried under a variety of
conditions to affect this transformation. The best result was obtained with lithium triethylborohydride in diethylether at

**Scheme XIV**

25°C which afforded triol 91 in a maximum yield of 30%. Although 91 could be converted to 92 in 52% yield (MeSO₂Cl, pyridine, followed by NaH) the problems associated with the reduction of hemiacetal 90 precluded our further investigation of this sequence.

It was clear that modifications of the synthetic plan were called for at this stage. We found, in contrast to the difficulties encountered with the reduction of 90, that oxidative cleavage (NaIO₄, water; or NaIO₄, 3 mol% (n-Bu)₄NBr, CH₂Cl₂−H₂O) proceeded smoothly to afford aldehydes 93a,b in high yields. We were
encouraged by this result since we imagined that aldehyde 93 would condense with appropriately functionalized intermediates suitable for elaboration to the required diene acid.

Initial experiments focused on attempts to convert 93 b acetylenic ester 86. Unfortunately, treatment of 93 b with allenyl magnesium bromide, $^{54}$ BrZnCH$_2$C≡CCO$_2$Me or BrMg(CH$_2$)$_3$CH(OEt)$_2$ afforded complex mixtures of uncharacterized materials. In contrast, condensation of 93a with trimethylsilylethynyl-methylenetriphenylphosphorane $^{94}$ $^{55}$ afforded ene-yne 95 as a 4:1 mixture (E:Z) of double bond isomers in 55% yield (Scheme XV).

Scheme XV
Removal of the trimethylsilyl group (KF, DMSO, 65%) followed by protection of the free hydroxyl group as a methoxyethoxymethyl ether (MEMCl, (iPr)₂NEt, CH₂Cl₂, 86%) and carbomethoxylation of the lithium acetylide (nBuLi, Et₂O, -78°C; ClCO₂Me, 0°C) afforded ester 96 in 61% yield (along with 30% of recovered starting material). Unfortunately, at no point during this sequence were the olefin isomers separable by thin layer chromatography. Separation of the olefin isomers was finally accomplished by semi-preparative reverse-phase HPLC of 96.

We were optimistic that 96a would serve as a suitable precursor to 79 since Crombie had reported the selective catalytic hydrogenation of several α,β-unsaturated acetylenic esters to afford exclusively the corresponding (E,Z)-dienes. This methodology seemed ideally suited for our purposes.

\[ \begin{align*}
\text{97} & \xrightarrow{\text{H}_2, \text{Lindlar cat.}} 75\% \quad \text{98}
\end{align*} \]

Unfortunately, several attempts to reduce 96a selectively with hydrogen and Lindlar catalyst were unsuccessful. After the consumption of one equivalent of hydrogen the reaction mixture contained some desired product 99 along with unreacted starting material and products of over reduction. This situation was further complicated since the components of this mixture
coeluted in several solvent systems. Since it was apparent that this approach to the synthesis of diene acid 99 was flawed, this sequence was also abandoned.

A synthesis of an octadieneoate ester (e.g. 101) was finally developed from aldehyde 93b via two successive Wittig olefinations (Scheme XVI). Thus, treatment of 93b with formyl-

methyleneetriphenylphosphorane in dichloromethane afforded (E)-unsaturated aldehyde 100 in 65% yield as a 10:1 mixture of (E):(Z) isomers. Unfortunately, the subsequent olefination of aldehyde 100 with carbomethoxymethyleneetriphenylphosphorane in methanol did not proceed with comparable stereoselectivity. This
reaction afforded a mixture of esters 101 and 102 in a ratio of 35:65 (62%), respectively, as determined by 250 MHz \textsuperscript{1}H NMR analysis.

Attempts to improve the selectivity of the conversion of 100 to 101 were not initiated since Fraser-Reid reported a synthesis of diene ester 104 by an analogous route while our work was in progress.\textsuperscript{28} Best results (2:1 selectivity) were obtained when the olefination of 103 was performed by using the Peterson olefination conditions (Table VIII).\textsuperscript{28,40} Even so, this level

\textbf{Table VIII}

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Ratio (104:105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EtO)\textsubscript{2}PCH\textsubscript{2}CO\textsubscript{2}Me, NaH, Et\textsubscript{2}O, -78</td>
<td>0 : 100</td>
</tr>
<tr>
<td>Ph\textsubscript{3}P=CHCO\textsubscript{2}Me, CH\textsubscript{3}CN</td>
<td>20 : 80</td>
</tr>
<tr>
<td>Ph\textsubscript{3}P=CHCO\textsubscript{2}Me, MeOH, 25\textdegree</td>
<td>35 : 65</td>
</tr>
<tr>
<td>Me\textsubscript{3}SiCH\textsubscript{2}CO\textsubscript{2}Me, n-BuLi, -78\textdegree</td>
<td>50 : 50</td>
</tr>
<tr>
<td>Me\textsubscript{3}SiCH\textsubscript{2}CO\textsubscript{2}Et, n-BuLi, -78\textdegree</td>
<td>67 : 33</td>
</tr>
</tbody>
</table>
of selectivity fell far short of our expectations. We decided, therefore, to completely redesign our approach to diene acid 79 to ensure that the (Z,E)-diene unit would be constructed in a highly selective manner (c.f. 83 + 79).\textsuperscript{58}

Our decision to redesign our approach to 79 was also influenced by the publication of Jarvis and coworkers of the structures of the trichooverroids, a new class of non-macrocyclic trichothecene mono and diesters (Table VI, Chapter I).\textsuperscript{27} Interestingly, these compounds possess (S)-stereochemistry at C(6') whereas this center in most of the macrocyclic roridins and baccharins is (R). As with roridins and baccharinoids, the stereocenter at C(13') of the trichooverroids can be either (S), (A series), or (R), (B series).

These observations suggested that it would be appropriate to develop a stereochemically general synthesis of diene acids 79 and 111 since derivatives of all four isomers of 79/111 exist in nature. We envisaged that 79 and 111 could be synthesized from propargyl alcohol 106 as outlined in Scheme XVII.

\textbf{Scheme XVII}

\begin{center}
\begin{tikzpicture}
  \node (79) at (0,0) {\includegraphics{79.png}};
  \node (107) at (2,0) {\includegraphics{107.png}};
  \node (106) at (4,0) {\includegraphics{106.png}};

  \node (108) at (1,1) {\includegraphics{108.png}};
  \node (109) at (1,-1) {\includegraphics{109.png}};

  \node (110) at (2,1) {\includegraphics{110.png}};
  \node (111) at (2,-1) {\includegraphics{111.png}};

  \draw[->] (79) -- (107);
  \draw[->] (107) -- (106);
  \draw[->] (79) -- (108);
  \draw[->] (108) -- (107);
  \draw[->] (107) -- (106);
  \draw[->] (110) -- (111);
  \draw[->] (111) -- (110);

end{tikzpicture}
\end{center}
Thus, reduction of 106 to either the (E)- or (Z)-allylic alcohol followed by stereoselective epoxidation would yield 107 and 109. Oxidative cleavage of the vinyl group to the carboxylic acid followed by lactonization and subsequent enolate oxidation would afford the required unsaturated lactones 108 and 110. Finally, base-promoted rearrangement of these lactones would afford the desired acids 79 and 111.

Our initial plan called for optically active 106 to be synthesized by an enantioselective reduction of the corresponding propargyl ketone 113, which was synthesized as outlined in Scheme XVIII. Thus, alkylation of the dianion of 3-butyne-2-ol

![Scheme XVIII](image)

112 with 1-bromo-4-pentene (i) 2.2 equiv. n-BuLi, 3 equiv. HMPT, THF, 0°C, 1h, (ii) 1-bromo-4-pentene, THF, 25°C, 2h) afforded racemic 106 in 65% yield. Oxidation of 106 with PCC then afforded propargyl ketone 113 in 92% yield.

The results of reduction of 113 with two chiral hydride reagents reagents are summarized in Table IX.
Table IX

\[
\begin{align*}
\text{Reagent} & \quad \text{Chemical Yield} & \quad \text{Optical Purity}^a \\
\text{LiAlH}_4, \text{Chiralald} & \quad 70-76\% & \quad 64-72\% \text{ ee} \\
\text{Et}_2\text{O} & \quad & \\
\text{LiAlH}_4, (R)-2,2'-\text{binapthol,} & \quad 50\% & \quad 76\% \text{ ee} \\
\text{EtOH, THF} & \quad & \\
\end{align*}
\]

(a) Optical purity of 106 was determined by analysis of the 250 MHz \(^1\text{H}\) NMR spectrum of the Mosher ester derivative.\(^{61}\)

The absolute configuration of 106 was determined to be (R) by degradation to the lactic acid derivative (-)-114. The absolute configuration of the (S)-(+) enantiomer of 114 is known.\(^{62}\)

Unfortunately, however, the enantioselective reduction of 113
with either of these reagents afforded alcohol (R)-106 in only moderate chemical and optical yields. Of the reagents currently available for enantioselective reduction of methyl propargyl ketones, Noyori's BINAL-H reagent is reported to give superior results.60,63 Since our results with this reagent were modest at best we did not pursue a lengthy investigation of other optically active hydride reagents.

Although the optical purity of 106 was lower than we had hoped for originally, we decided to demonstrate the feasibility of our proposed sequence to diene acid 121 before exploring alternative methods for the synthesis of optically pure 106 (see Scheme XIX).64 A satisfactory solution to this problem will be discussed in Chapter IV.

Scheme XIX

\[
\text{Lindlar, 96%}
\]

106 → 115 → 116

1. MEM-Cl, (iPr)_2NET
2. RuCl_3, NaIO_4, 71%

\[
\text{CSA, CHCl}_2, 97%
\]

118 → 119 → 120

1. LDA, THF
2. PhSeBr
3. H_2O_2, 52%

\[
\text{K^+ODu, THF, 0°, 59%}
\]

121
Lindlar hydrogenation of 106 afforded (Z)-allylic alcohol 115 in 96% yield. Epoxidation of 115 was accomplished by using tert-butylhydroperoxide (TBHP), and titanium tetraisopropoxide in dichloromethane to give epoxy alcohol 116 in 81% yield with 95% threo selectivity. 59b The free hydroxyl group of 116 was protected as a methoxyethoxymethyl ether 56 (MEM-Cl, (iPr)2NET, CH2Cl2, 82%) and the vinyl group was cleaved oxidatively (catalytic RuCl3, NaIO4, CH3CN-CCl4-H2O, 0°C) 65 to give crude 117 in 87% yield which contained approximately 10% of hydroxylactone 118. Cyclization of the remaining acid by treatment with catalytic camphorsulfonic acid gave hydroxy lactone 118 in 69% yield from 116. Protection of the free hydroxyl group of 118 as a tert-butyldimethylsilyl ether (TBDMS) required forcing conditions (TBDMS-Cl, DMF, 50°C, 5-7 days) but nonetheless proceeded in high yield (93%). Oxidation of the lithium enolate of 119 was accomplished by using the procedure of Reich and Renga 66 ((i) LDA, THF, -78°; (ii) PhSeBr, -78°; (iii) H2O2, CH2Cl2, 25°) to afford enone 120 in 50-60% overall yield. Unfortunately, however, this procedure was not entirely reproducible. The crucial rearrangement of 120, however, proceeded smoothly to afford isomerically pure diene acid 121 in 59% yield after silica gel chromatography.

The development of an efficient synthesis of an optically pure erythro-dihydroxy (E,Z) octadienoic acid derivative (c.f. 54) suitable for use in a synthesis of the trichoverrins (B series,
Table VI) centered around erythro epoxyalcohol 123 as a key intermediate. This substance was prepared from racemic 106 which was reduced to (E)-allylic alcohol 122 by use of LiAlH₄ in THF (96%). Epoxidation of 122 by the kinetic resolution protocol developed by Sharpless and co-workers⁵⁹b (-)diisopropyltartrate (DIPT), titanium tetraisopropoxide, 0.4 equiv. of tert-butylhydroperoxide (TBHP), -20°C, CH₂Cl₂, 20h afforded erythro-epoxyalcohol 123 in 33% yield along with 34% of kinetically resolved (-)-122. The optical purity of 123 and (-)-122 was determined to be 95% and 90%, respectively by the Mosher ester technique.⁶¹ It should be noted parenthetically that an analogous kinetic resolution in the roridin series (c.f., kinetic
resolution-enantioselective epoxidation of 115) was not pursued since (Z)-allylic alcohols are not satisfactory substrates for this procedure. 67,59b

Epoxyalcohol 123 was successfully elaborated to the trichoverroid diene systems 54 and 128 by the sequences outlined in Scheme XX. The preparation of intermediate 128 is completely analogous to the synthesis of 121 in Scheme XIX and requires no further comment.

Scheme XX

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

cat. CSA

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%

1. MEM-Cl, (iPr)$_2$NEt
2. RuCl$_3$, NaI$_2$
CH$_3$OH-H$_2$O-CCl$_4$

77%

80%
A more direct and highly efficient synthesis of the trichoerrin diene system 135 is outlined in Scheme XXI. This sequence is discussed in detail since 135 ultimately proved to be a useful acylating agent in our synthesis of trichoderrom B (31) discussed in Chapter 3.

Treatment of 95% optically pure epoxyalcohol 123 with tert-butyldimethylsilyl chloride and imidazole in DMF followed by oxidative cleavage of the vinyl group (cat. RuCl₃, NaIO₄, CCl₄-CH₃CN-H₂O) afforded epoxyacid 130 in 94% yield. Lactonization of 130 was then accomplished in 91% yield by treatment with catalytic p-toluenesulfonic acid in CH₂Cl₂. We had hoped

Scheme XXI
originally to protect 131 as the bis-TBDMS ether 136, so as to converge eventually with diene acid 54 (see Scheme XX). Unfortunately, we were frustrated in numerous attempts to accomplish this conversion even under very forcing conditions (TBDMS-Cl, 4-DMAP, DMF, 90°, 5 d.). Evidently, the hydroxyl

\[
\begin{align*}
\text{TBDMSSO} & & \text{TBDMSSO} \\
\text{HO} & & \text{HO} \\
131 & & 136
\end{align*}
\]

group of 131 is much more hindered than that in 125 (Scheme XVI). Interestingly, treatment of 131 with tert-butyldimethylsilyl triflate\(^{68}\) rapidly afforded ortho ester 137 in good yield.

\[
\begin{align*}
\text{TBDMSSO} & & \text{TBDMSSO} \\
\text{HO} & & \text{HO} \\
131 & & 137
\end{align*}
\]

In contrast, 131 underwent rapid trimethylsilylation with bis-hexamethyldisilizane and trimethylsilyl chloride in pyridine to give lactone 132 (93%), which was successfully elaborated to 135 as discussed below.

As mentioned previously we had encountered problems with the reproducibility of the α-phenylselenelation of δ-lactones
(c.f. Schemes XIX and XX).\textsuperscript{66} Given our past experiences with transformations of this type we fully expected to expend a great deal of effort optimizing the oxidation of \textbf{132} to \textbf{134}. Indeed, poor results realized in initial attempts to trap the enolate of \textbf{132} with PhSeBr or N-(phenylseleno)phthalimide\textsuperscript{69} served to substantiate our concerns. However, Dubs and coworkers had reported that lactone enolates could be monosulfenylated in high yield with 2,2'-dipyridyl disulfide (\textbf{139}).\textsuperscript{70} We were delighted to find that this reagent worked equally well with \textbf{132}, reproducibly affording monosulfenylated product \textbf{133} in high yield. Oxidation of \textbf{133} with mCPBA afforded the corresponding sulfoxide which, when heated in toluene at 110°C underwent elimination to give \textbf{134} in 75% yield from \textbf{132}.

Treatment of unsaturated lactone \textbf{134} with potassium tert-butoxide in THF followed by a mild acidic workup afforded a mixture of monosilylacids \textbf{141a} and \textbf{141b}. Thus, the trimethylsilyl group which had easily survived the three preceding transformations was extremely sensitive to acidic conditions after rearrangement of \textbf{134}. This problem was circumvented by quenching the intermediate potassium carboxylate with pivaloyl
chloride to afford the isolable mixed anhydride 135 in 94% overall yield. It is critical to note that the latter two step sequence never becomes acidic which ensures the stability of the trimethylsilyl ether. The overall yield of 135 from 123 was 56% (see Scheme XXI).

The stage was now set for initiating studies on the acylation of the trichothecene nucleus with diene systems such as 54 and 135. As will be discussed in the next chapter, mixed anhydride 135 proved to be a key intermediate in our synthesis of trichoverrol B.
CHAPTER III
SYNTHESIS OF TRICHOVERROL B
Having successfully developed methodology for the synthesis of the dihydroxyoctadienoate fragment of the trichoverrins and roridins, we turned our attention to the esterification of these acids to C(4)-OH of the trichothecene nucleus. We decided to concentrate initially on the synthesis of trichoverrol B since the requisite acid derivatives 54 and 135 were in hand in optically pure form. Moreover, we imagined that the methodology developed in connection with this synthesis would be applicable to our projected approach to the roridins and baccharinoids.

When we began our synthetic studies in 1980 none of the natural verrucarin or roridins had been synthesized. Indeed, very few acylations of the C(4)-hydroxyl group of verrucarol derivatives had been reported. Several cases, however, had been published by Tamm and coworkers in 1978 in connection with their synthesis of tetrahydroverrucarin J (142). For example, acetylation of verrucarol (8) with acetyl chloride
and pyridine afforded C(4)-monoacetate 143 in 38% yield (Scheme XXII). Similarly, acylation of verrucarol with 2,2,2-

Scheme XXII

trichloroethyl chloroformate in the presence of pyridine afforded carbonate 144 in excellent yield (95%). Finally, acylation of 8 with the acylimidazolide 146 in the presence of DBU provided C(4) monoester 145 in 35% yield.
These results implied that it should be possible to select-
ively esterify C(4)-OH of verrucarol with 54 or 135 under
appropriate conditions. Data published after 1980, however,
indicated that C(15)-OH is actually the more reactive of the
two hydroxyl groups under a range of acylation conditions.\textsuperscript{35,36}
For example, Fraser-Reid observed that verrucarol could be acyl-
ated with acetic anhydride and pyridine to afford the C(15)
monoacetate 58 in 70% yield.\textsuperscript{36} Similarly, Still and coworkers

\[ \text{Diagram of verrucarol with acetate groups} \]

noted in connection with their synthesis of verrucarin A that
DCC mediated esterification reactions were highly selective
for C(15)-OH.\textsuperscript{36} This method was used by Still to acylate
 verrucarol 8 with 35 to afford C(15) monoester 41 in 95% yield.
Analogous DCC-mediated coupling reactions were subsequently

\[ \text{Chemical reaction diagram} \]
used by Tamm\textsuperscript{39} and Rous\textsuperscript{41b} and Blizzard in their synthesis of verrucarins A and J, respectively.

A problem which has plagued all syntheses of the verrucarins is olefin isomerization during the coupling of $\alpha, \beta$-unsaturated acids to the trichothecene nucleus. Still, for example, observed significant isomerization to (E,E)-muconate derivatives during their coupling of 40\textsuperscript{b} to 41. This isomerization was avoided, however, by coupling 41 and 40 with DCC in the presence of 4-DMAP.\textsuperscript{36} In contrast, however, Tamm\textsuperscript{39} and Rous\textsuperscript{41} observed substantial isomerization in analogous experiments. For example, when 147 was treated with 40, DCC, and 4-pyrrolidinopyridine, Rous and Blizzard observed mostly (E,E)-diester 148.\textsuperscript{41c} Rous and Blizzard attempted to overcome this problem by performing the muconate esterification
intramolecularly, on the assumption that olefin isomers of the natural product would be too strained to be easily produced.\textsuperscript{41c} Unfortunately, cyclization of the (E,Z)- and (E,E)-seco acids 149 and 152 occurs readily to give a mixture of macrocycles.

A final result which had direct bearing on our work was published by Fraser-Reid and Jarvis shortly before our investigations of esterification methodology was initiated.\textsuperscript{40} These
workers reported that acylation of the sodium alkoxide of 58 with acylimidazolide 54b afforded a 1:1 mixture of (Z,E)- and (E,E)-diene ester products. The (Z,E)-isomer served as a key intermediate in the synthesis of trichovertin B and verrucarvin J. 40

It was clear from this analysis of the literature that the development of efficient syntheses of the macrocyclic epoxy-trichothecenes must focus on this olefin isomerization problem. Our work therefore began with the preparation of C(15)-monoo ester 155 which would serve as the starting material for our trichovertin B synthesis. The γ-[(tert-butyldimethylsilyl)oxy]-butyryl residue is a convenient protecting group for the C(15)-OH of the trichotheccene nucleus and is easily removed by treatment with (nBu)4F in THF. This protecting group was developed as an alternative to the levulinic acid protecting group by Blizzard in these laboratories.41a,b We prepared 155 in 55% yield by acylation of verrucarol with mixed anhydride 154, which was generated in situ from acid 153 and pivaloyl chloride.
Alternatively, Blizzard prepared 155 in 70% yield by acylation of verrucarol with 154, DCC and catalytic 4-DMAP in CH$_2$Cl$_2$.$^{41a,b}$

Our initial attempts to acylate 155 or other hindered alcohols with acid 54 gave disappointing results. For example,

treatment of C(15) monoprotected trichothecone 155, or other hindered alcohols, with acid 54 in the presence of a variety of dehydrating agents (N,N-bis(2-oxo-2-oxazolidinyl)phosphorodiamidic chloride, (BOP-Cl), Et$_3$N, menthol; N-methyl-2-chloropyridinium iodide, CsF, 155; DCC, 4PP, isopropanol; trifluoroacetic anhydride, 155; mesitylenesulfonyl chloride, pyridine, 155) afforded none of the desired product. It was noteworthy, however, that symmetrical anhydride 156 could be isolated in 70-80% yield from the Mukaiyama salt$^{71}$ and BOP-Cl$^{72}$ experiments. This result was encouraging since it established that 54 could
be activated without olefin isomerization.

Treatment of trichothecene 155 with anhydride 156 and 4-DMAP as an acylation catalyst afforded diester 157 as a 2:1 mixture of (Z,E)- and (E,E)-diene isomers in 25% yield. We were encouraged by this result and therefore sought to prepare mixed anhydrides for the obvious practical consideration of conserving the precious chiral diene acid 54. We found mixed anhydride 158 was easily prepared from 54, pivaloyl chloride and Et$_3$N.
Acylation of 155 with either 156 or 158 in the presence of 4-DMAP as an acylation catalyst afforded diester product (25-32 %) containing anywhere from a 1:1 mixture of (Z,E)- and (E,E)-diene isomers to one case in which the (E,E)-isomer was obtained exclusively. It is important to note that these preliminary experiments were carried out with an undetermined amount of acylation catalyst. Later experiments, summarized in Chapter 4, in which the amount of acylation catalyst was controlled gave reproducible results. 73

We suspected that the cause of these olefin isomerizations was reversible Michael addition of the nucleophilic acylation catalyst to the activated acylating agent, and reasoned that this problem could be avoided if such nucleophilic species were omitted from the reaction medium. Thus, treatment of 155 with NaH in DME followed by addition of mixed anhydride 158 (generated in situ) afforded isomerically pure (Z,E)-diester 157a in 50% yield. Subsequent acylations carried out with mixed
anhydride 135 afforded comparable results (50-55% yield of 157b).

Completion of the synthesis of trichoverrol B (31) was accomplished by removal of the three protecting groups via.
treatment of 157 with tetra n-butylammonium fluoride (5 equiv.

\[ \text{RO} \xrightarrow{(nBu)_4NF, THF} \text{31} \]

157  a: R = TBDMS  
 b: R = TMS

in THF, 20°C). This reaction afforded synthetic trichoverrol B identical in all respects to a sample of natural trichoverrol B supplied by Professor Bruce B. Jarvis. The 250 MHz ¹H NMR spectra of synthetic and natural trichoverrol B are reproduced in Figures 2-5.
Figure 2. 250 MHz $^1$H NMR spectrum of synthetic trichoverrol B (31)
Figure 3. 250 MHz $^1$H NMR spectrum of natural trichoverrol B (31)
Figure 4. 250 MHz $^1$H NMR spectrum of synthetic trichoverrol B (31) after $D_2O$ exchange
Figure 5. 250 MHz $^1$H NMR spectrum of natural trichoverrol B (31) after D$_2$O exchange
CHAPTER IV

STUDIES TOWARD THE SYNTHESIS
OF RORIDIN D
With the completion of the synthesis of trichoeverrol B described in the preceding chapter, we were ready to begin our investigations into the synthesis of the roridins. We selected roridin D (17) as the target of our initial studies since this compound possesses many of the same structural features as the baccharins, the ultimate goal of our work in this area. As was briefly outlined in Chapter 2, our general strategy called for trichothecene diester 159 to serve as the penultimate synthetic goal (Scheme XXIII). Needed for a synthesis of this subtarget was a source of optically pure threo-dialkxydiene acid 161, so we immediately turned to this as yet unsolved problem.

Our original synthesis of threo-diene acid 121, (Scheme XIX, Chapter 2) suffered from the fact that 121 was produced in only 65–74% optical purity, which we regarded as being too low
to be of use on the synthesis of roridin D (17). Two solutions to this problem were investigated. The first sequence originated from erythro-epoxyalcohol 123 (>95% ee), the enantiomer of which was an intermediate in our synthesis of trichoverrol B. Subjection of 123 to a Mitsunobu inversion sequence cleanly afforded epoxyalcohol 162 with the desired threeo relationship between C(6') and C(13'). (Scheme XXIV)

**Scheme XXIV**

Before we could continue with our synthesis of 161, however, one additional modification had to be made. We felt that conditions required for eventual removal of the MEM ether used as a protecting group for C(13')-OH of 121 would be too vigorous for the trichothecene nucleus to survive. One protecting group which seemed to fit our requirements was the
2-(trimethylsilyl)ethoxymethyl (SEM) ether.\textsuperscript{77}

Scheme XXV outlines our initial synthesis of mixed anhydride \textsuperscript{168}, an activated form of diene acid \textsuperscript{161}. Thus,

\textbf{Scheme XXV}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {1. SEM-Cl, (iPr)\textsubscript{2}NEt};
  \node at (1.5,0) {2. RuCl\textsubscript{3}, NaIO\textsubscript{4}};
  \node at (1.5,0.5) {CH\textsubscript{3}CN-CCl\textsubscript{4}-H\textsubscript{2}O, 71\%};
  \node at (3,0) {pTsCH, CH\textsubscript{2}Cl\textsubscript{2}};
  \node at (5,0) {164};
  \node at (0,-1) {TES-Cl, Py, 0°};
  \node at (2,-1) {SEM};
  \node at (1,-1) {O};
  \node at (0,-2) {OH};
  \node at (0,-3) {TESO};
  \node at (1.5,-3) {SEM};
  \node at (3,-3) {COOH};
  \node at (4.5,-3) {95\%};
  \node at (6,-3) {SEM};
  \node at (7,-3) {O};
  \node at (6,-4) {CH\textsubscript{3}CN-CCl\textsubscript{4}-H\textsubscript{2}O, 71\%};
  \node at (8,-3) {SEM};
  \node at (9,-3) {O};
  \node at (10,-3) {HO};
  \node at (11,-3) {164};
  \node at (0.5,-4) {SEM};
  \node at (0.5,-5) {O};
  \node at (1.5,-5) {C(CH\textsubscript{3})\textsubscript{3}};
  \node at (3,-5) {168};
  \node at (0.5,-6) {SEM};
  \node at (0.5,-7) {O};
  \node at (1,-7) {TESO};
  \node at (2,-7) {166};
  \node at (0.5,-8) {SEM};
  \node at (0.5,-9) {O};
  \node at (1,-9) {TESO};
  \node at (2,-9) {167};
  \node at (1.5,-10) {SEM};
  \node at (1.5,-11) {O};
  \node at (3,-11) {TESO};
  \node at (4,-11) {165};
  \node at (0,-12) {SEM};
  \node at (0,-13) {O};
  \node at (1,-13) {TESO};
  \node at (2,-13) {165};
\end{tikzpicture}
\end{center}

epoxyalcohol \textsuperscript{162} was protected as the corresponding SEM ether (SEM-Cl, (iPr)\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, 95\%) and the vinyl group oxidatively cleaved (cat. RuCl\textsubscript{3}, NaIO\textsubscript{4}, CCl\textsubscript{4}-CH\textsubscript{3}CN-H\textsubscript{2}O, 75\%)\textsuperscript{65} to give carboxylic acid \textsuperscript{163}. Lactonization of this intermediate was effected by treatment with catalytic p-toluenesulfonic acid (95\%). Masking of the free hydroxyl group of \textsuperscript{164} as a triethylsilyl ether proceeded smoothly to afford differentially protected lactone \textsuperscript{165} in 95\% yield.\textsuperscript{78} At this point we began to encounter
considerable difficulty in accomplishing the α-sulfenylation of lactone 165. This was completely unexpected since we had successfully employed an analogous procedure in the oxidation of 132 to 134 in our work on the synthesis of trichoverrol B (c.f. Scheme XXI). Thus, treatment of lactone 165 with 2 equiv. of LDA in THF at -78°C for 1h followed by addition of 2,2'-dipyridyldisulfide (DPDS) afforded 20-30% of the desired α-sulfenyl lactone 166 along with 70-89% of recovered 165. Addition of 4 equiv. of LDA and 4 equiv. of DPDS gave similar results.

A closer investigation of this reaction sequence revealed that the enolate of 165 was not forming completely under these conditions. Thus, treatment of lactone 165 with 2 equiv. of LDA at -78°C for 1h followed by quenching with 2 equiv. of D₂O afforded 165 with only ca. 20% deuterium incorporation. This result was surprising since the lithium enolate of lactone 132 is generated in high yield under these conditions. On the other hand, if the mixture of 165 and LDA was allowed to warm to -20°C for 1h before being recooled to -78°C still afforded only ca. 30% of 166 along with 70% of unreacted 165, as determined by ¹H NMR analysis of the crude reaction mixture. It is interesting to note that the sulfenylation step appeared to be complete within 20 min. at -78°C, since longer reaction times at this temperature did not significantly increase the amount of monosulfenylated product. Moreover, addition of fresh base (up to 6 equiv. of LDA) or additional DPDS did not increase the percentage of 166 produced, since the LDA appeared
to react instead with the DPDS. Other side reactions intervened if the reaction mixture was warmed to -20°C. Thus, under these conditions bissulfenylated 169 was observed at the expense of 164 and 165.

A number of other reagents and reaction conditions were explored in our attempts to obtain α-functionalized lactones for the purpose of generating α,β-unsaturated lactone 167 (see Table X). As can be seen from these results, very little success was realized in our repeated attempts to functionalize 165. Interesting, however, is the observation that the sodium and potassium enolates of 165 afforded bissulfenylated lactone 169 directly at -78°C with little or no trace of monc sulfenylated 166. A satisfactory solution to this problem has not yet been found.

In spite of these results, we were able to produce small amounts of unsaturated lactone 167 from 166 as outlined in Scheme XXV. In practice, 165 was treated with 2 equiv. of LDA at -78°C and warmed to -20°C for 1h before being recooled to -78°C and quenched with 2.2 equiv. of 2,2'-dipyridyl-disulfide, (DPDS). This crude reaction mixture was oxidized (mCPBA, CH₂Cl₂, 0°) and the intermediate sulfoxide (32% yield)
### Table X

**α-Functionalization Attempts**

<table>
<thead>
<tr>
<th>Base</th>
<th>Electrophile</th>
<th>Conditions$^a$</th>
<th>Products$^b$ &amp; $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA (2 equiv.)</td>
<td>DPDS (2 equiv.)</td>
<td>$-78^\circ, 2h$</td>
<td>60 30 - -</td>
</tr>
<tr>
<td>LDA (2 equiv.)</td>
<td>DPDS (2 equiv.)</td>
<td>$-78^\circ, 2h$</td>
<td>60 30 - -</td>
</tr>
<tr>
<td>HMPT (2 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDA (2 equiv.)</td>
<td>DPDS (2 equiv.)</td>
<td>$-20^\circ, 0.5h$</td>
<td>50 - - 50</td>
</tr>
<tr>
<td>LDA (1.1 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-78^\circ, 1h$</td>
<td>66 33 - -</td>
</tr>
<tr>
<td>(1.2 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDA (1.1 equiv.)</td>
<td></td>
<td>$-78^\circ, 2h$</td>
<td>&gt;90 trace$^c$ - -</td>
</tr>
<tr>
<td>(1.1 equiv.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KDA (1.3 equiv.)$^{80}$</td>
<td>DPDS (1.3 equiv.)</td>
<td>$-78^\circ, 1h$</td>
<td>30 - - 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$-20^\circ, 40min$</td>
<td></td>
</tr>
<tr>
<td>KH (1.2 equiv.)</td>
<td>DPDS (1.2 equiv.)</td>
<td>$-78^\circ, 1h$</td>
<td>50 - - 50</td>
</tr>
<tr>
<td>NaN (TMS)$_2$ (1.5 equiv.)$^{81}$</td>
<td>DPDS (1.5 equiv.)</td>
<td>$-78^\circ, 20min$</td>
<td>mostly 169</td>
</tr>
<tr>
<td>LDA (1.2 equiv.)</td>
<td>I$_2$ (1.2 equiv.)</td>
<td>$-78^\circ, 1h$</td>
<td>mixture of mono and diiodolactones</td>
</tr>
</tbody>
</table>

(a) Unless otherwise stated, all enolates were generated at $-20^\circ C$ for 1h, then recooled to $-78^\circ$ and quenched with the corresponding electrophile.

(b) Ratios were determined by $^1$H NMR (250 MHz).

(c) Product ratio determined after oxidation of the crude reaction mixture.
was separated by chromatography from unreacted 165 (47% yield) which could be recycled. Thermal sulfoxide elimination (toluene, 110°C) proceeded smoothly to afford 167 in 26% yield from 165 (48% if corrected for recovered 165). Exposure of 167 to KOtBu in THF at 0°C followed by quenching with pivaloyl chloride afforded mixed anhydride 168 in high yield (>95%).

A second approach to 168, which proved to be superior to that described above, was based on our original synthesis of 121 described in Chapter 2 (c.f. Scheme XIX, pg. 56). Preparation of 168 by modification of the original sequence required that we have access to optically pure propargyl alcohol 106. Given our previous experience with attempts to prepare optically pure 106 by enantioselective reduction of 113 (see Table IX, Chapter 2), we decided to resolve racemic 106 according to the procedure of Pirkle and coworkers.82

Treatment of 106 with (R)-(-)-α-napthylethyl isocyanate (98% ee)82b afforded a mixture of diastereomeric carbamates 171 and 172 in 76% yield82c (Scheme XXVI). These carbamates were separable by repeated flash column chromatography83 to afford 171 and 172 in 35% and 28% yields (based on racemic 106), respectively. The urethane functions of both diastereomers were removed by treatment with trichlorosilane (Et2O, 25°, 12h) afforded propargyl alcohols (S)-106 and (R)-106 in high optical purity (95%, Mosher ester analysis).61 Inversion of (S)-106 via the Mitsunobu protocol (diethyl azodicarboxylate (DEAD), Ph3P, p-nitrobenzoic acid (PNBA))38 followed by ester hydrolysis afforded additional (R)-106 (>95% ee) in 70% yield from (S)-106.
The overall yield of (R)-106 from racemic 106 was 49%.

With optically pure (R)-106 in hand we were in a position to proceed with the synthesis of 168 (Scheme XXVII). Thus, selective catalytic semihydrogenation of 106 followed by threeo-selective epoxidation of the resulting (Z)-allylic alcohol afforded epoxyalcohol 116 in 70% overall yield from 106.\(^{59b}\) The free hydroxyl group was protected as a 2-(trimethylsilylethoxy)methyl ether (SEM-Cl, (iPr)$_2$NEt, CH$_2$Cl$_2$, 5h)\(^{77}\) and the vinyl group cleaved oxidatively (cat. RuCl$_3$, NaIO$_4$, CCl$_4$-CH$_3$CN-H$_2$O)\(^{65}\) to give epoxycacid 173 (contaminated with approximately 5% of the hydroxy lactone 174) in 95% yield.
Scheme XXVII

from 116. Lactonization of the remaining epoxy acid (0.03 equiv. p-TsOH, CH₂Cl₂, 25°, 2h) followed by masking of the free hydroxyl group as a triethylysilyl ether afforded the differentially protected lactone 175 in 75% yield from carboxylic acid 173. Treatment of 175 with 2 equiv. of LDA at -78° and warming to -20°C for 1h followed by quenching at -78° with 2 equiv. of DPDS afforded a mixture containing approximately 80% of the desired monosulfide 176 and 20% of unreacted 175. This result, in contrast to our work with epimeric lactone 165 (vide supra) proved to be very reproducible. It is not obvious to us why 175 is well-behaved under these conditions whereas 165 is not. Oxidation of 176 with MCPBA (CH₂Cl₂, °, 1h)
followed by silica gel chromatography afforded 10\% of recovered 175 and 68\% of the desired sulfoxide as a diastereomeric mixture. Thermolysis (toluene, 110°C, 2h) of the diastereomeric sulfoxides afforded unsaturated lactone 177 in 80\% yield (55\% from 175, not corrected for recovered 175). Treatment of 177 with potassium tert-butoxide and quenching the intermediate carboxylate salt with pivaloyl chloride then gave mixed anhydride 168 in 92-98\% yield.

Having completed an efficient synthesis of 168 we turned our attention toward the preparation of the C(15)-acyl fragment 178 needed for our synthesis of roridin D.

**Scheme XXVIII**

The synthesis of 178 was straightforward and was first accomplished in these laboratories by Blizzard41a (Scheme XXVIII). Thus, ester 180 was prepared from 179 in 45\% yield by using Negishi's procedure ((i) Al(Me)$_3$, (3 equiv.); Zr (Cp)$_2$Cl$_2$, (0.1 equiv.); CH$_2$CH$_2$, 25°, 15h; ii) ClCO$_2$Me, (1.1 equiv.); 25°, 2h).\(^8\) Protection of the primary hydroxyl group as a tert-butyldimethylsilyl ether (TBDMS-Cl, imidazole, DMF, 25°, 5h) followed by reduction of the methyl ester with diisobutylaluminum hydride (DIBAL-H, Et$_2$O) afforded 181 in 92\% yield. Enantio-selective epoxidation of 181 ((-)-diethyltartrate, (DET);
tert-butylhydroperoxide, (TBHP); Ti(iPrO)₄, CH₂Cl₂, -20°C, 18h) smoothly afforded epoxyalcohol 185 in 81% yield (95% ee; Mosher ester analysis). Finally, oxidation of epoxyalcohol 182 to epoxyacid 178 was accomplished by using the Sharpless catalytic ruthenium tetroxide procedure (cat. RuCl₃, NaIO₄, CCl₄-CH₃CN-H₂O). Acid 178, obtained in 80-90% yield directly from this reaction, was used without further purification since glycidic acid 178 was not stable to silica gel chromatography.

With subunits 168 and 178 in hand, we were now ready to proceed with our plan for the synthesis of roridin D (c.f., Scheme XXIII). Selective acylation of the C(15)-hydroxyl group with 178 of verrucarol was accomplished by using a mixed anhydride procedure. Thus, treatment of 178 with pivaloyl chloride and Et₃N in CH₂Cl₂ smoothly afforded 183. Unlike the mixed anhydrides previously prepared from α,β-unsaturated acids and pivaloyl chloride, 183 proved to be too reactive to be isolated. Therefore 183 was prepared in situ and treated immediately with verrucarol₃⁶ and 4-pyrrolidinopyridine (4-PB) as an acylation catalyst, which afforded C(15)-mono
ester 184 in 59% yield after silica gel chromatography.\textsuperscript{86} In addition, verrucarol (20%), C(4)-monoester 185 (6%) and diester 186 (7%) were also obtained. It is interesting to note that the 5:1 selectivity for C(15)-OH under these conditions is somewhat better than the 3:1 selectivity realized by Blizzard in a closely related case:\textsuperscript{41a}

Attempts to esterify 184 with mixed anhydride 168 by using the methodology developed in our synthesis of trichoverrol B proved to be more complicated than originally anticipated owing to the sensitivity of the glycidic ester unit of 184 toward nucleophilic attack.\textsuperscript{87} Thus, treatment of the sodium alkoxide of 184 at -20° with 168 in a 1:1 DME-THF solvent system with warming to 0° for 1h afforded a mixture of products consisting of 10% of the desired diester 189, 20% of the C(4)-monoester 190, 20% of recovered 184 and verrucarol which was not isolated.
Reacylation of 190 with 183 and 4-PP afforded 189 in good yield (70%).

The significant amount of deacylation observed in the preparation of 189 was apparently the result of sodium hydroxide in the reaction mixture. Since deacylation occurred even under rigorously anhydrous conditions, we reasoned that the source of sodium hydroxide contamination was the sodium hydride itself.88

In order to circumvent this problem we investigated the use of other bases which could be purified, or ones which we were confident would have little hydroxide present.108 One base which appeared particularly attractive was sodium bis(tri-methylsilyl)amide, 81 which was purified by sublimation immediately prior to use. Thus, treatment of 184 with this crystalline amide base (1.3 equiv.) in THF at -20°C followed by addition
of 1.8 equiv. of mixed anhydride 168 afforded diester 189 (14%), 47% of recovered 184, 34% of recovered mixed anhydride 168 as well as some diene acid resulting from hydrolysis of 168. No C(15)-deacylation product 190 was observed. It is important to note, however, that if NaN(TMS)$_2$ was not sublimed prior to use, substantial deacylation of C(15) was realized.

Increasing the number of equivalents of base in an attempt to drive the reaction further afforded 40% of C(4)-acylated products. Unfortunately 189 so obtained contained 30% of an isomeric trichothecene diester, possibly the C(2') or C(6') epimer. 89 This isomeric structure was also present, but to a lesser extent, in the product obtained when 1.3 equiv. of base was used.

The use of the lithium alkoxide of 184 for these acylation reactions was also explored. Thus, treatment of 184 with n-butyllithium (1 equiv., -78°, THF) followed by quenching with 168 (1.3 equiv.) afforded diester 189 in 16% yield along with 66% recovered 184. Although the yield of this reaction is 80% based on recovered 184, the gross inefficiency of this method excluded it from further consideration. Similarly, treatment
of 184 with lithium hexamethyldisilazane (1.2 equiv., -20°, THF) afforded 189 in only 3% yield; trichothecene 184 and anhydride 168 were recovered in 44% and 41% yields, respectively.

Although we had circumvented the problem of loss of the C(15)-acyl group by using bases which were free of hydroxide, the efficiency of these reactions were so poor that we faced a serious practical problem in the preparation of significant quantities of diester 188. We decided, therefore, to explore the acylations of 184 and 168 with nucleophilic acylation catalysts, a protocol which we had rejected at the outset of this work as a consequence of the olefin isomerization problem discussed in Chapter 3. Other work in these laboratories concerning the synthesis of verrucarin B, however, had indicated that the extent of olefin isomerization and the rate of reaction in the esterification of (Z,E)-muconic acids to trichothecene C(4)-OH were functions of the amount of acylation catalyst present in the reaction medium (e.g., 191-26). 41a Higher ratios of catalyst to substrate led to greater amounts of olefin isomerization than in cases where the amount of catalyst was greatly restricted.

The results of several attempts to prepare 189 from 184 and 168 by use of acylation catalyst are summarized in Table XI. As can be seen, the selectivity and rate of reaction is very much dependent on the catalyst and its concentration. The conditions which gave the least olefin isomerization were 30 mol % N-methylimidazole in CH₂Cl₂ at 25°C. This reaction afforded 189 as an 8:1 mixture of (Z,E)- and (E,E)-isomers in 17% yield
after 15 days; 43% of 184 was recovered. Clearly, this reaction is much too slow to be practical for preparative scale experiments. The use of 4-PP as an acylation catalyst led to faster rates of reaction but also greater amounts of olefin isomerization.

It is clear from the preceding discussion that the best yield of C(4)-ester was realized when the acylation of 168 and 184 was performed in the presence of NaH in THF at 0°C. An unacceptable drawback to this reaction, however, was the concomitant loss of the C(15)-acyl fragment. Hence, for obvious practical considerations, we decided that it would be appropriate to reverse the order of the two acylation reactions leading to 189. For these purposes a C(15)-mono protected derivative of verrucarol would be required as a starting material. Given the constraints imposed by the
Table XI

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Conditions</th>
<th>Products^a</th>
<th>187 (190 : 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% 4PP</td>
<td>25°, 70h</td>
<td>100%</td>
<td>0 : 0</td>
</tr>
<tr>
<td>5% 4PP^b</td>
<td>25°, 7d</td>
<td>50%</td>
<td>17% (3 : 1)</td>
</tr>
<tr>
<td>10% 4PP</td>
<td>25°, 14h</td>
<td>16%</td>
<td>45% (3 : 2)</td>
</tr>
<tr>
<td>30% N-methylimidazole</td>
<td>25°, 15d</td>
<td>43%</td>
<td>17% (8 : 1)</td>
</tr>
</tbody>
</table>

(a) These isomers could be separated by preparative layer silica gel chromatography.

(b) It was necessary to add an additional 5% 4-PP after 2d since reaction had appeared to stop.
protecting groups and other reactive functionality present in the trichothecene monoester $^{190}$, we selected the C(15) monoacetate $^{58}$ for this work. $^{36}$ We thought that the acetate group of $^{193}$ could be selectively hydrolyzed since Fraser-Reid had accomplished this conversion on a very similar trichothecene diester. $^{40}$ Acylation of $^{190}$ with mixed anhydride $^{183}$ by using the conditions we had previously described would then afford diester $^{189}$. Thus, treatment of a mixture of $^{58}$ and $^{168}$ in DME and THF (1:1) at 0°C for 1h with 1.5 equiv. of NaH afforded diester $^{193}$ along with a small amount of $^{190}$ in 58% yield. The yield in this case was comparable to that obtained in our work on trichoverrol B. It is important to note, however, that if this reaction was performed at room temperature for 5h, substantial deacylation was observed. Under these
conditions C(4) monoester 190 and verrucarol (8) were obtained in 10% and 83% yield, respectively.

We were now ready to unmask the C(15)-OH group. Initially we intended to use the conditions published by Fraser-Reid for the selective hydrolysis of the C(15) acetate of 59 (c.f. Scheme VI). Unfortunately, initial attempts to accomplish this conversion revealed that no deacylation occurred in a 3:1 DME-H₂O solvent mixture (50°C, 15h) when the pH was 12 or lower. At pH 13, at which point the reaction mixture contained 10 equiv. of LiOH, deacylation occurred but with no selectivity, giving 8 and diene acid 194.

It was clear from these preliminary studies that the C(15)-acetate is not an acceptable protecting group for our purposes. Reduction of this plan to practice will require that an alternative protective group scheme be developed for C(15)-OH of the trichothecene skeleton as well as for C(6') and C(13') of the C(4)-diene acid fragment (vide infra). This problem will be addressed in future studies by other members of our research group.
With limited quantities of pure diester 189 in hand (a total of 20 mg was prepared during the course of these studies), we began an examination of methods for the macrocyclization reaction which would be required to complete the construction of the roridin ring system. As a necessary first step, diol 195 was prepared by acid catalyzed hydrolysis.

**Scheme XXIX**

\[
\begin{align*}
\text{HOAc, H}_2\text{O, THF (3:1:1), 25°C, 6h)} & \text{ of 189 in 88% yield.}
\end{align*}
\]

We imagined that cyclodehydration of 195 could be accomplished by using the Mitsunobu reaction. This method has been used for the synthesis of cyclic ethers from diols. Moreover, we imagined that cyclization of 195 would occur with retention of configuration at C(6') since C(5')-OH, the
least hindered hydroxyl group in this system, would probably be activated towards substitution.

Unfortunately, treatment of diol 195 under the standard Mitsunobu conditions (triphenylphosphine, diethyl azodicarboxylate (DEAD) toluene, 25°C) failed to effect any reaction. Increasing the reaction temperature to 65°C for 48h, or addition of fresh DEAD followed and 1 equiv. of diisopropylethylamine at 65°C also failed to yield any reaction. Chromatographic workup afforded quantitative recovery of 195. However, treatment of 195 with 1.5 equiv. of triphenylphosphine and 1.5 equiv. of DEAD in refluxing toluene for 24h consumed diol 195, but did not afford any product containing a macrocyclic structure.

Having failed to effect any cyclization under the Mitsunobu reaction conditions we attempted to prepare primary iodide 196 with the intent of accomplishing the macroetherification by using one of the variants of the Williamson ether synthesis. Attempts to prepare iodide 196 for this purpose, however, by using methyltriphenoxyphosphonium iodide afforded none of the desired product. Rather, a mixture of several uncharacterized trichotheccenes, all much more polar than the starting diol, were isolated. Of course many other means for selective activation of the C(5')-OH could also be envisaged.

The final step in our currently proposed synthesis of roridin D would be the cleavage of the SEM ether protecting group. Although we had not prepared macrocycle 197, we decided to test our original assumption that the SEM ether could be
removed at the end of the synthesis. (E,E)-Diene diester 198, prepared by hydrolysis of trichothecone 192, was used to examine conditions necessary for this deprotection. Treatment of 198 with (nBu)₄NF in wet THF at 45° as recommended by Lipshutz ⁷⁵,⁹³ afforded recovered 198 and C(15) deacylated product 199. The SEM ether was intact in both reaction products. Several other reagents and reaction conditions were examined in attempts to remove the SEM ethers of 198 and epoxy-ether 200, all to little avail (see Table XII). In contrast, however, treatment of 200 with 1.1 equiv. of trityl tetra-fluoroborate at −78° with slow warming to 25°C over a 2h period gave epoxyalcohol 116 in 62% yield after chromatography.⁹⁴
<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>198, (nBu)$_4$NF, THF</td>
<td>45°, 46h</td>
<td>50% 50% - -</td>
</tr>
<tr>
<td>198, KF·H$_2$O, DMSO</td>
<td>45°, 48h</td>
<td>100% - - -</td>
</tr>
<tr>
<td>198, KF·H$_2$O, DMSO, 18-crown-6</td>
<td>25°, 36h</td>
<td>100% - - -</td>
</tr>
<tr>
<td>200, KF (10 equiv.), ACOH, THF, H$_2$O (3:1:1)</td>
<td>25°, 36h</td>
<td>- - 100% -</td>
</tr>
<tr>
<td>200, [(Me)$_2$N]$_3$S$^\Theta$F$_2$Si$^\Theta$(Me)$_3$ (4 equiv.) in CH$_3$CN</td>
<td>55°, 48h</td>
<td>- - 60% 40%</td>
</tr>
<tr>
<td>198 [(Me)$_2$N]$_3$S$^\Theta$F$_2$Si$^\Theta$(Me)$_3$ (4 equiv.) in CH$_3$CN</td>
<td>55°, 12h</td>
<td>complete deacylation$^a$</td>
</tr>
</tbody>
</table>

(a) Determined by TLC analysis.
Unfortunately, treatment of trichothecene 195 under these conditions afforded a complex mixture of products.

$$\text{(Ph)}_2\text{CBF}_4, \text{CH}_2\text{Cl}_2$$

mixture of products

-78 $\rightarrow$ 25°

195

It became painfully obvious from these results that even if we were successful in developing conditions for macrocyclization of 195, we probably would not be able to complete a synthesis of roridin D. Clearly, the synthetic scheme must be reworked so as to incorporate mutually compatible protecting groups for the C(15), C(6') and C(13') hydroxyl functionality of various intermediates. One possible sequence is outlined in Scheme XXX. Ideally, our synthesis of 168 might be

Scheme XXX

1. (nBu)_4NF

2. esterify w/ 178

TBDMSO

155

NaH, DME, THF

OOC(CH)_3

TBDMSO

178

201

TBDMSO

202

KF·H_2O, DMSO

203

204

R:

TMS
modified to yield mixed anhydride 201. The 2-(trimethylsilyl)-ethyl carbonate as a protecting group for C(6')-OH has been selected on the basis of Blizzard's favorable results in his verrucarin B synthesis (e.g., 205 + 188). 4la

Coupling of 201 (diene system) with trichothecene monoo ester 155 according to the methodology developed in our synthesis of trichoverrol B would afford diester 202. Treatment of 202 with one equivalent of (n-Bu)4NF would remove the C(15)-acyl group and set the stage for introduction of glycidic acid 178. Finally, treatment of 203 with KF in wet DMSO would afford diol 204, a substrate for additional, more extensive macrocyclization studies. Of course, it should also be possible to esterify 155 with acids such as 206 which would
directly introduce functionality pertinent to the macrocyclization studies.

We must also develop contingency plans for future studies in the event that the cyclization of 204 cannot be readily accomplished. Indeed, our results with 195 are not particularly encouraging. On the other hand, we remain optimistic that this key ring closure reaction can be effected owing to a report by Jarvis that trichoverrin A (28) was cyclized in 10% yield to epi-isororidin E (207)\textsuperscript{24}

\[
\begin{array}{c}
\text{28} \\
\text{(Ph)}_3\text{P, DEAD} \\
toluene \\
10\% \\
\text{207}
\end{array}
\]

An alternative approach, which may also have biomimetic implications, would involve the acid or base catalyzed cyclizations of a trisepoxide substrate such as 208. It is interesting to speculate that an epoxide intermediate may be involved in the cyclization of 28 to 207, given the fact that the Mitsunobu reaction readily converts vicinal diols to epoxides\textsuperscript{90}. Finally, one could investigate an approach
wherein the intact macrocyclic side chain is attached to the trichothecene nucleus and the macrocyclization completed by a lactonization process (see Scheme XXXI). In fact, this approach is under current investigation by another member of the Roush research group.

Scheme XXXI

Clearly much more work remains to be done in our approach toward roridin D and the baccharins. The work described in this thesis, namely, that esters such as 218 can be prepared in isomerically pure form from trichothecene 216 and mixed anhydrides 217, lays the foundation for future studies in this area.
CHAPTER V

EXPERIMENTAL PROCEDURES
Proton ($^1$H) NMR spectra were measured at 60 MHz on a Varian T-60 or a Perkin-Elmer R-24B instrument, and at 250 or 270 MHz on Bruker WM250 and 270 instruments. Chemical shifts are reported in δ units using tetramethylsilane or the 7.24 ppm resonance of residual chloroform as internal reference. Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer calibrated with the 1601 cm$^{-1}$ absorption of polystyrene. IR spectra are reported in wave numbers (cm$^{-1}$). Ultraviolet spectra were measured on a Perkin-Elmer 330 UV-Visible Spectrophotometer. Wavelengths are reported in nanometers (nm). Optical rotations were measured on a Rudolph Autopol® III Automatic Polarimeter using a 1 cm$^3$ capacity quartz cell (10 cm path length). Mass spectra were measured on a Varian MAT 44 or a Finnegan MAT 8200 instrument. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, New Jersey. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected.

All reactions were conducted in oven dried (170°C) glassware with magnetic stirring under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and DME were distilled from sodium benzophenone ketyl. Methylene chloride (CH$_2$Cl$_2$), acetonitrile, t-butanol, diisopropylamine, were distilled from CaH$_2$. Benzene and toluene were distilled from sodium metal. DMF was dried over molecular sieves then distilled (reduced pressure). Triethylamine was predried over CaSO$_4$ then distilled from P$_2$O$_5$. Pyridine was distilled from sodium hydroxide. Diisopropylethyl amine and diisopropylamine were distilled from KOH and stored over activated 4Å
molecular sieves. 4-Pyrrolidinopyridine (4-PP) was recrystallized from hexane. 2,2' Dipyridyldisulfide (DPDS) was recrystallized (2X) from ether, hexane (1:1) and dried by concentration from toluene before use. Potassium tert-butoxide was purified by sublimation. The weighing of all moisture sensitive materials was done under an atmosphere of dry nitrogen. Pivaloyl chloride was distilled from K₂CO₃ at atmosphere pressure under nitrogen. Diisopropyl tartrate, diethyl tartrate and titanium tetra-iso-propoxide were distilled.

Lithium diisopropylamide was generated at -78°C as a stock solution in THF and titrated immediately prior to use. All enolates were generated from lactones which had been azotropically dried from either dry toluene or benzene before use.

Analytically thin layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.25-, 0.5-, and 1.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized with shortwave UV light, or by staining with either phosphomolybdic acid (PMA) or by charring with ethanolic H₂SO₄. Compounds containing the trichotheocene nucleus or a phosphonate group were eluted from the adsorbents with ethyl acetate; all other compounds were eluted with ether. Flash chromatography was performed as described by Still. All chromatography solvents were distilled prior to use.
n-Butyllithium (32.0 mL of a 2.5 M hexane solution, 80.0 mmol) was added dropwise under nitrogen purge to a solution of 1-butyne-3-ol (2.8 g, 40.0 mmol) in 20 mL of tetrahydrofuran and 20 mL (120 mmol) of hexamethylphosphoramide (HMPT) at 0°C. The resulting reddish-brown solution was stirred for 30 min at 0°C. 1-Bromo-4-pentene (5.9 g, 40.0 mmol) was added dropwise over a period of 5 min. The resulting pale yellow solution was warmed to room temperature over a period of 30 min. This mixture was maintained at room temperature for 3 hrs. Tetrahydrofuran and hexane were remained in vacuo. The resulting yellow oil was partitioned between 150 mL of a saturated aqueous solution of LiCl and 100 mL of pentane. The layers were separated and the aqueous layer was extracted with pentane (3x20 mL). The combined extracts were dried (MgSO₄), filtered and evaporated to give 5.46 g of crude product. The crude product was purified by flash chromatography (SiO₂, 45x210 mm, Et₂O, hexane, 1:1 Rf 0.65) to give 3.73 g (67%) of pure 106: NMR (¹H, 250 MHz, CDCl₃) δ 5.85-5.69 (m, 1 H, H₈), 5.05-4.94 (m, 2 H, H₉), 4.46-4.51 (m, 1 H, H₂), 2.19 (td, J=7.3 Hz, 1.9 Hz, 2 H, H₅), 2.11 (t, J=7.3 Hz, 2 H, H₄).
2 H, H_7), 1.63 (d, J=4.9 Hz, 1 H, -OH), 1.57 (quintet, J=6.8 Hz, 2 H, H_6), 1.41 (d, J=6.8 Hz, 3 H, H_1); IR (CH_2Cl_2), 3600, 3490, 3080, 2980, 2930, 2240, 1635 cm^{-1}; mass spectrum m/e 138 M^+; Anal. Calcd for C_9H_{14}O: C, 78.21; H, 10.21. Found: C, 77.90; H, 10.49.
To a solution of 106 (2.05 g, 14.9 mmol) in CH$_2$Cl$_2$ (100 mL) was added solid PCC (6.49 g, 30.1 mmol). This mixture was stirred vigorously at 25° for 4h. Addition of anhydrous Et$_2$O (100 mL) and trituration of the resulting solids afforded after filtration through a bed of Florisil, and concentration in vacuo, 1.92 g of a yellow oil. Distillation of this material (bulb-tc-bulb, 90-100°C, 10 mm) gave 1.81 g, 90%, of pure 113: NMR (H, 250 MHz, CDC$_3$) δ 5.85-5.65 (m, 1 H, H$_8$), 5.1-4.95 (m, 2 H, H$_9$), 2.35 (t, J=7 Hz, 2 H, H$_5$), 2.30 (s, 3 H, H$_1$), 2.21-2.11 (m, 2 H, H$_7$), 1.75-1.60 (m, 2 H, H$_6$); IR (CH$_2$Cl$_2$) 3040, 2940, 2860, 2210, 1680, 1640 cm$^{-1}$; mass spectrum m/e 136 M$^+$. Anal. Calcd for C$_5$H$_{12}$O: C, 79.37; H, 8.88. Found: C, 79.22; H, 9.13.
To a stirred suspension of LiAlH$_4$ (578 mg, 15.2 mmol) in anhydrous Et$_2$O (425 mL) at 0°C was added a precooled solution (0°C) of Chirald $^R$ (9.37 g, 33.1 mmol) in Et$_2$O (68 mL) over a period of 2 min. The resulting suspension was stirred under N$_2$ at 0°C for an additional 2 min then cooled to -78°C. Once the temperature of this suspension had reached -78°C (5 min) a solution of 113 (1.66 g, 12.2 mmol) in Et$_2$O (70 mL) was added over a period of 5 min. The resulting suspension was maintained at -78°C under N$_2$ for 6h. To this mixture was added Et$_2$O saturated with H$_2$O (100 mL). This suspension was warmed to ambient temperature and extracted with 3M HCl (1x50 mL). The aqueous phase was washed with Et$_2$O (3x50 mL) and the resulting organic extracts washed with 2M HCl (1x30 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to afford 1.77 g of crude product as a brown oil. Purification of (R)-106 was accomplished by flash column chromatography (50x185 mm, Et$_2$O:hexane, 1:1, $R_f$ 0.65) to afford 1.50 g of a pale yellow liquid which was further purified by distillation (bulb-to-bulb, 100-105°C, 5 mm) to yield 1.2 g (77%) of (R)-106. Mosher ester
analysis indicated that this material was 64% optically pure.

\([\alpha]_D^{21} + 14.8^\circ \ (C=0.7, \text{CH}_2\text{Cl}_2)\).
A solution of 523 mg of (R)-106 (3.8 mmol) in methanol 6 mL) containing Lindlar catalyst (52 mg, 10% by weight) was stirred vigorously under an atmosphere of hydrogen. After consuming 106 mL of H₂, 1.3 equiv.) the reaction mixture was filtered through a sintered glass frit. The resulting filter cake was washed with pentane (2x10 mL) and concentrated in vacuo to afford 513 mg (96%) of 115. In practice, this material was used without further purification. Analytically pure 115 could be obtained by preparative layer chromatography (SiO₂, 0.5 mm Et₂O, hexane, 1:1 Rₖ 0.53) for spectral data: [α]D²¹ + 4.0° (C = 0.86 CH₂Cl₂) (95% ee); NMR (¹H, 250 MHz, CDCl₃) δ 5.85-5.75 (m, 1 H, H₈), 5.50-5.41 (m, 2 H, H₃, H₄), 5.08-4.94 (m, 2 H, H₉), 4.70-4.60 (m, 1 H, H₂), 2.20-2.02 (m, 4 H, H₅, H₇), 1.63 (bs, 1 H, -OH), 1.48 (quintet, J = 6.7 Hz, 2 H, H₆), 1.25 (d, J = 6.1 Hz, 3 H, H₁); IR (CH₂Cl₂) 3600, 3070, 2980, 2920, 1640 cm⁻¹; mass spectrum m/e 122 (M⁺ - H₂O); Anal. Calcd for C₉H₁₆O: C, 77.09; H, 11.50. Found: C, 76.90; H, 11.59.
Catalytic hydrogenation of 106 was accomplished as described in the conversion of 106 to 115. Benzoylation of (Z)-allylic alcohol (27.1 mg, .19 mmol) with benzoyl chloride (40.8 mg, .29 mmol), pyridine (46 mg, .57 mmol) gave the intermediate benzoate derivative (56 mg), (R\textsubscript{f} .70, Et\textsubscript{2}O, hexane 1:1) after extractive workup. Without further purification, this material was oxidatively cleaved with RuCl\textsubscript{3}, NaIO\textsubscript{4} (5 mg, 2%; 364 mg, 1.71 mmol) in CCl\textsubscript{4}-CH\textsubscript{3}CN-H\textsubscript{2}O (.8 mL, .8 mL, 1.2 mL) at -25°C for 4h to afford, after standard workup 52 mg of the crude lactic acid derivative. Treatment of this material with CH\textsubscript{2}N\textsubscript{2} in Et\textsubscript{2}O gave, after chromatography (SiO\textsubscript{2}, .25 mm, Et\textsubscript{2}O, hexane 1:1, R\textsubscript{f} .60) 9 mg (24% from 106) of pure 114: [α]\textsubscript{D}\textsuperscript{21} - 8.0° (c=7.2, CHCl\textsubscript{3}) (Lit for enantiomer: [α]\textsubscript{D}\textsuperscript{21} + 13.9 (c=1.0, CHCl\textsubscript{3})).\textsuperscript{62} NMR (\textsuperscript{1}H, 250 MHz, CDCl\textsubscript{3}) δ 8.06 (d, J=7 Hz, 2 H), 7.61-7.40 (m, 3 H), 5.32 (q, 7 Hz, 1 H, H\textsubscript{2}), 3.76 (s, 3 H, OMe), 1.62 (d, J=7 Hz, 3 H, H\textsubscript{2}).
To a solution of Ti(OiPr)$_4$ (1.05 g, 3.7 mmol) in CH$_2$Cl$_2$ (40 mL) cooled to -20°C under a nitrogen atmosphere was added a solution of 115 (513 mg, 3.7 mmol) in CH$_2$Cl$_2$ (10 mL). After 5 min at -20°C TBHP (5.6 M in CH$_2$Cl$_2$, 7.3 mmol) was added and the resulting mixture maintained at -20°C for 15h. To this mixture was added Et$_2$O (10 mL) and saturated Na$_2$SO$_4$ (aq.) (1.1 mL) and the whole stirred vigorously at ambient temperature for 1h before being filtered through a bed of Celite. The filter cake was washed with Et$_2$O (5x20 mL) and the combined filtrates were concentrated in vacuo to afford 870 mg of crude 116 which was purified by flash column chromatography (SiO$_2$, 20x180 mm, Et$_2$O:hexane, 1:1, R$_f$ .25) to afford 415 mg (73%) of 116 as a 19:1 mixture of threo and erythro products: [α]$^D_{21}$ +16.3° (C=1.5 CH$_2$Cl$_2$) (95% ee); NMR ($^1$H, 250 MHz, CDCl$_3$) δ 5.85-5.70 (m, 1 H, H$_8$), 5.05-4.90 (m, 2 H, H$_9$), 3.70-3.59 (m, 1 H, H$_2$), 4.05-3.95 (m, 1 H, H$_4$), 2.80-2.90 (m, 1 H, H$_3$), 1.35 (bd, J=3 Hz, 1 H, OH), 1.15-1.05 (m, 2 H, H$_7$), 1.68-1.48 (m, 4 H, H$_5$, H$_6$), 1.23 (d, J=7 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) 3600-3200, 3080, 2980, 2920, 2860, 1640 cm$^{-1}$; mass spectrum m/e 111 (M$^+$ - 45, -CH$_3$CH$_2$O); Anal. Calcd for
C₉H₁₆O₂: C, 68.96; H, 10.52. Found: C, 69.11; H, 10.32.
To a solution of epoxyalcohol 116 (421 mg, 2.69 mmol, 64% ee) in CH$_2$Cl$_2$ (16 mL) was added MEM-Cl (672 mg, 5.39 mmol) followed by diisopropylethyl amine, (1.04 g, 8.07 mmol). The resulting mixture was maintained under nitrogen for 24h. The orange reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL) and extracted with NaHCO$_3$ (aq). The aqueous phase was washed with CH$_2$Cl$_2$ (2x20 ml), filtered through a cotton plug and concentrated to give 820 mg of a dark yellow oil. Pure epoxzyether was obtained by flash chromatography (SiO$_2$, 25x190 mm, Et$_2$O, hexane, 1:1, R$_f$ .49) as a colorless liquid (538 mg, 82%): $[\alpha]_D^{21} + 22.4^\circ$ (C=1.2, CH$_2$Cl$_2$) (72% ee) NMR (1H, 250 MHz, CDCl$_3$) $\delta$ 6.85-6.65 (m, 1 H, H$_8$), 6.00-5.85 (m, 2 H, H$_9$), 5.85 (A of AB, J=3.5 Hz, 1 H, -OCH$_2$O-), 5.72 (B of AB, J=3.5 Hz, 1 H, -OCH$_2$O-), 3.72-3.48 (m, 5 H, H$_2$, MEM), 3.32 (S, 3 H, MEM), 2.90-2.82 (m, 2 H, H$_3$, H$_4$), 2.00-2.11 (m, 2 H, H$_7$), 1.30-1.81 (m, 4 H, H$_5$, H$_6$), 1.80 (d, 6.5 Hz, 3 H, H$_1$); IR (CCl$_4$) 3070, 2975, 2920, 2880, 1640, 1450 cm$^{-1}$; mass spectrum m/e 185 (M-59, -MeOCHCH$_2$); Anal. Calcd. for C$_{13}$H$_{24}$O$_4$: C, 63.90; H, 9.90. Found: C, 63.78; H, 10.04.
A solution of this compound (495 mg, 2.03 mmol) in CH₃CN-CCl₄-H₂O (9 mL, 9 mL, 13.5 mL) to which was added NaIO₄ (1.94 g, 9.13 mmol) and RuCl₃ (30 mg, 2%) was cooled to 0°C and stirred vigorously for 3.5 h. This mixture was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL) being careful not to mix the phases on the first wash (very bad emulsions result). The phases were separated and the aqueous phase washed with CH₂Cl₂ (3x10 mL). The combined organic extracts were filtered through cotton and concentrated in vacuo to give 464 mg (87%) of a dark green oil which also contained between 5-10% of hydroxy lactone 118. Although this mixture could be obtained as a clear, colorless oil (for spectral data) by precipitation of the ruthenium salts with anhydrous ether, in practice this was not done as these salts did not interfere with the subsequent step: [α]²¹_D + 18.8° (C=0.5, CH₂Cl₂) (72% ee); NMR (¹H, 250 MHz, CDCl₃) δ 10-9.5 (bs, 1 H, -CO₂H), 4.85 (A of AB, J=6.8 Hz, 1 H, -OCH₂O-), 4.73 (B of AB, J=6.8 Hz, 1 H, -OCH₂O-), 3.75-3.50 (m, 5 H, H₂, MEM), 3.34 (s, 3 H, MEM), 2.95-2.85 (m, 2 H, H₂, H₃), 2.50-2.30 (m, 2 H, H₇), 1.90-1.35 (m, 4 H, H₅, H₆), 1.18 (d, 6.8 Hz, 3 H, H₁), IR (CH₂Cl₂), 3500-2500, 3040, 2940, 1710 cm⁻¹; mass spectrum m/e 217 (M-45).
To a solution of carboxylic acid 117 (464 mg, 1.77 mmol) in \( \text{CH}_2\text{Cl}_2 \) (10 mL) was added camphorsulfonic acid (30 mg, 10 mol %). This mixture was maintained at 25°C for 3 h, diluted with \( \text{CH}_2\text{Cl}_2 \) (30 mL) and extracted with \( \text{NaHCO}_3 \) (1/3 saturated, 10 mL). The aqueous phase was extracted with \( \text{CH}_2\text{Cl}_2 \) (10 mL, 3x), filtered through a cotton plug and concentrated in vacuo to give 451 mg (97%) of hydroxy lactone 118. Although in practice 118 was used without further purification analytically pure 118 could be obtained by flash chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\), MeOH, 9:1, \( R_f \) .58): [\( \alpha \)]\(_D\) \( ^{21} \) - 14.7° (c = 0.2, CH\(_2\)Cl\(_2\)) (64% ee); NMR (\( ^1\text{H} \), 250 MHz, CDCl\(_3\)) \( \delta \) 4.80 (A of AB, \( J \)=7 Hz, 1 H, -OCH\(_2\)O-), 4.70 (B of AB, \( J \)=7 Hz, 1 H, -OCH\(_2\)O-), 4.42-4.35 (m, 1 H, H\(_5\)), 4.0-3.5 (m, 5 H, H\(_7\), MEM), 3.38 (s, 3 H, MEM), 3.30-3.25 (m, 1 H, H\(_6\)), 2.65-2.35 (m, 3 H, H\(_2\), OH), 2.05-1.50 (m, 4 H, H\(_3\), H\(_4\)), 1.20 (d, \( J \)=7 H, 3 H, H\(_7\)); IR (CH\(_2\)Cl\(_2\)) 3660, 3560, 3420, 3020, 2920, 2880, 1730 cm\(^{-1}\); mass spectrum m/e 262 (M\(^+\)); Anal. Ca\`cd for \( \text{C}_{12}\text{H}_{22}\text{O}_6 \): C, 54.95; H, 8.45. Found: C, 54.77; H, 8.61.
To a solution of 118 (450 mg, 1.71 mmol) in DMF (12 mL) was added TBDMS-Cl (517 mg, 3.43 mmol) followed by imidazole (351 mg, 5.15 mmol). The mixture was then heated to 60°C under N₂ for 82h. The reaction mixture was cooled to ambient temperature and partitioned between Et₂O (20 mL) and H₂O (20 mL). The phases were separated and the aqueous phase was washed with Et₂O (3x50 mL). The combined organic extracts were washed with H₂O (1x30 mL), dried over Na₂SO₄ and concentrated in vacuo to leave 870 mg of a pale yellow oil which was purified by flash chromatography (SiO₂, 30x210 mm, Et₂O (100%), Rᵢ 0.50) to afford 598 mg (93%) of pure 119: [α]²¹_D + 11.6° (c = 0.8, CH₂Cl₂) (72% ee); NMR (¹H, 250 MHz, CDCl₃) δ 4.78 (A of AB, J=6.8 Hz, 1 H, -OCH₂O-), 4.70 (B of AB, J=6.8 Hz, 1 H, -OCH₂O-), 4.40 (m, 1 H, H₅), 3.82 (quintet, J=7.0 Hz, 1 H, H₇), 4.70-4.50 (m, 5 H, H₆, MEM), 3.36 (s, 3 H, MEM), 2.62-2.30 (m, 2 H, H₂), 2.0-1.60 (m, 4 H, H₃, H₄), 1.25 (d, J=7.0, 3 H, H₈), 0.87 (s, 9 H, tBuSi), 0.10 (s, 3 H, MeSi-), 0.06 (S, 3 H, MeSi-); IR (CH₂Cl₂), 3040, 2930, 2880, 2850, 1730 cm⁻¹; mass spectrum m/e 319 (M-57, -tBu).
To a solution of 119 (222 mg, 0.59 mmol) in THF (5 mL) at 
-78°C under nitrogen was added LDA (1 M in THF, 1.0 equiv.).
The resulting pale yellow solution was maintained at -78°C for
1h and quenched with PhSeBr (0.62 mmol) which was prepared in
THF immediately before use according to the procedure of Reich
and Regna.66 This reaction mixture was quenched after 35
min. with sat. NH₄Cl (1 mL) at -78°C. The quenched mixture was
warmed to room temperature, diluted with CH₂Cl₂ (10 mL) and
the phases separated. The aqueous phase was washed with CH₂Cl₂
(2x10 mL) and the combined organic extracts were filtered through
a cotton plug and concentrated in vacuo to give 461 mg of
a thick yellow oil.

The crude α-selenolactone was dissolved in CH₂Cl₂ (8 mL)
to which was added a catalytic amount of AcOH (4 mg, 1% by
weight) followed by 30% H₂O₂ (361 μL, 120 mg, 3.54 mmol, 6
equiv. based on a theoretical yield of 0.59 mmol of selenolactone).
This mixture was stirred vigorously at 25°C for 45 min., diluted
with CH₂Cl₂ (20 mL) and extracted with 20% NaHSO₃ (5 mL). The
aqueous extract was washed with CH₂Cl₂ (10 mL) and the combined organic extracts were washed with H₂O (30 mL), filtered through a cotton plug and concentrated in vacuo to afford 208 mg of crude 120 which was purified on two 0.5 mm SiO₂ prep plates (Et₂O, 100%) to afford 122 mg (55%) of pure 120 as a heavy oil: [α]₂¹_D -26.3° (c = 4.2, CH₂Cl₂) (64% ee); NMR (¹H, 250 MHz, CDCl₃) δ 6.9-6.8 (m, 1 H, H₃), 5.9 (dd, J=10 Hz, 3 Hz, 1 H, H₂), 4.77 (A of AB, J=7 Hz, 1 H, -OCH₂O-), 4.70 (B of AB, J=7 Hz, 1 H, -OCH₂O-), 4.55-4.45 (m, 1 H, H₅), 3.9-3.5 (m, 6 H, H₆, H₇, MEM), 3.36 (s, 3 H, MEM), 2.60-2.45 (m, 2 H, H₄), 1.27 (d, J=6 Hz, 3 H, H₈), 0.87 (s, 9 H, t-BuSi-), 0.11 (s, 3 H, MeSi-), 0.08 (s, 3 H, MeSi-); IR (CH₂Cl₂), 2920, 2880, 2850, 1720 cm⁻¹; mass spectrum m/e 317 (M⁻57, -t-Bu); UV (EtOH) 212 nm (ε = 4,000); Anal. Calcd for C₁₈H₃₄SiO₆: C, 57.67; H, 9.15. Found: C, 57.41; H, 9.11.
A solution of 120 (43 mg, 0.12 mmol) in THF (0.9 mL) was added to a stirred suspension of K\textsuperscript{t}OBu (20 mg, 0.18 mmol, sublimed) in THF (0.4 mL) at 0°C. This mixture was maintained at 0°C under a nitrogen atmosphere for 30 min, quenched with \( \text{NH}_4\text{Cl}^- \) (5 mL, saturated aqueous solution) and extracted with EtOAc (3x20 mL). The organic extracts were concentrated in vacuo to afford 33 mg of crude acid 121 (one spot on analytical tlc) which was purified by flash chromatography (SiO\(_2\), 10x190 mm, \( \text{CH}_2\text{Cl}_2\), MeOH, 9:1, \( R_f \) 0.5) to yield 25 mg of pure 121: [\( \alpha \)]\textsubscript{D}\textsuperscript{21} + 39.7° (c = 2.5, \( \text{CH}_2\text{Cl}_2 \)) (64% ee); NMR (\( ^1\text{H} \), 250 MHz, CDCl\(_3 \)) δ 7.58 (dd, J=15.2 Hz, 11.1 Hz, 1 H, H\(_4\)), 6.70 (t, J=11.1 Hz, 1 H, H\(_3\)), 6.16 (dd, J=15.2 Hz, 5.7 Hz, 1 H, H\(_5\)), 5.67 (d, J=11.1 Hz, 1 H, H\(_2\)), 4.80 (s, 2 H, -OCH\(_2\text{O}-\)), 4.35 (t, J=5.7 Hz, 1 H, H\(_6\)), 3.80-3.50 (m, 5 H, H\(_7\), MEM), 3.40 (s, 3 H, MEM), 1.10 (d, J=6.4 Hz, 3 H, H\(_8\)), 0.91 (s, 9 H, \( \text{t} \text{BuSi}-\)), 0.07 (s, 3 H, MeSi-), 0.06 (s, 3 H, MeSi-); IR (\( \text{CH}_2\text{Cl}_2 \)) 3200-2500, 2920, 2880, 2860, 1725, 1690, 1635, 1600 cm\(^{-1}\); UV (EtOH) 259 nm, (\( \varepsilon \) = 11,000); mass spectrum m/e 317 (M-57); \textit{Anal.} Calcd for \( \text{C}_{18}\text{H}_{34}\text{O}_6\text{Si} \): C, 57.72; H, 9.15. Found: C, 54.29; H, 8.41.
A solution of 106 (1.30 g, 9.42 mmol) in 10 mL of tetrahydrofuran was added in one portion, via cannula, to a solution of lithium aluminum hydride (14.7 ml of a 1.6 M tetrahydrofuran solution, 23.5 mmol) at 0°C. The cooling bath was removed and the mixture was refluxed for 1h under nitrogen. The mixture was cooled to 0°C and water (890 μL) was added cautiously with vigorous stirring. To the resulting white suspension was added 15% NaOH solution (890 μL) affording a granular white precipitate. This mixture was filtered over 1 inch of Celite and the filter cake washed with ether (3x50 mL). Concentration of the filtrate in vacuo afforded 1.27 g of a clear, colorless oil. In practice 122 was carried on without purification.
Analytically pure 122 was obtained by distillation (90°C, 2 mm):
NMR (\(^1\)H, 250 MHz, CDCl\(_3\)) \(\delta\) 5.86-5.69 (m, 1 H, H\(_8\)), 5.66-5.46 (m, 2 H, H\(_3\), H\(_4\)), 5.02-4.90 (m, 2 H, H\(_9\)), 4.29-4.21 (m, 1 H, H\(_2\)), 2.07-1.97 (m, 4 H, H\(_5\), H\(_7\)), 1.44 (quintet, J=8.0 Hz, 2 H, H\(_6\)), 1.42 (br s, 1 H, OH), 1.23 (d, J=6.4 Hz, 3 H, H\(_1\)); IR (CCl\(_4\)) 3610, 3360, 3080, 2980, 2920, 2860, 1665, 1604; mass spectrum m/e 140 M\(^+\), 122 (M-18); Anal. Calcd for C\(_9\)H\(_{16}\):
C, 77.09; H, 11.50. Found: C, 77.33; H, 11.65.
(+)-Diisopropyl tartrate (1.01 g, 4.3 mmol) was added to a flask containing dichloromethane (75 mL) at -20°C under an atmosphere of nitrogen. To this solution was added titanium tetraisopropoxide (1.03 g, 3.62 mmol) and the resulting mixture was stirred for 10 min. To this mixture was added a solution of 122 (1.27 g, 9.07 mmol) in 30 mL of dichloromethane and the resulting mixture stirred for 10 min. tert-Butylhydroperoxide (0.71 ml of a 5.75 M dichloromethane solution, 4.08 mmol) was added and the mixture was maintained at -20° for 18 h. The mixture was then diluted with ether (50 mL) and saturated aqueous Na₂SO₄ (1.1 mL). This mixture was stirred vigorously at room temperature for 1 h. The resulting white suspension was filtered through a 1 inch bed of Celite and the filter cake washed with ether (5x40 mL). Concentration of the filtrate in vacuo gave a colorless oil (2.5 g). The crude product mixture was dissolved in ether (20 mL) and cooled to 0°C. To this solution was added saturated aqueous NaCl (20 mL) and 15% NaOH (6.8 ml, 25.5 mmol). The biphasic mixture was stirred vigorously with a mechanical stirring apparatus. After
4h the phases were separated and the aqueous phase extracted with ether (3x20 mL). The combined extracts were dried over Na₂SO₄ powder and filtered. The filtrate was diluted with an equal volume of dichloromethane, filtered through cotton and concentrated in vacuo to afford 1.57 g of crude product. ¹H NMR analysis of this mixture indicated that some diisopropyltartrate remained. This mixture was further purified by flash column chromatography (190 x 50 mm of 70-230 mesh SiO₂, 1:1, ether: hexane) affording 503 mg (40%) of allylic alcohol 122 and 740 mg of a mixture of epoxyalcohol 123 and diisopropyltartrate. The epoxy alcohol/tartrate mixture was dissolved in ether (10 mL) and cooled to 0°C. To this solution was added saturated aqueous NaCl (10 mL) and 15% NaOH (3.4 mL, 12.75 mmol). The biphasic mixture was stirred as before. After 2 h the phases were separated and the aqueous phase was extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x10 mL). The ether extracts were diluted with an equal volume of dichloromethane and filtered through cotton. Concentration, in vacuo, afforded 572 mg (40%, 90% based on oxidant) of (-)-123. The optical purity of this sample was determined by the method of Mosher et al to be greater than 95% ee.

(-)-123: [α]D²⁰ = -8.9° (c = 1.28, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 5.86-5.69 (m, 1 H, H₈), 5.04-4.92 (m, 2 H, H₉), 3.00-2.95 (m, 1 H, H₄), 2.75-2.73 (m, 1 H, H₃), 2.12-2.04 (m, 2 H, H₇), 1.85 (d, J=3 Hz, -OH), 1.56-1.49 (m, 4 H, H₅, H₆), 1.23 (d, 3 H, H₁); IR (CH₂Cl₂), 3560, 3042, 2970, 2930, 2860, 1735, 1640; mass spectrum m/e 156 (M⁺); Anal. Calcd for C₉H₁₆O₂:
C, 69.19; H, 10.32. Found: C, 68.96; H, 10.61.

(+)-122: $\left[\alpha\right]_{D}^{20} = +9.48$ (C = .58, CH$_2$Cl$_2$).

The enantiomeric erythro-epoxyalcohol (+)-123 was prepared in an identical manner: $\left[\alpha\right]_{D}^{20} = +8.60$ (C = 2.02, CH$_2$Cl$_2$).
The preparation of 124 from 123 (77%) was accomplished by a procedure completely analogous to that described for the conversion of 116 to 117: $R_F$ .5, (Et$_2$O, hexane 1:1); $[\alpha]^2_{D} + 36.2^\circ$ (C = 1.58, CH$_2$Cl$_2$); NMR ($^1$H, 60 MHz, CDCl$_3$) $\delta$ 6.2-5.5 (m, 1 H, H$_8$), 5.3-4.7 (m, 2 H, Hg), 3.8-3.5 (m, 5 H, H$_2$, MEM), 3.4 (s, 3 H, MEM), 3.0-2.6 (m, 2 H, H$_3$, H$_4$), 2.4-1.9 (m, 2 H, H$_7$), 1.7-1.5 (m, 4 H, H$_5$, H$_6$), 1.21 (d, J=6 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) 3040, 2920, 2880, 1640 cm$^{-1}$; mass spectrum m/e 185 (M-59); 124: $[\alpha]^2_{D} + 28.6$ (C = 1.1, CH$_2$Cl$_2$); NMR ($^1$H, 60 MHz, CDCl$_3$) $\delta$ 5.1-4.8 (m, 2 H, MEM), 4.5-3.6 (m, 5 H, H$_2$, MEM), 3.4 (s, 3 H, MEM), 3.2-2.9 (m, 2 H, H$_3$, H$_4$), 2.7-2.2 (m, 2 H, H$_7$), 2.1-1.8 (m, 4 H, H$_5$, H$_6$), 1.2 (d, J=7 Hz, 3 H, H$_1$), IR (CH$_2$Cl$_2$) 3500-2500, 2940, 2880, 1710 cm$^{-1}$.
Lactone 125 was prepared from 124 using a procedure completely analogous to that used for the preparation of 118 from 117: \( R_f 0.2 \) (Et\(_2\)O, 100%); \([\alpha]_D^{21} = -36.0^\circ\) (C = 1.2, CH\(_2\)Cl\(_2\)); NMR \( ^1\text{H}, 60 \text{ MHz, CDCl}_3 \) \( \delta 5.0 \) (bs, 2 H, MEM), 4.7-4.5 (m, 1 H, H\(_5\)), 4.2-3.8 (m, 5 H, H\(_2\), MEM), 3.4 (s, 3 H, MEM), 2.8-2.6 (m, 2 H, H\(_2\)), 2.3-1.9 (m, 4 H, H\(_3\), H\(_4\)), 1.2 (d, J=7 H, 3 H, H\(_1\)); IR (CH\(_2\)Cl\(_2\)) 3580, 2940, 2920, 2880, 730 cm\(^{-1}\); mass spectrum m/e 263 (M+1). Anal. Calcd for C\(_{12}\)H\(_{22}\)O\(_6\): C, 54.95; H, 8.45. Found: C, 54.78; H, 8.59.
Lactone 126 was prepared (92%) by a procedure analogous to that used for the preparation of 119 from 118: \( R_f \) 0.5 (Et\(_2\)O, 100%); \([\alpha]\)\(_D\)\(^{21}\) = 19.9° (C = 2, CH\(_2\)Cl\(_2\)); NMR (\(^1\)H, 60 MHz, CDCl\(_3\)) \( \delta \) 4.8 (bs, 2 H, MEM), 4.6-4.4 (m, 1 H, H\(_5\)), 3.8-3.6 (m, 5 H, H\(_2\), MEM), 2.1-1.8 (m, 4 H, H\(_3\), H\(_4\)), 1.2 (d, J=7 Hz, 3 H, H\(_1\)), 1.0 (s, 9 H, tBu), 0.1 (s, 6 H, Si(Me)\(_2\)); IR (CH\(_2\)Cl\(_2\)) 2920, 2880, 2860, 1730 cm\(^{-1}\); mass spectrum m/z 320 (M-57).
Unsaturated lactone 127 was prepared (25%) by a procedure analogous to that described for the preparation of 120 from 119:

Rf 0.55 (Et2O, 100%); [α]D21 = 114.7° (C = 2.21, CH2Cl2); NMR
(1H, 250 MHz, CDCl3) δ 6.95-6.85 (m, 1 H, H3), 5.98 (dd, J=10 Hz, 2 Hz, 1 H, H2), 4.75 (A of AB, J=8 Hz, 1 H, -OCH2O-), 4.65 (B of AB, J=8 Hz, 1 H, -OCH2O-), 3.87-3.40 (me, 6 H, H6, H7, MEM), 3.36 (s, 3 H, MEM), 2.70-2.30 (m, 2 H, H3), 1.20 (d, J=6 Hz, 3 H, H8), 0.87 (s, 9 H, t-Bu), 0.0 (s, 6 H, -Si(Me)2); IR
(CH2Cl2) 2970, 2920, 2880, 2860, 1720 cm⁻¹; UV (EtOH) 212 nm
Diene acid 128 was prepared (57%) by a procedure identical to that outlined for the preparation of 121 from 120: $R_f$ 0.5 (CH$_2$Cl$_2$, MeOH, 9:1); $[\alpha]_D^{21}$ + 1.5 (C =1.6, CH$_2$Cl$_2$); NMR ($^1$H. 250 MHz, CDCl$_3$) $\delta$ 8.00 (dd, J=15 Hz, 10 Hz, 1 H, H$_4$), 6.62 (t, J=10 Hz, 1 H, H$_3$), 6.05 (dd, J=15 Hz, 6 Hz, 1 H, H$_5$), 5.65 (d, J=10 Hz, 1 H, H$_2$), 4.75 (bs, 2 H, MEM), 4.19 (t, J=6 Hz, 1 H, H$_6$), 3.80-3.50 (m, 5 H, H$_7$, MEM), 3.39 (s, 3 H, MEM), 1.12 (d, J=6 H, 3 H, H$_1$), 0.90 (s, 9 H, t-Bu), 0.05 (s, 3 H, TBDMS), 0.03 (s, 3 H, TBDMS); IR (CH$_2$Cl$_2$) 3400-2500, 2920, 2880, 2850, 1720, 1685, 1635, 1595 cm$^{-1}$; UV (EtOH) 262 nm, ($\epsilon$ = 11,100).
A solution of 128 (30 mg, 0.8 mmol) in MeOH containing Dowex 50W-X8 resin (210 mg) was heated to reflux for 5d. This mixture was cooled to ambient temperature, filtered through a sintered glass frit and concentrated in vacuo to leave 22 mg of crude 129 which was purified by flash chromatography (SiO₂, 10 x 190, mm, Rₜ .60, CH₂Cl₂, MeOH, 9:1), to afford 12.7 mg (86%) of pure 129: [α]D²¹ - 36.6° (C = 1.27, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 7.58 (dd, J=15 Hz, 9 Hz, 1 H, H₄), 6.60 (t, J=9 Hz, 1 H, H₃), 6.09 (dd, J=15 Hz, 6 Hz, 1 H, H₅), 4.0-3.90 (m, 1 H), 3.72 (s, 3 H, -OMe), 2.40-2.10 (bs, 1 H, -OH), 1.80-1.60 (bs, 1 H, OH), 1.15 (d, J=6 Hz, 3 H, H₈); IR (CH₂Cl₂) 3680, 3580, 3040, 2980, 1710, 1640, 1600 cm⁻¹; mass spectrum m/e 169 (M-15).
To a solution of 129 (9 mg, .05 mmol) in CH$_2$Cl$_2$ (.25 mL) was added 2,6-lutidine (26 mg, .24 mmol) followed by TBDMS-OTf (39 mg, .147 mmol). This mixture was maintained at 25°C under N$_2$ for 1h, solvents removed in vacuo and the residue purified by preparative layer chromatography (SiO$_2$, .25 mm, Et$_2$O, hexane 1:1, R$_f$ 0.8) to yield 11 mg (51%) of the bis TBDMS ether: NMR (1H, 250 MHz, CDCl$_3$) $\delta$ 7.40 (dd, J=15 Hz, 11 Hz, 1 H, H$_4$), 6.55 (t, J=11 Hz, 1 H, H$_3$), 5.01 (dd, J=15 Hz, 6 Hz, 1 H, H$_5$), 5.62 (d, J=11 Hz, 1 H, H$_2$), 3.98 (t, J=6 Hz, 1 H, H$_6$), 3.71 (s, 3 H, -OMe), 3.70-3.60 (m, 1 H, H$_7$), 1.12 (d, J=7 Hz, 1 H, H$_1$), 0.90 (s, 9 H, t-Bu), 0.83 (s, 9 H, t-Bu), 0.5-0.0 (m, 12 H, TBDMS).

This material was dissolved in a 3:1 mixture of DME : H$_2$O (0.5 mL) containing LiOH (3.2 mg, .158 mmol) and heated to 45°C for 4h. This mixture was diluted with CH$_2$Cl$_2$ (10 mL) and extracted with sat. NH$_4^+$Cl$^-$ (5 mL). The aqueous extract was washed with CH$_2$Cl$_2$ (4x20 mL) and the combined organic extracts were filtered through a cotton plug, concentrated in vacuo to leave 10.8 mg of crude 54 which was purified by prep plate
chromatography (SiO₂, Et₂O, hexane, HCO₂H, 1:2:1%, Rf 0.6) to yield 7.3 mg of pure 54: m.p. 76-78° (lit:77-79°); ¹⁰⁷D -22.3° (C = 1.28, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 7.48 (dd, J=15 Hz, 10 Hz, 1 H, H₄), 6.65 (t, J=10 Hz, 1 H, H₃), 6.10 (dd, J=15 Hz, 7 Hz, 1 H, H₅), 5.65 (d, J=10 Hz, 1 H, H₂), 3.98 (t, J=7 Hz, 1 H, H₆), 3.64 (dq, 7 Hz, 1 H, H₇), 1.13 (d, J=7 Hz, 3 H, H₈), 0.90 (s, 9 H, t-Bu), 0.85 (s, 9 H, t-Bu), 0.05-0.0 (m, 12 H, TBDMS); IR (CH₂Cl₂) 3070, 2980, 2890, 2880, 1730, 1695, 1640, 1600 cm⁻¹; UV (EtOH) 250 nm (ε = 11,400); mass spectrum m/e 355 (M-45).
Imidazole (2.40 g, 3.51 mmol) and tert-butyldimethylsilylchloride (3.53 g, 23.4 mmol) were added to a solution of epoxyalcohol (1.8 g, 11.7 mmol) in dimethylformamide (20 mL). This mixture was heated to 50°C under an atmosphere of nitrogen and then was partitioned between ether (20 mL) and water (20 mL). The organic extract was washed with water (4x50 mL). The combined aqueous extracts were washed with ether (3x20 mL) and combined with the initial ether extracts, diluted with an equal volume of dichloromethane, filtered through cotton and concentrated in vacuo affording 4.3 g of a clear, colorless oil. The crude product was purified by flash column chromatography (SiO₂, 45x120 mm, hexane, 500 mL, Et₂O, hexane, 1:1 Rₜ 0.80) to afford 3.0 g (98%) of pure TBDMS ether: [α]²¹{D} = +4.6° (C = 7.0, CH₂Cl₂) NMR (¹H, 250 MHz, CDCl₃) δ 5.85-5.70 (m, 1 H, H₈), 6.03-5.93 (m, 2 H, H₉), 3.65 (dd, J=5 Hz, 1 H, H₂), 2.85-2.80 (m, 1 H, H₄), 2.59 (dd, J=5 Hz, 2.7 Hz, 1 H, H₃), 2.15-2.00 (m, 2 H, H₇), 1.60-1.50 (m, 4 H, H₅, H₆), 1.2 (d, J=5.9 Hz, 3 H, H₁), 0.85 (s, 9 H, t-Bu), 0.02 (s, 6 H, Si(Me)₂); IR
(CH₂Cl₂) 3020, 2930, 2850, 1640; mass spectrum m/e 213 (M-57); Anal. Calcd for C₁₅H₃₀SiO₂.

To a solution of 3.0 g (11.6 mmol) of the TBDMS ether in CH₃CN (29 mL), CCl₄ (29 mL) and H₂O (50 mL) was added solid NaIO₄ (11.3 g, 52.9 mmol). To this mixture was added RuCl₃·3H₂O (120 mg, 4%). The resulting biphasic mixture was stirred vigorously at 25°C for 7h. The resulting mixture was partitioned between CH₂Cl₂ (50 mL) H₂O (50 mL). Without being mixed, the phases were separated and the aqueous phase was washed with CH₂Cl₂ (2x50 mL). The combined extracts were filtered through a cotton plug and concentrated in vacuo. The resulting dark green oil was suspended in anhydrous ether (100 mL) and allowed to stand at 25°C for 30 min. This solution was filtered through a pad of celite (20 x 50 mm) and concentrated in vacuo to leave 3.22 g of a green oil (94% from 123) containing ca. 10% of hydroxylactone 131.
To a solution of 3.0 g (11.0 mmol) of carboxylic acid 130 in CH₂Cl₂ (100 mL) was added pTsOH·H₂O (320 mg). This mixture was maintained at 25°C for 3.5h, and extracted with 1/2 saturated aqueous NaHCO₃ (50 mL). The resulting emulsion was filtered through a cotton plug and concentrated to afford 4g of a mixture of crude product. This mixture was suspended in 200 mL of anhydrous CH₂Cl₂ and filtered through a pad of Celite. The filter cake washed with CH₂Cl₂ (3x100 mL) and concentrated in vacuo to afford crude 131 (3.6 g) which was purified by flash column chromatography (SiO₂, 50x180 mm, Et₂O, hexane, 2:1, Rf 0.45 to afford 2.95 g (91%) of pure 131: [α]D²¹ = -5.0° (C = 2.39, CH₂Cl₂), NMR (¹H, 250 MHz, CDCl₃) δ 4.35-4.25 (m, 1 H, H₅), 4.01 (dd, J=5.6 Hz, 1 H, H₇), 3.62 (dd, J=6.4 Hz, 5.3 Hz, 1 H, H₆), 2.70-2.40 (m, 2 H, H₂), 2.30 (br s, 1 H, OH), 2.15-1.60 (m, 4 H, H₃, H₄), 1.15 (d, J=6.2, H₈), 0.85 (s, 9 H, tert butyl), .06 (s, 3 H, Si(Me)), .05 (s, 3 H, Si(Me)); IR (CH₂Cl₂) 3550, 2980, 2960, 2860, 1735, mass spectrum m/e 231 (M-57); Anal. Calcd. for C₁₄H₂₈SiO₄: C, 58.29; H, 9.78. Found: C, 57.99; H, 9.80.
To a solution of **131** (300 mg, 1.03 mmol) in dry pyridine (1.5 mL) was added bishexamethyldisilazane (332 mg, 2.06 mmol) followed by addition of TMS-Cl (224 mg, 2.06 mmol). This mixture was maintained at 25°C under an atmosphere of dry nitrogen. After 20 min. reaction was quenched with brine (5 mL) and diluted with CH₂Cl₂ (20 mL). The phases were separated and the aqueous phase washed with CH₂Cl₂ (2x10 mL). The combined organic extracts were filtered through cotton, diluted with n-heptane (20 mL) and concentrated in vacuo to afford 350 mg (93%) of **132** as a colorless oil. In practice **132** was used without further purification. Analytically pure **132** could be obtained by preparative layer chromatography (SiO₂, 0.25 mm, Et₂O, hexane, 1:1, Rf .50): [α]₂¹⁰ D = -18.45 (C = 1.36, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 4.50 (dt, J=10.3, 3.7 Hz, 1 H, H₅), 3.75-3.65 (m, 1 H, H₇), 3.63 (dd, J=5.6, 3.7 Hz, 1 H, H₆), 2.61-2.30 (m, 2 H, H₂), 2.61-2.30 (m, 2 H, H₂), 1.65-1.98 (m, 4 H, H₃, H₄), 1.13 (d, J=5.6 Hz, 3 H, H₄), 0.84 (s, 9 H, tert butyl), 0.10 (s, 9 H, TMS), 0.04 (s, 3 H, MeSi), 0.01 (s, 3 H, MeSi); IR (CH₂Cl₂) 3025, 2960, 2935, 2895, 2860, 1730 cm⁻¹; mass
spectrum m/e 345 (M-15), 303 (M-57); **Anal.** Calcd for $\text{C}_{17}\text{H}_{36}\text{Si}_2\text{O}_4$:

C, 56.67; H, 10.06. Found: C, 56.90; H, 9.95.
To a solution of 132 (350 mg, 0.96 mmol) in THF (3 mL) cooled to -78°C under N₂ was added a solution of LDA in THF (0.84 M, 2.3 mL, 1.93 mmol). After 1 h, at -78°C the enolate was quenched with a cold solution (-78°C) of DPDS (424 mg, 1.93 mmol) in THF (2 mL). The resulting mixture was maintained at -78°C for 1 h, quenched (at -78°C) with saturated aqueous NH₄Cl (2 mL) and extracted, after warming to 25°C, with CH₂Cl₂ (10 mL x 1). The combined organic extracts were filtered through a cotton plug and concentrated in vacuo to afford 774 mg of crude 133 as a mixture of diastereomeric sulfides (Rf .55, Et₂O, hexane 1:1). This mixture was used without further purification.
To a solution of the crude sulfonylation product (456 mg, 0.96 mmol, theoretical yield from 132) in CH₂Cl₂ (10 mL) at 0°C was added a solution of MCPBA (430 mg, 2.2 mmol) in CH₂Cl₂ (10 mL). This mixture was maintained at 0°C for 30 min, diluted with CH₂Cl₂ (10 mL) and extracted with 1/3 saturated aqueous NaHCO₃ (2x20 mL). The aqueous phase was washed with CH₂Cl₂ (2x10 mL) and the combined organic extracts were filtered through cotton and concentrated in vacuo to afford 780 mg of a mixture of diastereomeric sulfoxides, (Rᶠ 0.20, Et₂O, hexane 1:1). This mixture was used without further purification.

A solution of the diastereomeric sulfoxides in dry toluene (6 mL) was heated to reflux. After 30 min the mixture was cooled to ambient temperature and concentrated in vacuo to afford 707 mg of a pale yellow oil, which was purified by flash chromatography (SiO₂, 30x205 mm, Et₂O, hexane, 1:1, Rᶠ 0.50) to afford 260 mg of pure 134 (75% from 132); [α]D²¹ = -85.9° (C = 1.62, CH₂Cl₂), NMR (¹H, 250 MHz, CDCl₃) δ 6.89 (ddd, J=2.1, 5.6, 10.1 Hz, 1 H, H₃), 5.97 (dd, J=2.6, 10.1 Hz, 1 H, H₂), 4.62 (dt J=11.6, 3.7 Hz, 1 H, H₅), 3.7-3.8 (m, 2 H, H₆, H₇), 2.58 (ddt, J=19.8, 11.6, 2.1 Hz, 1 H, H₄α), 2.25 (ddd,
J=19.8, 5.6, 3.7 Hz, 1 H, H₄), 1.15 (d, J=7.5 Hz, 3 H, H₈),
0.83 (s, 9 H, tert BuSi), 0.12 (s, 9 H, Si(Me)₃), .05 (s, 3 H,
Si(Me)), .01 (s, 3 H, Si(Me)); IR (film) 2955, 2930, 2890,
2875, 1735; UV (EtOH), λ max 217, ε = 2,650; mass spectrum m/e
343 (M-15), 301 (M-57); Anal. Calcd for C₁₇H₃₄SiO₄: C, 56.93; H,
To a solution of 134 (68 mg, 0.19 mmol) in THF (0.8 mL) at 0°C was added a suspension of KtOBu (23 mg, 0.21 mmol) in THF (1.4 mL). The resulting yellow solution was maintained under N₂ at 0°C. After 1h the intermediate potassium carboxylate was quenched with freshly distilled pivaloyl chloride (25 mg, 0.21 mmol). This mixture was maintained at 0°C for 20 min, warmed to ambient temperature and filtered (under nitrogen) through a bed of Florisil. The filter cake was washed with anhydrous THF (4x5 mL) and concentrated in vacuo to afford 79 mg of 135 (94%). This material was used without additional purification: [α]²¹_D = -16.3° (C = 0.44, CH₂Cl₂) NMR (¹H, 250 MHz, CDCl₃) δ 7.43 (dd, J=15.5, 11.5, 1 H, H₄, H₄), 6.75 (t, J=11.5 Hz, 1 H, H₃), 6.20 (dd, J=5.5, 15.5, 1 H, H₅), 5.70 (d, J=11.5 H, 1 H, H₂). IR (CH₂Cl₂) 2960, 2935, 2890, 2860, 1798, 1725, 1635, 1593. Mass Spectrum m/e 341 (M-101, (CH₃)₃CO₂), 313, 101.
A solution of 1,2-butanediol (1.2 g, 13.5 mmol) in THF (25 mL) was cooled to -78°C and nBuLi (12.9 mmol) was added over a period of 10 min. This mixture was warmed to ambient temperature, maintained under N₂ for 13 h, extracted with brine (2×10 mL) and concentrated to give 2.2 g of crude mono TBDMS ether. This material was used without further purification: NMR (¹H, 60 MHz, CDCl₃) δ 3.7–3.6 (m, 4H), 3.1 (bs, 1 H, OH), 1.7–1.6 (m, 4H), 1.0 (s, 9 H, tBu), 0.3 (s, 6 H, TBDMS).

To a solution of this alcohol (192 mg, 0.95 mmol) in CH₃CN (1.8 mL), CCl₄ (1.8 mL) and H₂O (2.7 mL) was added NaIO₄ (612 mg, 2.87 mmol) followed by RuCl₃·(H₂O)₃ (10 mg, 2 mol %). This mixture was stirred vigorously at 25°C for 1 h. The reaction mixture was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL). The aqueous phase was washed with CH₂Cl₂ (3×20 mL) and the combined organic extracts were filtered through a cotton plug and concentrated to give 167 mg of crude 153. Purification of 153 was accomplished by flash chromatography (SiO₂, 20×170 mm, Et₂O, hexane, H₂CO₂ (1:1:1%) Rf .6) to give 138 mg (66%) of
pure 153: NMR \( ^1H, 60 \text{ MHz, CDCl}_3 \) δ 3.7 (t, J=6 Hz, 2 H, H\textsubscript{4}), 2.4 (t, J=7 Hz, 2 H, H\textsubscript{2}), 2.1-1.7 (m, 2 H, H\textsubscript{3}), 0.90 (s, 9 H, tBu), 0.1 (s, 6 H, TBDMS); IR (CH\textsubscript{2}Cl\textsubscript{2}) 2920, 2800, 1710 cm\textsuperscript{-1}; Anal. Calcd for C\textsubscript{10}H\textsubscript{22}SiO\textsubscript{3}: C, 45.09; H, 8.32. Found:
Method A:

To a solution of 153 (27 mg, 0.123 mmol) in THF (0.20 mL) was added triethyl amine (28 mg, 0.24 mmol), followed by pivaloyl chloride (16.5 mg, 0.137 mmol). This mixture was maintained at under nitrogen for 1.5 h. To this mixture was added a solution of verrucarol 8 (30 mg, 0.112 mmol) in THF (0.40 mL) and pyridine (128 mg, 1.62 mmol). The resulting mixture was maintained at 25°C under nitrogen for 76 h, concentrated in vacuo from heptane (2 x 15 mL) and purified by prep plate chromatography (SiO₂, 0.25 mm, Et₂O, CH₂Cl₂, 1:1, Rₐ .5) to afford 28 mg (56%) of pure 155.

Method B:

A solution of dicyclohexylcarbodiimide (DCC)(19 mg, 0.092 mmol) and 4-pyrrolidinopyridine (3 crystals) in CH₂Cl₂ (0.150 mL) was added to a solution of verrucarol 8 (12.3 mg, 0.46 mmol) and carboxylic acid 153 (12.1 mg, 0.054 mmol) in
CH$_2$Cl$_2$ (0.125 mL) and maintained at 25°C, under N$_2$, for 4.5 h. This mixture was filtered, the solids washed with CH$_2$Cl$_2$ (2 x 10 mL). The combined filtrate and washes were concentrated in vacuo and purified by prep plate chromatography (SiO$_2$, 0.25 mm, Et$_2$O, CH$_2$Cl$_2$, 1:1, R$_f$ 0.5) to afford 15.2 mg (70%) of pure 155: m.p. 83-84°C; [α]$^D_{21}$ = 31.3° C (C = 1.12, CH$_2$Cl$_2$); NMR ($^1$H, 250 MHz, CDCl$_3$) δ 5.42-5.35 (m, 1 H, H$_{10}$), 4.50-4.40 (m, 1 H, H$_4$), 4.12 (A of AB, J=11 Hz, 1H, H$_{15a}$), 3.88 (B of AB, J=11 Hz, 1 H, H$_{15b}$), 3.81 (d, J=5 Hz, 1 H, H$_2$), 3.65-3.55 (m, 3 H, H$_4$, H$_{11}$), 3.10 (d, J=4 Hz, 1 H, H$_{13a}$), 2.79 (d, J=4 Hz, H$_{13b}$), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H$_{3a}$), 2.39 (t, J=8 Hz, 2 H, H$_2$), 2.01-1.71 (m, 8 H, H$_7$, H$_8$, H$_{3b}$, H$_3'$, -OH), 1.70 (s, 3 H, H$_{16}$), 0.85 (s, 9 H, TBDMS), 0.81 (s, 3 H, H$_{14}$), 0.03 (s, 6 H, TBDMS); IR (CH$_2$Cl$_2$) 3680, 2960, 2880, 1735 cm$^{-1}$; mass spectrum m/e 466 (M$^+$).
To a solution of 54 (4.4 mg, 0.011 mmol) in CH₂Cl₂ (0.2 mL), under an atmosphere of N₂, was added triethylamine (2.8 mg, 0.027 mmol) followed by pivaloyl chloride (1.6 mg, 0.0132 mmol). This mixture was maintained at -25°C for 45 min and a solution of 155 (5.1 mg, 0.011 mmol) in CH₂Cl₂ (0.5 mL) containing several crystals of 4-dimethylaminopyridine (4-DMAP). After 20h the mixture was concentrated in vacuo and purified by prep plate chromatography (SiO₂, 0.25 mm, CH₂Cl₂, Et₂O, 1:1, Rf .6) to give exclusively (E,E)-157 (contaminated with (E,E)-isomer of 54) along with recovered 155 (3 mg, 60%). Data for (E,E)-31: NMR (¹H, 250 MHz, CDCl₃) δ 7.30 (dd, J=16 Hz, 11 Hz, 1 H, H₇'), 6.45 (dd, J=16 Hz, 11 Hz, 1 H, H₉'), 6.20–6.10 (m, 2 H, H₇', H₄'), 5.96 (d, J=16 Hz, 1 H, H₁₀'), 5.52–5.45 (m, 1 H, H₁₀), 3.12 (d, J=4 Hz, 1 H, H₁₃a'), 2.81 (d, J=4 Hz, 1 H, H₁₃b'), 2.48 (dd, J=16 Hz, 8 Hz, 1 H, H₃'), 1.71 (s, 3 H, H₆'), 1.50 (d, J=7 Hz, 3 H, H₁₄'), 0.81 (s, 3 H, H₁₄).
To a solution of NaH (7.7 mg, 0.321 mmol, oil free) in DME (0.5 mL) was added a solution of 155 (25 mg, 0.054 mmol) in DME (1.5 mL). This mixture was stirred at 25°C for 30 min and a solution of 135 (48 mg, 0.018 mmol) in DME (1 mL) was added. The resulting mixture was maintained at 25°C for 1.5 h, filtered through a bed of Florisil® and concentrated in vacuo to afford crude 157b (59 mg) which was purified by flash chromatography (SiO₂, Et₂O, hexane 1:1, Rf .40) to yield 24 mg (55%) of pure 157b: [α]D21 -3.25° (C = 1.20, CH₂Cl₂); NMR (1H, 250 MHz, CDCl₃) δ 7.49 (J=15 Hz, 11 Hz, 1 H, H₈'), 6.55 (t, J=11 Hz, 1 H, H₉), 6.05 (dd, J=15 Hz, 7 Hz, 1 H, H₇), 5.70-5.65 (m, 1 H, H₄), 5.65 (d, J=11 Hz, 1 H, H₁₀'), 5.46-5.40 (m, 1 H, H₁₀), 4.18 (A of AB, J=12 Hz, 1 H, H₁₅a), 4.05 (B of AB, J=12 Hz, 1 H, H₁₅b), 3.98 (t, J=7 Hz, 1 H, H₆'), 3.81 (d, J=5 Hz, 1 H, H₂), 3.75-3.60 (m, 4 H, H₁₁, H₄', H₁₃'), 3.12 (d, J=4 Hz, 1 H, H₁₃a), 2.81 (d, J=4 Hz, 1 H, H₁₃b), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H₃d), 2.39 (t, J=8 Hz, 1 H, H₂), 2.05-1.60 (m, 7 H, H₇, H₈', H₉', H₆', H₅', H₄', H₁₀').
H_3', H_38), -0.70 (s, 3 H, H_{16}), 1.12 (d, J=7 Hz, 3 H, H_{14}), 0.85 (s, 18 H, TBDMS), 0.81 (s, 3 H, H_{14}), 0.15-0.0 (m, 21 H, -SiMe); IR (CH_2Cl_2) 2950, 2930, 2860, 1730, 1710 (shoulder), 1640, 1600 cm^{-1}; UV (MeOH) 262 nm (ε = 21,000) (Taken of 157b); mass spectrum m/e 618 (M-188; -TMS, -TBDMS).
To a solution of 157b (20 mg, 0.24 mmol) in THF (2 mL) was added (nBu)_4NF (0.119 mmol, 5 equiv). The resulting yellow solution was maintained at 25°C, under N₂, for 10 min, and quenched with sat. NH₄Cl (2 mL). The phases were separated and the aqueous phase was washed with Et₂O (2 x 20 mL). The combined organic extracts were diluted with CH₂Cl₂ (10 mL), filtered through a plug of cotton and concentrated in vacuo to leave 17 mg of a yellow oil. Pure 31 (9.1 mg, 90%) was obtained by flash column chromatography (SiO₂, 10 x 135 mm EtOAc (100%). R_f .25) which proved to be identical in all respects to a sample of natural trichoverrol B supplied by Professor Bruce B. Jarvis: [α]D²¹ - 9.3° (C = 0.27, CHCl₃) (natural); [α]D²¹ - 8.7° (C = 0.25, CHCl₃) synthetic); NMR (¹H, 250 MHz, CDC₁₃) δ 7.57 (dd, J=16 Hz, 11 Hz, 1 H, H₈), 6.61 (t, J=11 Hz, 1 H, H₉), 6.18-6.08 (m, 2 H, H₄, H₇), 5.80 (d, J=11 Hz, 1 H, H₁₀), 5.50-5.55 (m, 1 H, H₁₀), 4.30-4.20 (m, 1 H, H₆), 4.95-4.60 (m, 5 H, H₂, H₁₁, H₁₅), 3.15 (d, J=5 Hz, 1 H, H₁₃a), 2.81 (d, J=5 Hz, 1 H, H₁₃b), 2.70-2.45 (m, 3 H, 2(-OH), H₃a),
2.15-1.90 (3 H, H₈, OH), 1.70 (s, 3 H, H₁₆), 1.60-1.50 (m, 2 H, H₇), 1.23 (d, J=6 Hz, 3 H, H₁₄'), 0.80 (s, 3 H, H₁₄'); IR (CH₂Cl₂) 3600, 3650-3200, 3050, 2985, 2940, 2880, 1690, 1640, 1600 cm⁻¹; UV (MeOH) 260 nm, (ε = 41,000); mass spectrum m/e 402 (M-18).
Triphenylphosphine (1.24 g, 5.43 mmol) and para-nitrobenzoic acid (907 mg, 5.43 mmol) were added to a solution of epoxyalcohol (565 mg, 3.62 mmol) dry toluene (10 mL). To this solution was added diethylazodicarboxylate (922 mg, 5.07 mmol) and mixture stirred, under nitrogen atmosphere, at ambient temperature. After 1.5 h, the solvent was removed in vacuo leaving a heterogeneous mixture of a yellow oil and a white solid. The crude product was purified by flash column chromatography (SiO$_2$, 40x190 mm, Et$_2$O, hexane, 1:1, R$_f$ .60), [Applied the crude mixture to column in dichloromethane (5 ml)], affording 1.03 g (93%) of a clear oil of the PNBA ester: [$\alpha$]$^21_D$ -35.5$^\circ$ (C = 0.84, CH$_2$Cl$_2$); NMR ($^1$H, 250 MHz, CDCl$_3$) $\delta$ 7.28 (A of AB, J=8 Hz, 2 H), 7.18 (B of AB, J=8 Hz, 2 H), 5.82-5.69 (m, 1 H, H$_8$), 5.05-4.90 (m, 3 H, H$_9$, H$_2$), 2.99-2.95 (m, 1 H), 2.91-2.87 (m, 1 H), 2.12-2.00 (m, 2 H, H$_7$), 1.70-1.50 (m, 4 H, H$_5$, H$_6$), 1.42 (d, J=7 Hz, 3 H, H$_1$); IR (CH$_2$Cl$_2$) 3060, 2940, 2860, 1725, 1640, 1600 cm$^{-1}$; mass spectrum m/e 155 (M-150, -C$_7$H$_4$NO$_3$).

A solution of sodium methoxide in methanol (4 mL of a 0.4 M solution) was added to para-nitrobenzoate 162. The resulting
solution was stirred at ambient temperature. After 30 min several drops of 1M HCl was added to lower the pH to approximately 6. This mixture was partitioned between ether (30 mL) and 1/3 saturated aqueous NaCl solution. Phases were separated and the aqueous phase was extracted with ether (4x30 mL). The ether extracts were diluted with an equal volume of CH₂Cl₂ filtered through a cotton plug and concentrated in vacuo to afford an off-white solid. Crude product was purified by flash column chromatography (SiO₂, 40x200 mm, Et₂O, hexane, 1:1, Rf .20) to afford 416 mg (80%) of pure 162: [α]D²¹ = -12.2° (C =0.38, CH₂Cl₂); NMR (¹H 250 MHz, CDCl₃) δ 5.85-5.69 (m, 1 H, H₈), 5.03-4.92 (m, 2 H, H₉), 3.68-3.58 (m, 1 H, H₂), 2.88 (m, 1 H, H₄), 2.70 (dd, J=4.61, 2.43 Hz, 1 H, H₃), 2.18 (m, 2 H, H₇), 1.89 (d, J=5.39, 1 H, OH), 1.55 (m, 4 H, H₅, H₆), 1.25 (d, J=6.5, 3 H, H₁); IR (CH₂Cl₂) 3590, 3480, 3050, 2975, 2935, 2865, 1640 cm⁻¹; mass spectrum m/e 111 (M⁺-45, CH₃COH); Anal. Calcd for C₉H₁₆O₂: C, 68.96; H, 10.52. Found: C, 68.80; H, 10.64.
To a solution of 106 (2.56 g, 18.6 mmol) in CH$_2$Cl$_2$ (30 mL) was added triethylamine (9.5 mL, 68.2 mmol) followed by isocyanate 170 (4.75 g, 24.1 mmol). This mixture was heated to reflux under N$_2$ for 17h. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL) and washed with H$_2$O (100 mL). The aqueous phase was washed with CH$_2$Cl$_2$ (2x30 mL) and the combined organic extracts were filtered through a cotton plug and concentrated in vacuo to leave 5.5 g of a gray oil. Flash column chromatography (SiO$_2$, 40x200 mm, Et$_2$O, hexane, 1:4, R$_f$ .25) afforded a mixture of pure diastereomers 171 and 172, 4.76 g (76%). These diastereomers were separated by repeated flash chromatography (SiO$_2$, 90x250 mm, Et$_2$O, hexane, 1:5) afforded 1.86 g (35%) of pure 171, (R$_f$ 0.65, Et$_2$O, hexane, 1:5, 3 developments) and 1.74 g (32%) of pure 172, (R$_f$ 0.55, Et$_2$O, hexane 1:5, 3 developments). 171: [$\alpha$]$^{21}_D$ + 47.1$^\circ$ (C = 1.13, CH$_2$Cl$_2$), NMR ($^1$H, 250 MHz, CDCl$_3$) $\delta$ 8.15 (d, J=8 Hz, 1 H), 7.85 (d, J=8 Hz, 1 H), 7.75 (d, J=8 Hz, 1 H), 7.60-7.50 (m, 4 H), 5.82-5.60 (m, 2 H,
H$_8$, H$_2$), 5.50-5.40 (m, 1 H), 5.20-5.10 (m, 1 H), 5.05-4.95 (m, 2 H, H$_9$), 2.25-2.05 (m, 4 H, H$_5$, H$_7$), 1.80-1.45 (m, 8 H, H$_1$, H$_6$, CH$_3^-$); IR (CH$_2$Cl$_2$) 3660, 3430, 3040, 2850, 1710 cm$^{-1}$. [a]$^D$_{$21$} - 40.9° (CH$_2$Cl$_2$, 1.4); NMR ($^1$H, 250 MHz, CDCl$_3$) δ 8.15 (d, J=8 Hz, 1 H), 7.85 (d, J=8 Hz, 1 H), 7.75 (d, J=8 Hz, 1 H), 7.60-7.50 (m, 4 H), 5.82-5.60 (m, 2 H, H$_8$, H$_2$), 5.50-5.40 (m, 1 H), 5.20-5.10 (m, 1 H), 5.05-4.95 (m, 2 H, H$_9$), 2.25-2.05 (m, 4 H, H$_5$, H$_7$), 1.80-1.45 (m, 8 H, H$_1$, H$_6$, CH$_3^-$); IR (CH$_2$Cl$_2$) 3430, 3040, 2980, 2940, 1715 cm$^{-1}$.
To a solution of \(\text{172} (1.74 \text{ g}, 5.2 \text{ mmol})\) in \(\text{Et}_2\text{O} (150 \text{ mL})\) was added triethylamine \((5.32 \text{ g}, 52.6 \text{ mmol})\) and trichlorosilane \((3.56 \text{ g}, 26.3 \text{ mmol})\). The resulting white slurry was stirred at 25°C under a nitrogen atmosphere for 16h, cooled to 0°C and sat. \(\text{NH}_4^+\text{Cl}^-\) was added slowly with vigorous stirring. The resulting solids were filtered, washed with \(\text{Et}_2\text{O} (4\times50 \text{ mL}),\) concentrated \textit{in vacuo} \((1.42 \text{ g})\) and chromatographed \((\text{SiO}_2, 40\times200 \text{ mm, Et}_2\text{O, hexane 1:1})\) to yield 640 mg \((90\%)\) of pure \((S)-\text{106}: [\alpha]_D^{21} - 19.7^\circ \quad (C = 1.31, \text{CH}_2\text{Cl}_2).\) \((R)-\text{106}\) was prepared by a completely analogous procedure \([\alpha]_D^{21} + 19.2^\circ \quad (C = .91, \text{CH}_2\text{Cl}_2).\)
To a solution of (S)-106 (203 mg, 1.47 mmol) in toluene (8 mL) was added triphenylphosphine (575 mg, 2.20 mmol) followed by para-nitrobenzoic acid (PNBA) (368 mg, 2.20 mmol) and diethylazodicarboxylate (DEAD) (376 mg, 2.05 mmol). This mixture was maintained under nitrogen at 25°C for 1h, concentrated in vacuo to yield crude product which was purified by flash chromatography (SiO₂, 30x230 mm, Et₂O, hexane, 2:1, Rf .55) to afford 378 mg (90%) of pure p-nitrobenzoate: [α]D²¹ + 1.30 (C = 3.3, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 8.28 (A of AB, J=9 Hz, 1 H), 8.20 (B of AB, J=9 Hz, 1 H), 5.82-5.62 (m, 2 H, H₂,H₇), 5.04-4.92 (m, 2 H, H₉), 2.28-2.07 (m, 4 H, H₅, H₇), 1.65-1.55 (m, 5 H, H₁, H₆).

p-Nitrobenzoate (370 mg, 1.28 mmol) was dissolved in 0.4 M NaOMe, MeOH (3 mL) and stirred at 25°C for 20 min. This mixture was neutralized (ca pH 6) with 1N HCl, diluted with CH₂Cl₂ (10 mL), extracted with brine (10 mL) filtered through cotton and concentrated in vacuo to give a crystalline solid (methyl p-nitrobenzoate). This material was triturated with pentane (4x50 mL), concentrated in vacuo and purified by
flash chromatography (SiO$_2$, 30x190 mm, Et$_2$O, hexane, 3:1, R$_f$ 0.4) to give 125 mg (70% from (S)-106) of pure (R)-106 (>95% ee, Mosher ester analysis).
To a solution of 116 (414 mg, 2.65 mmol) in CH₂Cl₂ (15 mL) was added diisopropylethyl amine (1.7 g, 13.25 mmol) followed by SEM-Cl (885 mg, 5.30 mmol). This mixture was maintained at 25°C for 16h, then was diluted with CH₂Cl₂ (20 mL) and extracted with 1/3 saturated NaHCO₃ (2x10 mL). The combined organic extracts were filtered through a cotton plug and concentrated in vacuo to afford 1.0 g of crude product which was purified by flash column chromatography (SiO₂, 30x190 mm, Et₂O, hexane, 1:3, Rₚ 0.4) to yield 719 mg (95) of pure material: [α]D²¹ + 43.3° (C = .66, CH₂Cl₂); NMR (1H, 250 MHz, CDC1₃) δ 5.85-5.70 (m, 1 H, H₈), 5.02-4.90 (m, 2 H, Hg), 4.87 (A of AB, J=7 Hz, 1H, -OCH₂O-), 4.71 (B of AB, J=7 Hz, 1 H, -OCH₂O-), 3.75-3.50 (m, 3 H, H₂, SEM), 2.91-2.85 (m, 2 H, H₃, H₄), 2.15-2.01 (m, 2 H, H₇), 1.70-1.30 (m, 4 H, H₅, H₆), 1.20 (d, J=6 Hz, 3 H, H₁), 0.92 (t, J=7 Hz, 2 H, SEM), 0.0 (s, 9 H, SEM); IR (CH₂Cl₂) 3040, 2960, 1640 cm⁻¹; mass spectrum m/e 213 (M-73); Anal. Calcd for C₁₅H₃₀SiO₃: C, 62.88; H, 10.55. Found: C, 63.10; H, 10.84.

To a solution of this material (719 mg, 2.5 mmol) in CCl₄-CH₃CN-H₂O (5 mL, 5 mL, 7.5 mL) was added NaIO₄ (2.4 g, 11.3
mmol) followed by 20 mg of RuCl₃. This heterogeneous mixture was stirred vigorously for 5h at 25°C, diluted with CH₂Cl₂ (20 mL) and extracted with water (10 mL). The aqueous phase was washed with CH₂Cl₂ (3x10 mL) and the combined organic extracts were filtered through a cotton plug and concentrated in vacuo to give 760 mg (98%) of acid 173 which also contained ca. 10% of hydroxylactone 174. This mixture was used without further purification: [α]D²¹ 28.6° (c = .44, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 10.1-9.5 (bs, 1 H, OH), 4.83 (A of AB, J=8 Hz, 1 H, -OCH₂O-), 4.79 (B of AB, J=8 Hz, 1 H, -OCH₂O-), 3.70-3.40 (m, 3 H, H₂, SEM), 2.95-2.85 (m, 2 H, H₃, H₄), 2.50-2.30 (m, 2 H, H₇), 1.90-1.30 (m, 4 H, H₅, H₆), 1.18 (d, J=7 Hz, 3 H, H₁), 0.90 (t, J=9 Hz, 2 H, SEM), -0.04 (s, 9 H, SEM); IR (CH₂Cl₂) 3500-2500, 3040, 2960, 1710 cm⁻¹.
Carboxylic acid 163 was prepared in a manner completely analogous to that described for the preparation of 173 from 116: SEM ether, 95% after chromatography (SiO₂, Et₂O, hexane, 1:1, R₉ 0.65); [α]D²¹ = +11.2° (C = 1.2, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 5.85-5.68 (m, 1 H, H₈), 5.03-4.93 (m, 2 H, H₉), 4.77 (A of AB, J=13.7 Hz, 1 H, -OCH₂O-), 4.73 (B of AB, J=13.7 Hz, 1 H, -OCH₂O-), 3.71-3.49 (m, 3 H, H₂, SEM), 2.80-2.70 (m, 2 H, H₃, H₄), 2.15-2.03 (m, 2 H, H₇), 1.60-1.50 (m, 4 H, H₅, H₆), 1.22 (d, J=6.7 Hz, 3 H, H₁), 0.91 (t, J=8.6 Hz, 3 H, SEM), 0.0 (s, 9 H, TMS); IR (CH₂Cl₂) 3050, 2950, 2900, 1640 cm⁻¹; mass spectrum m/e 213 (M⁻73, TMS); Anal. Calcd for C₁₅H₃₀SiO₃: C, 62.88; H, 10.55. Found: C, 63.19; H, 10.79.  

163: [α]D²¹ = +15.0° (C = 1.13, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 4.79 (A of AB, J=6.8 Hz, 1 H, OCH₂O), 4.68 (B of AB, J=6.8 Hz, 1 H, OCH₂O), 3.70-3.40 (m, 3 H, H₂, SEM), 2.80-2.70 (m, 2 H, H₃, H₄), 2.39 (t, J=7.4 Hz, H₇), 1.80-1.48 (m, 4 H, H₅, H₆), 1.19 (d, J=5.97 Hz, 3 H, H₁), 0.90 (t, J=8.55 Hz, 2 H, SEM), -0.02 (s, 9 H, SEM); IR (CH₂Cl₂) 3400-2500, 3050, 2975, 2900, 1713 cm⁻¹.
To a solution of 173 (760 mg, 2.5 mmol) in CH₂Cl₂ (12 mL) was added pTSOH (14 mg, 3 mol%). This mixture was stirred at 25°C for 3h, diluted with CH₂Cl₂ (20 mL), extracted with 1/3 saturated NaHCO₃ (1 x 10 mL). The aqueous extract was washed with CH₂Cl₂ (2 x 20 mL) and the combined organic extracts were filtered through a cotton plug and concentrated in vacuo to leave 617 mg (81%) of a dark green oil. In practice this material was used without further purification. Analytically pure 174 was obtained by preparative layer chromatography (SiO₂, .25 mm, Et₂O (100%), Rᵣ .30): [α]_{D}^{21} - 28.1° (C = 1.05, CH₂Cl₂); NMR (⁺H, 250 MHz, CDCl₃) δ 5.71 (m, 2 H, -OCH₂O-), 5.30-5.40 (m, 1 H, H₅), 4.87 (quintet, J=7 Hz, 1 H, H₇), 3.70-3.35 (m, 4 H, H₆, -OH, SEM), 2.38-2.65 (m, 2 H, H₂), 2.05-1.75 (m, 4 H, H₃, H₄), 1.23 (d, J=7 Hz, 3 H, H₈), 0.92 (t, 8 Hz, 2 H, SEM), 0.0 (s, 9 H, SEM); IR (CH₂Cl₂) 3680, 3580, 3400, 2960, 2890, 1735 cm⁻¹; mass spectrum m/e 289 (M-15); Anal. Calcd for C₁₄H₂₈SiO₅: C, 55.23; H, 9.27. Found: C, 54.99; H, 9.08.
Hydroxylactone 164 was prepared (95%) by an analogous procedure for that described for the preparation of 174 from 173: Rp .30, Et2O (100%); [α]21°D - 41.01° (C = 4.93, CH2Cl2); NMR (1H, 250 MHz, CDCl3) δ 4.70 (m, 2 H, -OCH2O-), 4.31-4.20 (m, 1 H, H5), 4.05-3.95 (m, 1 H, H7), 3.62-3.55 (m, 2 H, SEM), 3.41-3.36 (m, 1 H, H6), 2.75-2.34 (m, 3 H, H2, -OH), 2.13-1.60 (m, 4 H, H3, H4), 1.23 (d, J=7 Hz, 3 H, H1), 0.95-0.85 (m, 2 H, SEM), -.05 (s, 9 H, SEM); IR (CH2Cl2) 3700-3500, 3040, 2960, 1730 cm-1; mass spectrum m/e 289 (M-15).
To a solution of 174 (617 mg, 2.03 mmol) in pyridine (5 mL) was added triethylsilyl chloride (TES-Cl), (612 mg, 4.06 mmol) which was maintained at 25° under an atmosphere of nitrogen for 2h. This mixture was diluted with CH₂Cl₂ (30 mL) and extracted with H₂O (20 mL). After the resulting emulsion separated (ca 10 min.) the phases were separated and the aqueous phase washed with CH₂Cl₂ (2 x 30 mL). The combined organic extracts were filtered through a plug of cotton and concentrated in vacuo. The resulting green oil was concentrated from n-heptane (2 x 20 mL) to remove residual pyridine to leave 1.26 g of crude 175. This material was purified by flash chromatography (SiO₂, 40 x 190 mm, Et₂O, hexane, 2:1, Rf .55) to afford 630 mg (58% from 116) of pure 175: [α]₂¹ D + 9.7° (C = 1.52, CH₂Cl₂); NMR H, 250 MHz, CDCl₃) δ 5.70 (A of AB, J=7 Hz, 1 H, -OCH₂O-), 5.61 (B of AB, J=7 Hz), 5.41-5.32 (m, 1 H, H₅), 4.85-4.73 (m, 1 H, H₇), 4.61-4.52 (m, 3 H, H₆, SEM), 2.61-2.30 (m, 2 H, H₂), 2.00-2.59 (m, 4 H, H₃, H₄), 1.23 (d, J=7 Hz, 3 H, H₈), 1.00-0.05 (m, 11 H, TES, SEM), 0.70-0.51 (m, 6 H, TES), -0.1 (s, 9 H, SEM); IR (CH₂Cl₂) 2960, 2880, 1735 cm⁻¹; mass spectrum m/e 403 (M-15).
Diprotected lactone 165 was prepared (95%) by a procedure analogous to that described for the preparation of 175 from 174: $R_f$ .45 (Et$_2$O, 100%). $[\alpha]^2_{D}^{1} + 26.4^\circ$ (C = .44, CH$_2$Cl$_2$), NMR (1H, 250, CDCl$_3$) $\delta$ 4.69-4.72 (m, 2 H, -OCH$_2$O-), 4.45-4.35 (m, 1 H, H$_5$), 3.87-3.49 (m, 4 H, H$_6$, H$_7$, SEM), 2.62-2.30 (m, 2 H, H$_2$), 2.00-1.75 (m, 4 H, H$_3$, H$_4$), 1.15 (d, J=7 Hz, 3 H, H$_1$), 1.00-.90 (m, 11 H, SEM, TES), 0.70-0.59 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH$_2$Cl$_2$) 3050, 2960, 2880, 1730, cm$^{-1}$; mass spectrum m/e 361 (M-57); Anal. Calcd for C$_{20}$H$_{42}$Si$_2$O$_5$: C, 57.37; H, 10.11. Found: C, 57.64; H, 10.37.
To solution of 175 (418 mg, 1.00 mmol) in THF (4 mL) at -78°C under an atmosphere of N₂ was added LDA (2.0 mmol, 0.65 M in THF prepared and titrated immediately before use). This mixture was maintained at -78°C for 10 min then warmed to -20°C for 1h. The resulting pale yellow solution was recooled to -78°C and a solution of 2,2'-dipyridyldisulfide (DPDS) (440 mg, 2.0 mmol) in THF (4 mL), precooled to -78°C, was added rapidly in one portion. This mixture was maintained at -78°C for 1h, quenched with 1 ml of sat. NH₄Cl⁻, warmed to ambient temperature, diluted with CH₂Cl₂ (10 mL) and washed with water (10 mL). The aqueous phase was washed with CH₂Cl₂ (2 x 10 mL) and the combined organic extracts filtered through a cotton plug and concentrated in vacuo to leave 970 mg of a yellow oil which consisted of ca. 80% 176 as a mixture of diastereomers and 20% of 175. This material was used without purification.
Lactone 166 was prepared by a procedure analogous to that described for the preparation of 176 from 175, to afford 30% of 166 and 60% of recovered 165. These materials were separated by flash chromatography (SiO₂, Et₂O, hexane, 2:1, Rf 0.8 (sulfide diastereomers), Rf 0.7 (165).
To a cold (0°C) solution of crude 176 (1.00 mmol, theory) in CH$_2$Cl$_2$ (6 mL) was added a solution of MCPBA (88% titrated) (396 mg, 2.0 mmol) in CH$_2$Cl$_2$ (6 mL). This mixture was maintained at 0°C for 1h, diluted with CH$_2$Cl$_2$ (20 mL) and extracted with 1/3 saturated NaHCO$_3$ (10 mL x 2). The combined organic extracts were filtered through cotton, concentrated in vacuo (905 mg) and purified by flash chromatography (SiO$_2$, 30x200 mm, Et$_2$O, (100%), R$_f$ .40) to afford 340 mg of the corresponding diastereomeric sulfoxides and 31 mg of unsubstituted lactone 175. Data for diastereomeric sulfoxides: NMR (1H, 250 MHz, CDCl$_3$) δ 8.65-8.55 (m, 1 H, α-py), 8.00-7.90 (m, 2 H, β-py), 7.40-7.30 (m, 1 H, γ-py), 4.80-4.70, 2 H, SEM, appears as doubled AB pattern), 4.55-4.20 (m, 1 H, H$_5$), 4.25-4.18 (m, 1 H), 3.80-3.70 (m, 1 H), 3.65-3.40 (m, 3 H), 2.8-1.3 (m, 4 H, H$_3$, H$_4$), 1.28-1.18 (m, 3 H, H$_8$), 1.00-1.85 (m, 11 H, SEM, TES), 0.70-0.55 (m, 6 H, TES), 0.01-0.01 (m, 9 H, SEM).

A solution of this sulfoxide material (335 mg, 0.62 mmol) in dry toluene (5 mL) was heated to reflux for 2 h and the
solvent concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂, 30x200 mm, Et₂O (100%), Rf .80) to give 228 mg (89%, 75% from 173) of pure 177: [α] D
21
64.61° (C = 1.17, CH₂Cl₂); NMR (1H, 250 MHz, CDCl₃) δ 6.80-
6.70 (m, 1 H, H₃), 5.97 (bd, J=10 Hz, 1 H, H₂), 4.71 (A of AB,
J=7 Hz, 1 H, -OCH₂O-), 4.65 (B of AB, J=7 Hz, 1 H, -OCH₂O-),
4.52-4.45 (m, 1 H, H₅), 4.83 (quintet, J=6 Hz, 1 H, H₇), 4.73-
4.67 (m, 1 H, H₆), 4.58 (t, J=9 Hz, 2 H, SEM), 2.50-2.40 (m,
2 H, H₄), 1.24 (d, J=6 Hz, 3 H, H₈), 1.00-0.85 (m, 11 H, TES,
SEM), 1.75-1.60 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH₂Cl₂)
2970, 2880, 1720 cm⁻¹; UV (EtOH) 205 nm (ε = 4,100); mass spectrum
m/e 401 (M-15); Anal. Calcd for C₂₀H₄₀Si₂O₅: C, 57.65; H, 9.67.
Found: C, 56.95; H, 10.21.
Enone 167 was prepared (77%) by a procedure analogous to that described for the preparation of 177 from 176.

167: R_f 0.67, Et_2O (100%); [α]_D^{21} + 67.8° (C = 0.45, CH_2Cl_2);
NMR (1H, 250 MHz, CDC_3) δ 6.91-6.83 (m, 1H, H_3), 5.96 (dd, J=10 Hz, 3 Hz, 1H, H_2), 4.71-4.69 (m, 2H, -OCH_2O-), 4.60-4.50 (m, 1H, H_5), 3.97-3.91 (m, 1H, H_6), 3.80-3.50 (m, 3H, H_7, SEM), 2.80-2.65 (m, 1H, H_4a), 2.37-2.20 (m, 1H, H_4b), 1.15 (d, J=7 Hz, 3H, H_8), 1.00-0.87 (m, 11H, TES, SEM), 0.70-0.60 (m, 6H, TES), 0.0 (s, 9H, SEM); IR (CH_2Cl_2) 3050, 2960, 2880, 1720 cm^{-1}; UV (EtOH) 208 nm (ε = 4,200); mass spectrum m/e 359 (M-57).
To a solution of 177 (23 mg, 0.05 mmol) in THF (0.2 mL) at 0°C was added a solution of KtOBu (7.8 mg, 0.07 mmol) in THF (0.5 mL) which was maintained at 0°C, under N₂ for 45 min. To this yellow solution was added pivaloyl chloride (8.4 mg, 0.70 mmol), the resulting mixture maintained at 0°C under N₂ for 30 min and filtered through a bed of Florisil® under an atmosphere of N₂. The filter cake was washed with Et₂O (100%) (3 x 10 mL) and concentrated in vacuo to give 27 mg (93%) of 168. This material was used without further purification: 

\[ [\alpha]_{D}^{21} + 53.7^\circ \quad (C = 0.8, \text{CH}_2\text{Cl}_2) \]; NMR \( ^1\text{H}, 250 \text{ MHz, CDCl}_3 \)

δ 7.52 (dd, J=15 Hz, 11 Hz, 1 H, H₄), 6.73 (t, J=11 Hz, 1 H, H₃), 6.22 (dd, J=15 Hz, 6 Hz, 1 H, H₅), 5.61 (d, J=11 Hz, 1 H, H₂), 4.70 (s, 2 H, -OCH₂O-), 4.32 (t, J=6 Hz, 1 H, H₆), 3.72 (dq, J=6 Hz, 1 H, H₇), 3.60-3.50 (m, 2 H, SEM), 1.23 (s, 9 H, t-Bu), 1.08 (d, J=6 Hz, 3 H, H₈), 0.90-0.85 (m, 11 H, TES, SEM), 0.70-0.65 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH₂Cl₂) 2950, 2880, 1795, 1725, 1635, 1590 cm⁻¹; mass spectrum m/e 428 (M-72).
194 (diene acid): NMR $^1$H, 250 MHz, CDCl$_3$ $\delta$ 7.55 (dd, $J$=16 Hz, 10 Hz, 1 H, H$_4$), 6.69 (t, $J$=10 Hz, 1 H, H$_3$), 6.15 (dd, $J$=16 Hz, 6 Hz, 1 H, H$_5$), 5.66 (d, $J$=10 Hz, 1 H, H$_2$), 4.70 (s, 2 H, -OCH$_2$O-), 4.32 (t, $J$=6 Hz, 1 H, H$_6$), 3.72 (dq, $J$=6 Hz, 1 H, H$_7$), 3.65-3.58 (m, 2 H, SEM), 1.08 (d, $J$=6 Hz, 3 H, H$_8$), 1.00-0.8 (m, 11 H, SEM, TES), 0.68-0.50 (m, 6 H, TES), 0.0 (s, 9 H, SEM); UV (EtOH 262 nm ($\epsilon$ = 12,800); mass spectrum m/e 372 (M-44); Anal. Calcd for C$_{20}$H$_{40}$O$_5$Si$_2$; C, 57.65; H, 9.67. Found: C, 57.80; H, 9.41.
Mixed anhydride was prepared by the identical procedure described for the conversion of 177 to 168 (95%).
A solution of 182 (46 mg, 0.186 mmol) in CCl₄ (0.37 mL), CH₃CN (0.37 mL) and H₂O (0.56 mL) containing NaIO₄ (137 mg, 0.65 mmol) and RuCl₃ (1 mg, 2 mol%) was stirred vigorously at 25°C for 4 h, diluted with CH₂Cl₂ (10 mL) and the phases separated. The organic phase was filtered through a cotton plug and concentrated to afford 37 mg (76%) of crude 178: [α]D²¹ + 14.4° (c 0.84, CHCl₃); NMR (1H 250 MHz, CDCl₃) δ 3.74 (t, J=6 Hz, 2 H, H₂a), 3.53 (s, 1 H, H₂b), 1.98 (dt, J=14 Hz, 6 Hz, 1 H, H₄a), 1.74 (dt, J=14 Hz, 6 Hz, 1 H, H₄b); IR (film) 3600-2500, 2946, 2928, 2858, 1752, 1732 cm⁻¹.
To a solution of 178 (138 mg, 0.531 mmol) in CH₂Cl₂ (1.5 mL) was added triethylamine (124 mg, 1.22 mmol) followed by pivaloyl chloride (74 mg, 0.612 mmol). The resulting mixture was maintained, under a N₂ atmosphere, at 25°C for 1.5 h and verrucarol 8 (103 mg, 0.387 mmol) was added as a solution in CH₂Cl₂ (3 mL) containing 4-pyrrolidinopyrididine (6 mg, 0.04 mmol). This mixture was kept at 25°C under N₂ for 2 h, concentrated in vacuo and purified by flash chromatography (SiO₂, 30 x 160 mm, Et₂O, CH₂Cl₂ 1:1, Rf 0.20) to afford 116 mg (59%) of pure 184, in addition 17 mg of verrucarol (Rf 0.1), 17 mg of diester (Rf 0.6) and 12 mg of C(4) monoester (Rf 0.4) were recovered. Data for 184: mp 93-94°C; [α]D²¹ -29.8° (C = 1.29, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 5.45-5.35 (m, 1 H, H₁₀), 4.50-4.40 (m, 1 H, H₄), 4.22 (A of AB, J=13 Hz, 1 H, H₁₅a), 4.00 (B of AB, J=13 Hz, 1 H, H₁₅b), 3.81 (d, J=5 Hz, 1 H, H₂), 3.69 (t, J=5 Hz, 2 H, H₅), 3.56 (bd, J=5 Hz, 1 H, H₁₁), 3.48 (s, 1 H, H₂), 3.10 (d, J=4 Hz, 1 H,
H_{13a}, 2.78 (d, J=4 Hz, 1 H, H_{13b}), 2.57 (dd, J=16 Hz, 8 Hz, 1 H, H_{3a}), 2.02-1.72 (m, 7 H, H_{4}, H_{7}, H_{8}, H_{3b}, 1.70 (s, 3 H, H_{16}), 1.38 (s, 3 H, H_{12}), 1.20 (d, J=7 Hz, H_{14}), 0.85 (s, 9 H, TBDMS), 0.81 (s, 3 H, H_{14}), 0.03 (s, 6 H, TBDMS); IR (CH_{2}Cl_{2}) 3580, 2940, 2860, 1750 cm^{-1}; mass spectrum m/e 508 (M^+); Anal. Calcd for C_{27}H_{44}SiO_{4}: C, 63.74; H, 8.72. Found: C, 63.53; H, 8.76.
A solution of 184 (5 mg, 0.009 mmol, concentrated from toluene 2 x before use) and 168 (9 mg, 0.02 mmol) in a DME, THF mixture (1:1, 0.5 mL) was added to a suspension of NaH (1.1 mg, 0.047 mmol) in DME (0.2 mL) at -20°C under an atmosphere of N₂. This mixture was maintained at -20°C under N₂ for 30 min, warmed to 0°C for 12 hr, neutralized with AcOH, THF, H₂O (3:1:1) (0.02mL), and concentrated in vacuo from heptane yielding crude 189 which was purified by prep plate chromatography (SiO₂, 0.25 mm, Et₂O, hexane, 2:1, Rf 0.45) to afford 0.9 mg (ca. 10%) of pure 189 along with 1.1 mg (20%) of 190 and 1 mg (20%) of recovered 184 and unreclaimed verrucarol 8. 189: [α]_D^{21} + 32.8° (C = 1.0, CH₂Cl₂); NMR (¹H, 250 MHz, CDCl₃) δ 7.50 (dd, J=15 Hz, 11 Hz, 1 H, H₈'), 6.57 (t, J=11 Hz, 1 H, H₉'), 6.05 (dd, J=15 Hz, 7 Hz, 1 H, H₇'), 5.65 (d, J=11 Hz, 1 H, H₁₀'), 5.75-5.68 (m, 1 H, H₄), 5.45-5.40 (m, 1 H, H₁₀), 4.75-4.68 (m, 2 H, SEM), 4.31-4.13 (m, 3 H, H₆'), H 15), 3.81 (d, J=5Hz, 1 H, H₂), 3.71-3.55 (m, 6 H, H₁₃', H₁₁',
H₅', SEM), 3.50 (s, 1 H, H₂'), 3.13 (d, J=4 Hz, 1 H, H₁₃a'), 2.80 (d, J=4 Hz, 1 H, H₁₃b'), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H₂), 2.08-1.70 (m, 7 H, H₄', H₇, H₈, H₃₈), 1.70 (bs, 3 H, H₁₆), 1.37 (s, 3 H, H₁₂'), 1.09 (d, J=7 Hz, 3 H, H₁₄'), 1.00-0.85 (m, 20 H, SEM, TES, tBu), 0.81 (s, 3 H, H₁₄), 0.59 (q, J=8Hz, 6 H, TES), 0.05-0.00 (m, 18 H, TBDMS, SEM); IR (CH₂Cl₂) 2970, 2880, 1750, 1710, 1640, 1600 cm⁻¹, UV (EtOH) 262 nm (ε = 25,400), mass spectrum m/e 804 (M-Me₃SiCHCH₂), HRMS Calcd for C₄₇H₈₂Si₃O₁₁ m/e 906.516, Found m/e 906.511.

¹⁹₀: NMR (¹H, 250 MHz, CDCl₃) δ 7.57 (dd, J=15 Hz, 11 Hz, H₈'), 6.60 (t, J=11 Hz, 1 H, H₁₀'), 6.20-6.02 (m, 2 H, H₄, H₇'), 5.69 (d, J=11 Hz, H₁₀'), 5.55-5.45 (m, 1 H, H₁₀'), 4.71 (s, 2 H, SEM), 4.30 (t, J=6 Hz, 1 H, H₆'), 4.00 (d, J=5 Hz, 1 H, H₂), 3.81-3.05 (m, 9 H, H₂, H₁₁, H₁₅, H₅', H₁₃', SEM), 3.13 (d, J=4 Hz, 1 H, H₁₃a'), 2.95 (bt, J=6 Hz, 1 H, -OH), 2.79 (d, J=4 Hz, 1 H, H₁₃b'), 2.57 (dd, J=16 Hz, 8 Hz, 1 H, H₂), 2.18-1.95 (m, 7 H, H₄', H₇, H₈, H₃₈), 1.70 (bs, 3 H, H₁₆), 1.10 (d, J=7 Hz, 3 H, H₁₄'), 0.98-0.89 (m, 11 H, SEM, TES), 0.81 (s, 3 H, H₁₄), 0.61 (q, J=8 Hz, 6 H, TES), 0.00 (s, 9 H, SEM).

To a solution of acid ¹⁷₈ (3.5 mg, 0.013 mmol) in CH₂Cl₂ (0.05 mL) was added triethylamine (4.5 mg, 0.045 mmol) followed by pivaloyl chloride (2 mg, 0.015 mmol). The resulting mixture was maintained, under N₂, at 25°C for 1 h and ¹⁹₀ (2 mg, 0.003 mmol) was added as a solution in CH₂Cl₂ (0.2 mL) containing 0.2 mg of 4-pyrrolidinopyridine.
22 h this mixture was concentrated in vacuo and purified by prep plate chromatography (SiO₂, 0.25 mm, Et₂O, hexane, 2:1, Rf .55) to afford 1.9 mg (70%) of pure 189.
To a solution of 184 (32 mg, 0.063 mmol) in CH₂Cl₂ (0.8 mL) containing 4-pyrrolidinopyridine (0.52 mg, 5 mol %) was added a solution of 168 (35 mg, 0.07 mmol) in CH₂Cl₂ (1.0 mL) and maintained at 25°C under N₂. After 7 d the crude reaction mixture was concentrated in vacuo and purified by prep plate chromatography (SiO₂, 0.25 mm, Et₂O, hexane, 2:1, Rf 0.40) to afford 10 mg (17%) of a 3:1 mixture of 189: 192, respectively. These isomers could be separated by prep plate chromatography (SiO₂, 0.25 mm, EtOAc, hexane, 5:1, 5 developments, 189 Rf 0.55; 192 Rf 0.48) to afford 4 mg (7%) of 189 and 1 mg (1%) of 192. Also isolated from the first chromatography was 18 mg (50%) of 184. Data for 192: NMR (¹H, 250 MHz, CDCl₃) δ 7.28 (dd, J=15 Hz, 11 Hz), 6.40 (dd, J=15 Hz, 11 Hz, 1 H, H₉'), 6.20 (dd, J=15 Hz, 5 Hz, 1 H, H₈'), 5.88 (J=15 Hz, 1 H, H₁₀'), 5.75-5.65 (m, 1 H, H₄), 5.45-5.40 (m, 1 H, H₁₀), 4.70 (s, 2 H, SEM), 4.32 (bt, J=5 Hz, 1 H, H₆'), 4.28 (A of AB, J=12 Hz, 1 H, H₁₅a'), 4.18 (B of AB, J=12 Hz, 1 H, H₁₅b'),
3.83 (d, J=5 Hz, 1 H, H_2'), 3.75-3.65 (m, 6 H, H_{11'}, H_5', H_{13'}), SEM) 3.50 (s, 1 H, H_2'), 3.33 (d, J=4 Hz, 1 H, H_{13a}), 2.81 (d, J=4 Hz, 1 H, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H_{3a}), 2.10-1.70 (m, 7 H, H_{4'}, H_7', H_8', H_{3b}), 1.70 (bs, 3 H, H_{16}), 1.38 (s, 3 H, H_{12'}), 1.05 (d, J=6 Hz, 3 H, H_{14'}), 1.00-0.85 (m, 20 H, SEM, TES, TBDMS), 0.82 (s, 3 H, H_{14}), 0.60 (q, J=8 Hz, 6 H, TES), 0.05-0.00 (m, 18 H, TBDMS, SEM).
A solution of 189 (8 mg, 0.008 mmol) in a mixture of AcOH, THF, \(H_2O\) (3:1:1) (0.40 mL) was stirred at 25°C for 6 h and concentrated in vacuo from n-heptane (2 x 10 mL) to afford crude 195. This material was purified by prep plate chromatography (\(SiO_2\), 0.25 mm, EtOAc (100%), \(R_f\) 0.4) to afford 5.3 mg (88%) of pure 195: \([\alpha]^{21}_D + 32.4^\circ\) (C = 0.53, \(CH_2Cl_2\)); NMR (\(^1H\), 250 MHz, CDCl\(_3\)) \(\delta\) 7.62 (dd, \(J=15\ Hz\), 11 Hz, 1 H, \(H_8'\)), 6.60 (t, \(J=11\ Hz\), 1 H, \(H_9'\)), 6.11-5.95 (m, 2 H, \(H_7', H_4\)), 5.68 (d, \(J=11\ Hz\), 1 H, \(H_{10}'\)), 5.50-5.40 (m, 1 H, \(H_{10}\)), 4.72 (s, 2 H, SEM), 4.32 (A of AB, \(J=13\ Hz\), \(H_{15a}\)), 4.18-4.09 (m, 2 H), 3.84 (d, \(J=4\ Hz\), 1 H, \(H_2\)), 4.80-4.40 (m, 7 H), 3.58 (s, 1 H, \(H_2'\)), 3.15 (d, \(J=4\ Hz\), 1 H, \(H_{13a}\)), 2.82 (d, \(J=4\ Hz\), 1 H, \(H_{13b}\)), 2.55 (dd, \(J=16\ Hz\), 8 Hz, 1 H, \(H_3d\)) 2.18-1.80 (m, 7 H, \(H_4', H_7, H_8, H_3\)), 1.70 (bs, 3 H, \(H_{10}\)), 1.40 (s, 3 H, \(H_{12}'\)), 1.16 (d, \(J=7\ Hz\), 3 H, \(H_{14}'\)), 0.91 (t, \(J=8\ Hz\), 2 H, SEM), 0.61 (s, 3 H, \(H_{14}\)), 0.0 (s, 9 H, SEM); IR (\(CH_2Cl_2\)) 3680, 3600-3300, 2970, 2890, 1735, 1720 (shoulder), 1680, 1600 cm\(^{-1}\); UV (EtOH)
262 nm ($\epsilon = 19,500$); mass spectrum (sample did not volatilize).
REFERENCES
1. Reviews:


10. For leading references, see: (a) Gutzwiller, J.; Mauli, R.; Sigg, H.P.; Tamm, Ch. Helv. Chim. Acta 1964, 47, 2234;


43. Fraser-Reid and coworkers\(^\text{28}\) also synthesized the C(4) dienoic portion of the trichoverroid A series starting from triacetoxyl-galactal by a route completely analogous to that outlined in Scheme V, thus confirming the absolute stereochemistry of the A series as C(6')\((S)\); C(13')\((S)\) and the B series as C(6')\((R)\); C(13')\((R)\).

44. In response to this problem, Still\(^\text{45}\) has developed methodology which utilizes trifluoromethylphosphonoacetic ester in the Horner-Emmons reaction. With this reagent, very high (Z:E) ratios are obtained with simple \(\alpha,\beta\) unsaturated aldehydes. This method, however, has not yet been applied to the macrocyclization of the roridin precursors.


46. A second method for the preparation of the roridins and baccharins which is under active consideration in our laboratory involves the acylation of 155 with 209. Un-
masking the C(15) acid fragment followed by lactonization and deprotection would yield the natural product.


51. Levene, P.H.; Raymond, A.C. J. Biol. Chem. 1934, 102, 317.


53. Among those reagents tried were NaBH₄, EtOH; LiAlH₄, Et₂O; NaCNBH₃, CH₃CN, pH 3; 5% Ru on carbon, H₂, H₂O; Na₂SO₄, (1:1) dioxane, H₂O (de Vries, J.G.; van Bergens, T.J.; Kellogg, R.M. Synthesis, 1977, 246) and 2.5% Na(Hg), isopropanol. Unreacted starting material was recovered from the NaBH₄, LiAlH₄, and NaCNBH₃ reductions. Ru/C, H₂ and 2.5% Na(Hg) reduced the hemiacetal but also removed the benzyl protecting group. Finally, sodium dithionite afforded a mixture of five unidentified products.


58. It should be noted at this point that Still's recently reported synthesis of roridin E(18) and baccharin B5(21) utilized D-xylene as a starting material. The initial stages of Still's sequence is virtually identical to our synthesis of 89 described in Scheme VII.


62. (a) Hasen, A.J.; Kimland, B.; Engell, C.R. Acta. Chem. Scand. 1973, 27, 2107; (b) A rotation of $[\alpha]_D^20 + 13.9^\circ$ (C 4.5, CHCl$_3$) was reported for (S)-113.

63. (a) Representative literature results for the enantioselective reduction of methyl propargyl ketones are summarized below.

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\[ \begin{array}{ccc}
  R & \text{Reagent} & \text{Optical Purity (ee)} \\
  \text{n-C}_4\text{H}_9 & \text{BINAL-H}^{60d} & 84\% \\
  \text{H} & \text{LiAlH}_4, \text{N-methylephedrine}^{60e} & 79\% \\
  \text{Ph} & \text{Midland Reagent}^{60f} & 72\% \\
  \text{tert-Butyl} & \text{Midland Reagent}^{60f} & 73\% 
\end{array} \]
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(b) Optically active (R)-2,2'-binapthol was purchased from Aldrich Chemical Co., [α]$_D^{20}$ + 35.8° (C .87,THF), lit. [α]$_D^{20}$ + 34.3 (C 1.0 THF)$^{63c}$; (c) Kyba, E.P.; Gokel, G.W.; de Jong, F.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Kaplan, L.; Soga, G.D.Y.; Cram, D.J. J. Org. Chem. 1977, 42, 4173.

64. The syntheses of 121 (Scheme XIX) and 128 (Scheme XX) have been published in preliminary form: Roush, W.R.; Spada, A.P. Tetrahedron Lett. 1982, 23, 3773.


67. Attempts to increase the optical purity of (Z)-allylic alcohol (+)-115 by the kinetic resolution/epoxidation protocol were not successful.$^{59b}$


69. Dr. William P. Jackson, personal communication.


73. (a) For a recent review of acylation methods see: Haslam, E. Tetrahedron 1980, 36, 2409; (b) For a recent review of nucleophilic acylation catalysts see: Scriven, E.F.V. Chem. Soc. Rev. 1983, 12, 129.
74. We observed that it was important that intermediate 157 be chromatographed prior to the deprotection step, otherwise, a significant amount of decylation occurred.

75. A preliminary account of the studies discussed in Chapter 3 has been published: Roush, W.R.; Spada, A.P. *Tetrahedron Lett.* 1983, 24, 3693.

76. For example, the trichothecene nucleus rearranges to the apotrichothecene skeleton in 0.1N HCl. We suspect that

![Diagram](image)

a similar rearrangement would also occur with weak Lewis acids.


82. (a) Pirkle, W.H.; Haske, J.R. *J. Org. Chem.* 1977, 42, 1839; (b) (S)-(+)−Napthylethylisocyanate was purchased from Norse Laboratories; (c) The author wishes to thank Jotham W. Coe for his assistance in the resolution of 106.


85. In addition we found that this oxidation was sensitive to scale, with best results realized in small scale reactions (50 mg of 182 appears to be an optimum scale). Marked decrease in yield were obtained in larger scale experiments (e.g. a 200 mg scale reaction afforded 178 in only 30% yield). Similar results were observed by Blizzard, who used KMnO₄, 18-crown-6, in benzene ("purple benzene") for this oxidation.41a

86. Acylation of verrucarol with glycidic acid 178 afforded 184 in only 14% yield.


88. Identical results were obtained from a reaction in which the NaH was used from a can freshly opened under a N₂ atmosphere.

89. The desired (Z,E)-isomer 189 was very difficult to separate from this isomeric impurity. Although 189 could be purified from this mixture by a sacrificial chromatographic procedure, the isomer was never obtained in pure form. As a consequence, this product has not been fully characterized.


