SYNTHESIS OF VERRUCARINS

by

TIMOTHY ALLEN BLIZZARD

B.S., University of Virginia
(1979)

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TIMOTHY ALLEN BLIZZARD

Submitted to the Department of Chemistry on March 12, 1984 in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

ABSTRACT

The development of methodology for the synthesis of the macrocyclic verrucarins from verrucarol is discussed. Syntheses of verrucarin J (3) and verrucarin B (4) as well as a number of unnatural isomers have been accomplished.

The synthesis of the acyclic portions of the verrucarins was examined first. These studies culminated in successful syntheses of acids 86 and racemic 103 which correspond to the acyclic portions of verrucarins J (3) and A (5) respectively.

Acids 86 and 92 synthesized in the initial studies proved unsuited as intermediates in a synthesis of verrucarin J. Two alternative routes, however, in which verrol (11) served as an intermediate, ultimately led to successful completion of the verrucarin J synthesis. In addition, syntheses of unnatural isomers (E,E,E)-verrucarin 158 (E,Z,E)-verrucarin 159, (Z,E,Z)-verrucarin 19 and (Z,E,E)-verrucarin 165 were accomplished. The synthesis of isomer 19 is especially noteworthy as this isomer possesses the structure initially assigned to verrucarin J. Aspects of the chemical, physical, and biological properties of these verrucarin J isomers are discussed.

A synthesis of verrucarin B (4) by using improved methodology is also discussed. This synthesis proceeds from verrucarol via the differentially protected triester 173. Two isomers of verrucarin B, (E,E,)-isomer 183 and (Z,E)-isomer 184 were also encountered in the course of this work.

Thesis Supervisor: Dr. William R. Roush

Title: Roger and Georges Firmenich Career Development Associate Professor of Natural Products Chemistry
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parents, John and Betty Blizzard, for their love and support
which has been so important to me throughout my life. I could
not have done this without them.
FORWARD

This thesis describes research which was performed from September, 1981 until January, 1984. Portions of this work have been published (see references 37f, 51a, and 51b). Research performed from January, 1980 until August, 1981 was directed initially towards the synthesis of verrucarol by an intramolecular Diels-Alder approach and later towards the synthesis of antibiotic X-14766A. These studies are not discussed in this thesis.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BOP</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>
</tr>
<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>
</tr>
<tr>
<td>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>HMPA</td>
<td>hexamethyldiphosphorotriamide</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>4-PP</td>
<td>4-pyrrolidinopyridine</td>
</tr>
<tr>
<td>Sia</td>
<td>iso-amyl</td>
</tr>
<tr>
<td>TBMDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</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>TsCl</td>
<td>p-toluenesulfonylchloride</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-toluenesulfonic acid</td>
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To my parents
CHAPTER I

INTRODUCTION
The verrucarins\textsuperscript{1} are members of the large family of epoxytrichotheceane mycotoxins.\textsuperscript{2} This family of over 50 fungal metabolites is characterized by the presence of the trichotheceane ring system. Most of the naturally occurring trichotheceanes contain a 12,13 epoxide and a 9,10 double bond as well as varying degrees of oxygenation at C(3), C(4), C(7), C(8), and C(15). The trichotheceanes can be divided into two major subgroups: the non-macrocyclic trichotheceanes\textsuperscript{3} (Table I), as exemplified by anguidine (1) and verrucarol (2), and the macrocyclic trichotheceanes.\textsuperscript{4} The macrocyclic epoxytrichotheceanes include the verrucarins (Table II), e.g. verrucarin J (3) and verrucarin B (4), as well as the roridins (Table III) and baccharins (Table IV), which are a group of plant-modified roridins.\textsuperscript{4e,f} Several additional macrocycles have been isolated (Table V) which do not fit into either category of macrocycles. Very recently, a third major group of trichotheceanes, known as the
trichoverroids, has been isolated (Table VI). The trichoverroids are thought to be intermediates in the biosynthesis of the verrucarins and roridins from verrucarol. Supporting evidence for this hypothesis has been provided by Jarvis and coworkers, who fed samples of natural trichoverrins A and B to M. verrucaria. Each of these experiments afforded approximately 13% of verrucarin A, 5% of verrucarin B, 2-5% each of verrucarin J, roridin A and isororidin E, along with 50% of unchanged trichoverrins. These results strongly suggest that the trichoverrins are, in fact, precursors of the verrucarins and roridins. Thus, one possible sequence by which verrucarol could be converted to the macrocyclic trichothecenes is outlined in Scheme I. This general sequence reasonably accounts for the biogenesis of the macrocycles, but it should be noted that several individual pathways may occur. For example, the recent isolation of trichoverrol B (10) and verrol (11) suggests that there are several different routes from the simple trichothecenes to the trichoverrins. The mechanism by which the macrocyclization occurs is not yet known, but it is interesting to speculate that an intermediate
Table I

Representative Non-Macro cyclic Trichothecenes

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4</th>
<th>R^5</th>
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<tr>
<td>Anguidine 1</td>
<td>OH</td>
<td>OAc</td>
<td>OAc</td>
<td>H</td>
<td>H</td>
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<tr>
<td>Verrucarol 2</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>T-2 Toxin</td>
<td>OH</td>
<td>OAc</td>
<td>OAc</td>
<td>O^Val</td>
<td>H</td>
</tr>
<tr>
<td>Calonectrin</td>
<td>OAc</td>
<td>H</td>
<td>OAc</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Trichodermol</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Trichothe colone</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td></td>
<td>=O</td>
</tr>
<tr>
<td>Trichodermin</td>
<td>H</td>
<td>OAc</td>
<td>H</td>
<td>H</td>
<td>H</td>
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Table II
Representative Verrucarins

<table>
<thead>
<tr>
<th>Compound</th>
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<tr>
<td>Verrucarin J (3)</td>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td>Verrucarin B (4)</td>
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<td>Verrucarin A (5)</td>
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<td>2'-dehydroverrucarin A (6)</td>
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Representative Roridins

<table>
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<tr>
<td>Roridin A</td>
<td><img src="image" alt="Roridin A" /></td>
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<tr>
<td>Roridin D</td>
<td><img src="image" alt="Roridin D" /></td>
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<tr>
<td>Roridin E (7)</td>
<td><img src="image" alt="Roridin E" /></td>
</tr>
<tr>
<td>Roridin H</td>
<td><img src="image" alt="Roridin H" /></td>
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</table>
Table IV

Representative Baccharins

A

B

Compound

Baccharin B5 (8)  

Baccharin B9

Baccharinol B3

Structure

A, R=

A, R=

B, R=
Table V

Other Macrocycles

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
</tr>
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<tr>
<td>Vertisporin</td>
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<tr>
<td>Satratoxin F</td>
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<tr>
<td>Satratoxin H</td>
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Table VI
Representative Trichoverroids

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
</tr>
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<tbody>
<tr>
<td>Trichoverrin B (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichoverrol B (10)</td>
<td></td>
<td>OH</td>
</tr>
<tr>
<td>Verrol (11)</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>Trichodermadiene (12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scheme I

 verrucarol (2)  \rightarrow  \text{trichoverrol B (10)}  \rightarrow  \text{trichoverrin B (9)}

 baccharin B5 (8)  \leftarrow  \text{roridin E (7)}  \leftarrow  \text{verrucar J (9)}

 other roridins  \downarrow  \text{other verrucarins}
related to trichodermadiene (12)\(^7\) may be involved.

A proposal by Tamm\(^8\) regarding the biosynthesis of verrucarinc acid 17 is outlined in Scheme II. It is known that mevalonic acid 13 is incorporated into the verrucarins.\(^1\)

![Scheme II](image)

One can readily imagine that mevalonic acid (13) could dehydrate to form anhydromevalonic acid 14 (e.g. verrucarin J, 3) which after epoxidation would produce the glycidic acid 15 ( verrucarin B, 4). This could possibly rearrange to form keto-acid 16 (2'-dehydroverrucarin A, 6) which might then be reduced to verrucarinc acid 17 ( verrucarin A, 5). As such, this proposal provides a reasonable mechanism for the incorporation of the mevalonic acid skeleton into each of the verrucarins. Although it is not known with certainty, it is probable that these transformations occur after the macrocyclization of the trichohertrins (recall the Jarvis experiment).

The first trichothecene to be isolated was glutinosin,\(^9a\) which was discovered during a search for antibiotics in 1946. Glutinosin was later shown\(^9b\) to be an approximately 4:1 mixture of verrucarins A and B. More than a dozen additional trichotheceenes were isolated during the following two decades. It
was not until 1964, however, that the structure of the tricho-
theticene nucleus was correctly assigned by an X-ray crystal
structure determination of trichodermol p-bromobenzoate. \(^\text{18}\)\(^\text{10}\)

Soon thereafter structures of many of the macrocyclic tricho-
theticenes, including verrucarins A, \(^\text{11}\) B, \(^\text{12}\) and J \(^\text{13}\) were assigned.
Tamm originally proposed structure \(^\text{19}\) for verrucarin J on the
basis of chemical and spectroscopic evidence. This structure
was later amended \(^\text{14}\) to the correct one, \(^\text{3}\). Finally, the

absolute stereochemistries of verrucarins \(^\text{A}\) \(^\text{15}\) and \(^\text{B}\) \(^\text{8}\) have been
determined by X-ray crystallography.

A considerable amount of attention has been devoted to the biological
properties of the epoxytrichothecene mycotoxins. \(^\text{16}\) The trichothecenes have
been implicated as the toxic agents responsible for cases of food poisoning of humans and livestock on almost every continent. These widespread incidents have been largely the consequence of ingestion of rice, corn, or other grains which have been contaminated with any of the numerous fungi which produce these toxins. In particular, the epoxytrichotheccenes are believed to be responsible for the toxic effect associated with alimentary toxic aleukia (ATA) and stachybotryotoxicosis as well as several other types of food poisoning. Contamination of cereal grains by trichotheccene producing fungi remains a major concern to this day and much current research is directed at finding a solution to this problem.

Another problem involving trichotheccene toxins that has received considerable attention recently is the hotly debated "yellow rain" controversy, which involves allegations of the use of crude epoxytrichotheccene formulations as chemical warfare agents.

In addition to their toxic effects on humans and animals, the trichotheccenes also possess a wide range of potentially useful biological properties, including antifungal, antibacterial, insecticidal, phytostatic, and/or cytostatic activity. At the molecular level the trichotheccenes are very specific inhibitors of eukaryotic protein synthesis, a property which has stimulated considerable interest in their use as antitumor agents. One member of the group, anguidine, which is readily available by fermentation, has been examined in phase I and II clinical trials against solid tumors. The results
of these studies, however, have been somewhat disappointing and it seems unlikely that anguidine, or any other simple trichothecone, will proceed to phase III clinical trials. Nonetheless, interest remains high in the macrocyclic trichothecones\textsuperscript{2a,4a} which possess promising activity in the in vivo P388 mouse leukemia assay system (Table VII).\textsuperscript{26,27} It is hoped that one of these compounds, or a derivative, will eventually prove useful as an anticancer drug.

Although some work has been done on structure-activity relationships of the macrocyclic trichothecones,\textsuperscript{27} most of this effort has concentrated on modification of the trichothecone nucleus. For example, Jarvis has shown that peracid oxidation of the 9,10-double bond of verrucarin A, which produces the $\beta$-epoxide, leads to a substantial increase in activity in the P388 assay.\textsuperscript{27} Additional examples which illustrate the effect of nuclear structure modifications are summarized in Table VII. By comparison relatively little is known about the effect of structural changes within the macrocyclic unit. Apparently the unsaturated ester is necessary since hydrogenation leads to a loss of activity.\textsuperscript{1} It also seems that the intact macrocycle is necessary for maximal biological potency. For example, trichoverrin B (9) is an order of magnitude
Table VIIa

Activities of Some Trichothecenes Against P388 Mouse Leukemia in vivo

<table>
<thead>
<tr>
<th>Compound</th>
<th>Optimum dose (mg/kg)</th>
<th>T/Cb</th>
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<tbody>
<tr>
<td>anguidine</td>
<td>1.6</td>
<td>150-219</td>
</tr>
<tr>
<td>verrucarin A</td>
<td>2</td>
<td>127</td>
</tr>
<tr>
<td>verrucarin B</td>
<td>5</td>
<td>142</td>
</tr>
<tr>
<td>verrucarin J</td>
<td>0.8</td>
<td>150</td>
</tr>
<tr>
<td>β-9,10-epoxyverrucarin A</td>
<td>8</td>
<td>210</td>
</tr>
<tr>
<td>α-9,10-epoxyverrucarin A</td>
<td>2.5</td>
<td>118</td>
</tr>
<tr>
<td>16-hydroxyverrucarin A</td>
<td>4</td>
<td>252</td>
</tr>
<tr>
<td>8-β-hydroxyverrucarin A</td>
<td>1.25</td>
<td>132</td>
</tr>
<tr>
<td>8-β-hydroxy-9,10-β-epoxyverrucarin A</td>
<td>20</td>
<td>321</td>
</tr>
<tr>
<td>16-hydroxy-9,10-β-epoxyverrucarin A</td>
<td>6</td>
<td>203</td>
</tr>
<tr>
<td>9,10-β-epoxyverrucarin J</td>
<td>8</td>
<td>172</td>
</tr>
<tr>
<td>8-β-hydroxyverrucarin J</td>
<td>1.25</td>
<td>181</td>
</tr>
<tr>
<td>roridin A</td>
<td>0.06</td>
<td>128</td>
</tr>
<tr>
<td>roridin D</td>
<td>12.5</td>
<td>131</td>
</tr>
<tr>
<td>9,10-β-epoxyroridin A</td>
<td>10</td>
<td>205</td>
</tr>
<tr>
<td>8-β-hydroxyroridin A</td>
<td>0.2</td>
<td>156</td>
</tr>
<tr>
<td>8-β-hydroxy-9,10-β-epoxyroridin A</td>
<td>20</td>
<td>321</td>
</tr>
<tr>
<td>baccharin B5</td>
<td>5</td>
<td>311</td>
</tr>
</tbody>
</table>

aData for anguidine is from reference 26, data for all other compounds is from reference 27; (b) T/C=(days test animals live/days control animals live x 100).
less active in the in vitro L1210 mouse leukemia assay than the corresponding macrocycle roridin E (7).\textsuperscript{4a, c}

There is clearly a need for more work on the biological consequences of structural variations within the macrocyclic portions of these compounds. One approach to this problem would be to chemically modify the known macrocycles. The scope of this approach, however, will probably be limited by the reactive nature of some of the functional groups present, thereby restricting the types of modifications that can be made. An alternative and more flexible approach would be to develop a general synthesis of the macrocycles starting from a readily available trichothecene such as anguidine.\textsuperscript{23, 28} It is towards this goal that the studies described in this thesis were directed.

The most convergent approach to the macrocyclic trichothecenes would involve the coupling of the intact side chain to the trichothecene nucleus. In this manner the number of transformations involving the trichothecene skeleton would be minimized. Obviously, then, the major chemical questions which would have to be addressed in the development of this strategy were how to synthesize the side chains and how to attach them to the trichothecene nucleus.

These questions had not yet attracted a great deal of attention when the studies outlined in this thesis were initiated. At that time, only two model studies by Tamm and co-workers had been published. The first of these, a synthesis of tetrahydroverrucarmin J (28), is outlined in Scheme III.\textsuperscript{14} Three points
Scheme III

Scheme details are not provided in the text.
about this synthesis should be noted. First, this work illustrated two examples of selective esterification of C(4)-OH of verrucarol (with acetyl chloride and the acyl imidazolide generated in situ from adipic acid derivative 23) leading, respectively, to 20 and 24. Second, it is noteworthy that the cyclization of the mixture of seco acids (E,Z)-27 afforded only the (E) isomer of 28. Both of these observations affected our original strategy for the synthesis of verrucarin J (3). Finally, it is also interesting to note that the esterification of acid (Z)-25 and verrucarol derivative 24 led to an (E,Z)-mixture of esters.29 As we will see the occurrence of olefin isomerization was to be a major problem in our synthetic efforts.

The second model study published prior to the initiation of our work was the synthesis of 3′-hydroxy-2′-deoxytetrahydroverrucarin A (33) (a mixture of diastereomers) outlined in Scheme IV.30 One interesting feature of this synthesis in comparison to the earlier synthesis of 28 is the final macrocyclization step. In this instance the final bond formed was the ester linkage between the C(4)-hydroxyl and the C(6")-carboxyl rather than the C(5\')-hydroxyl and the C(1")-carboxylic acid as in the synthesis of 28. It should be noted, however, that Tamm had originally planned to synthesize 33 by lactonization of 34. Unfortunately this intermediate was rather unstable and readily eliminated mevalonolactone (35) via a facile intramolecular acyl transfer reaction. Thus no attempt was made to macrolactonize 34 and the synthesis was completed instead via
Scheme IV

1) $\text{H}^+$, CH$_2$CH$_2$

2) Zn, AcOH, H$_2$O, THF

R = CH$_2$COC$_6$H$_5$
This observation, along with some of our results which will be discussed subsequently, leads us to speculate that the isolation of only (E)-28 from the cyclization of (E,Z)-27 may be a consequence of selective destruction of (Z)-27 (by loss of anhydromevalonolactone) rather than a failure to produce (Z)-28 owing to strain in the (Z)-macrocycle.

Shortly after the synthesis of 33 was published the first synthesis of a natural macrocyclic trichothecene, verrucarin A (5), was reported by Still. This synthesis, outlined in Scheme V, is noteworthy for several reasons. First, this is a relatively efficient synthesis, affording verrucarin A in 29% overall yield from anguidine-derived verrucanol. Also important is the selective acylation of the C(15)-hydroxyl group of verrucanol with acid 37. This was only the second selective esterification of C(15)-OH reported in the literature. Another significant observation was that the CDI esterification method used by Tamm in his synthesis of tetrahydroverrucarins 28 and 33 was not applicable to esterifications involving (E,Z)-muconic acid derivatives as this procedure led to considerable isomerization to (E,E)-muconates. Muconate isomerization, however, was
Scheme V

1) EtO, H+  
2) P-4MeCl, Ph  
3) TBDPS-Cl  
4) AcOH, H2O  
5) H2, Lindlar  

92%

1) Sharpless epox.  
2) RuCl3, NaIO4  

69%

1) AlCl3  
2) Ac2O  

78%

R = TBDPS  
R' = CH2CH2TMS
not a complication in DCC mediated esterification of 40. One final result of special importance was Still's observation that cyclization of a mixture of (E,Z)- and (E,E)-muconate seco acids 42 led only to the (E,Z)-macrocycle. As we will see the latter observation had an important influence on the direction of our efforts toward the synthesis of the verrucarins.

A second synthesis of verrucarin A, along with a synthesis of an unnatural analogue, 3a-hydroxy verrucarin A (53), was published in 1982 by Tamm and coworkers (Scheme VI). In contrast to the results reported by Still, Tamm's group observed substantial olefin isomerization in the DCC mediated esterification of muconic acid derivative 40 and verrucarol leading to 51. They also reported, in agreement with Still, that when a mixture of (E,Z)- and (E,E)-seco acids 51 was cyclized, only the (E,Z)-macrolide was obtained.

Immediately after this paper appeared syntheses of trichoeverrin B (9) and verrucarin J (3) were published from the Fraser-Reid and Jarvis laboratories at Maryland (Scheme VII). One interesting aspect of this work is the oxidative cyclization of trichoeverrin B (9) to verrucarin J (3) which follows a chemical logic related to a possible step in the biosynthesis of the verrucarins. A major problem with this synthesis, however, is the olefin isomerization which occurs upon esterification of imidazolide 55 with verrucarol mono-acetate (58). A 1:1 mixture of (E,Z)- and (E,E)-59 was obtained.

This problem of olefin isomerization was solved by Roush and Spada in their synthesis of trichoeverrol B (10), which was
Scheme VI

1) DHP, $H^+$
2) $KOH$, $CH_3OH$

1) $DCC$, $DMAP$
2) 47, $DCC$, $DMAP$
3) $nBu_4NF$, THF
Scheme VII

54 \[\xrightarrow{10 \text{ steps, 19\%}}\] TBDMSO

55

56 \[\xrightarrow{8 \text{ steps}}\] OTBDPS

57

58 \[\xrightarrow{\text{Nal}, \text{THF, HMBA}}\] TBDMSO

55, 54

59

60

59 \[\xrightarrow{\text{1) separate isomers, 2) LiOH, DME, H}_2\text{O, 3) Nal, 57}}\] TBDMSO

59

60

9 \[\xrightarrow{\text{nBu}_4\text{NF, THF}}\] TBDMS

R = TBDMS

6

3 \[\xrightarrow{\text{PDC, DMF, 3 days, 25\%}}\] TBDPS

R = TBDPS
the next synthesis of a complicated trichothecone ester to be published (see Scheme VIII). These investigators selected

Scheme VIII

acylation conditions which avoided the use of strong nucleophiles on the hypothesis that such nucleophilic species were responsible for the earlier problems of olefin isomerization via participation in Michael addition-retro Michael addition sequences. Their successful solution to this problem (Scheme VIII) has important implications for the synthesis of sterically hindered esters of unsymmetrical α,β-unsaturated acids.

Very recently, Still and co-workers have reported the first synthesis of two naturally occurring roridins, roridin E (7) and baccharin B5 (8) (see Scheme IX). This synthesis relies on an intramolecular Horner-Emmons reaction for closure of the macrocycle, and on the conformational preference of the 18-membered roridin-like macrocycle for stereochemical control. Unfortunately, a mixture of isomeric macrocycles was obtained in the olefination step (71 → 72), and extensive functionalization of 72 (six steps) was required in order to complete the synthesis of baccharin B5. Nonetheless, the preparation of two unnatural isomers of roridin E (72 and especially 73) is of special
Scheme IX

1) cyclopentanone, H⁺
2) 0.24 HCl
3) p-TsCl
4) LiAlH₄

63

64

1) TBDS-Cl
2) n-BuLi
3) ClCO₂Et
4) (CH₂)₂C≡C
5) LiAlH₄

65

OR

1) NCS
2) NaH, 64
3) nBu₄NF, THF
4) Jones oxidation

70-75%

66

67

1) DCC, 2
2) DCC, HO₂CO₂HPO(O)N₂₂₂

68

95%

69

1) TsOH, H₂O, AcOH
2) NaIO₄
3) Et₃N, CH₂OH
4) (C₆H₅)₃P=CHOH (70)
5) separate isomers

52%

71

K₂CO₃, toluene
18-crown-6

72 (45%)

1) TBDMSCl
2) MCPBA
3) KO-tBu, 1PrOH
60%

73 (30%)

1) BuOOH, VO(acac)₂
2) P(C₆H₅)₃, DEAD, HCO₂H
3) nBu₄NF, THF

81%

8

74

R = TBDMS
interest since this work confirmed our observations that the epoxytrichothecene macrocycles can accommodate a number of unnatural structural and/or stereochemical features (vide infra).

In addition to the synthetic efforts described above, much effort has been expended on the synthesis of the trichothecene nucleus. Noteworthy among these are total syntheses of verrucarol, anguidine, calonectrin, trichodermol, and trichodermin.

As we have seen, considerable progress in the synthesis of trichothecenes has been recorded in the last few years. However, as noted previously, very little was known about the chemistry of the macrocyclic trichothecenes when we began the studies described in this thesis. Our objective was to develop an efficient strategy for the synthesis of the macrocycles and at the same time learn something about the chemistry and biology of these compounds. We began by developing syntheses of the acyclic portions of verrucarins A and J, which are described in the next chapter.
CHAPTER II
SYNTHESIS OF THE ACYCLIC PORTIONS
Our initial synthetic strategy for the verrucarins involved an approach in which a differentiated diacid such as 76 would be attached to the C(4)-OH of verrucarol (2).

Scheme X

Deprotection of the resulting ester would lead to seco acid 75 which we imagined could be cyclized by any of a number of macro-lactonization methods to afford the verrucarin. As was outlined in the previous chapter, evidence which suggested that selective acylation of verrucarol C(4)-OH would be possible was available in the literature. 14, 30

In order to pursue this approach to the verrucarins it was necessary to develop an efficient synthesis of differentially protected side chains such as 76. We decided to focus our attention initially on the synthesis of model side chain 80 (Scheme XI). Hydroboration-oxidation of the known olefin 77 followed by esterification of the intermediate alcohol with bromoacetyl bromide afforded bromoacetate 78 in 58% overall yield. 45 Treatment of 78 with excess trimethyl phosphite in
refluxing toluene led to phosphonate 79 in very good yield. When 79 was allowed to react with potassium tert-butoxide and malealdehydeic acid (39) in an ether/tert-butanol solvent mixture the desired side chain 80 was obtained in 73% yield along with ~7% of the corresponding (Z,Z)-isomer 81. These isomers were readily separated by preparative TLC. Acid 80 was obtained in much lower yield (30%) when ylid 82 (prepared from 78 by standard techniques) was treated with malealdehydeic
acid in CH$_2$Cl$_2$ at room temperature.\textsuperscript{45} Hence, the Horner-Emmons olefination method was used in all of our subsequent studies.

We turned next to a synthesis of acid 86 which possesses the olefinic geometry of verrucarin J (Scheme XII). This synthesis begins with the known alcohol 83, prepared in one synthetic operation from 3-butyn-1-ol (65) by using Negishi's procedure.\textsuperscript{48} Acylation of 83 with bromoacetyl bromide smoothly afforded (94\% yield) bromoacetate 84 which was converted to phosphonate 85 in 98\% yield. Treatment of 85 with malealdehydic acid as before afforded the protected verrucarin J monoacid 86 in 83\% yield along with 8\% of (Z,Z)-isomer 87. A differentially protected form of the verrucarin J side chain was thus available in 76\% overall yield from 83. By using similar procedures we also synthesized acid 92 which possesses the 2',3'-(Z)-double
bond geometry originally assigned to verrucarin J (Scheme XIII).

Scheme XIII

The synthesis of 86 and its isomer 92 provided evidence supporting Tamm's reassignment\(^\text{14}\) of the structure of verrucarin J from 19 to 3. As shown in Table VIII the NMR data for verrucarin J is much more consistent with the NMR data for 86 than that of 92. It should also be noted that shortly after this

Table VIII
Selected \(^1\text{H}\) NMR Data\(^\text{a}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>C(4')-H</th>
<th>C(6')-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.50 (t, J=6Hz)</td>
<td>2.28 (d, J=1.5Hz)</td>
</tr>
<tr>
<td>86</td>
<td>2.50 (t, J=6.3Hz)</td>
<td>2.19 (d, J=1.7Hz)</td>
</tr>
<tr>
<td>92</td>
<td>2.99 (t, J=6.8Hz)</td>
<td>1.99 (d, J=1.5Hz)</td>
</tr>
</tbody>
</table>

\(^\text{a}\)Chemical shifts are reported in \(\delta\) units.
work was completed White and coworkers published syntheses of 86 and 92 by routes that were essentially identical to ours. This group also observed that the NMR data for 86 and 92 supported Tamm's reassignment of the verrucarin J structure. We have since completed syntheses of both 3 and 19 and have confirmed that 3 is indeed the correct structure for verrucarin J.

Having achieved an efficient synthesis of the verrucarin J side chain we decided to turn our attention to the more challenging target posed by verrucarin A. The main synthetic problem here was the establishment of the correct relationship between the stereocenters at C(2') and C(3'). We decided to pursue an approach in which the necessary anti relationship would be established by nucleophilic opening of trans-epoxide 94 by a synthetic equivalent of anion 95 (see Scheme XIV).

Thus, treatment of the known\textsuperscript{52} racemic epoxide 94 with excess alkynylaluminum reagent \textsuperscript{9753} in toluene afforded the expected alcohol 98 in 87% yield.\textsuperscript{54} None of the isomeric
adduct 104 was detected in this reaction. Removal of the trimethylsilyl group by using potassium fluoride in wet DMSO afforded acetylene 99 in 92% yield. Protection of the free hydroxyl group as the tert-butyldimethylsilyl ether followed by careful Lindlar hydrogenation of the acetylene smoothly afforded olefin 100 (85% yield). Hydrobororation-oxidation of 100 by sequential treatment with disiamylborane and aqueous alkaline hydrogen peroxide followed immediately by acylation of the resulting unstable alcohol with mixed anhydride 101.
led to phosphonate 102 in 75% yield. Treatment of 102 with malealdehydic acid as before led smoothly to the protected acid 103 in 68% yield (8% of the (Z,Z)-isomer was also isolated). The stereochemistry of intermediates 98-102 in Scheme XIV was confirmed by conversion of alcohol 105 to racemic verrucarino-lactone 106, (mp 71-72°C; lit56 mp 71-72.5°C). The NMR data for 106 was in complete agreement with literature values.56

Attempts to shorten our synthesis by employing diethyl ethynylaluminum 107,57, diethylethynylaluminum etherate 108,57 or diethylvinylaluminum 10958 in the epoxide opening step were unsuccessful. Although we were unable to shorten the synthesis, 103 was still available in 35% overall yield from epoxide 94. It should be noted that shortly after our work was published37f an analogous synthesis of optically active verrucarinic acid was reported by Trost.37c In addition, synthetic efforts by Tamm37i and numerous other workers in this area should also be noted.37b,d,j-l
The syntheses of 86, 92, and 103 described above demonstrated the potential utility of our methodology for constructing the acyclic portions of the verrucarins. We recognized, however, that the methyl ester present in 86, 92, and 103 would not be a suitable protecting group for the C(1')-carboxyl in eventual synthetic work on the verrucarins. Specifically, we anticipated that considerable difficulty would be encountered in attempts to cleave\textsuperscript{59a} the methyl ester in intermediates resulting from coupling of these side chains to C(4)-OH of verrucarol.

It was necessary, therefore, to identify protecting groups which would be compatible both with the synthetic routes outlined above as well as with the trichothecene skeleton which would be introduced at later stages of the work. Attempts to substitute a p-methoxybenzyl\textsuperscript{59b} or trimethylsilylmethyl\textsuperscript{59c} ester for the methyl ester in Scheme XIV by performing the initial transformation with epoxides 110\textsuperscript{60} or 111\textsuperscript{60} were unsuccessful. Epoxide 112,\textsuperscript{60} however, could be substituted for 94 in Scheme XIV (alcohol 113 was obtained in 21\% yield), but this intermediate was abandoned when other experiments revealed that muconic acid residues are not stable under the conditions required.
to cleave a trichloroethyl ester. These experiments involved deprotection of ester 114 with zinc dust both alone and in the presence of muconate ester 115. Reduction of 114 alone cleanly afforded the corresponding acid in essentially quantitative yield. When the same reaction was carried out in the presence of 115 a substantial amount of competitive reduction of the muconate residue was observed. This result indicated that a trichloroethyl ester was not a suitable protecting group for use in our approach to the verrucarins.

Concurrent efforts aimed at developing a synthesis of more usefully protected verrucarin J precursors ultimately led to the synthesis of acid 121 as outlined in Scheme XV. Our initial

Scheme XV
target, however, was 122 and we had already synthesized the intermediate trichloroethyl ester 117 when it became apparent that the trichloroethyl ester protecting group was, in fact, unsuitable for our purposes. Trichloroethyl ester 117 was prepared in variable yield by treatment of a methylene chloride solution of 3-butyn-1-ol with 3 equivalents of trimethylaluminum and 0.25 equivalents of zirconocene dichloride (116) followed by quenching with trichloroethyl chloroformate. This transformation was best carried out on a small scale (32% yield on 1 mmol scale) as the yield dropped considerably when the reaction was scaled up (21% on 5 mmol scale). An attempt to prepare trimethylsilylethyl ester 125 by an analogous procedure, however, was a total failure. None of the desired product 125

was detected in the reaction mixture, possibly as a consequence of the destruction of 2-trimethylsilylethyl chloroformate 124 by the alkyl aluminum species present in the mixtures.
This latter result prompted us to proceed with the synthesis of 121 via intermediate 117. Acylation of 117 with mixed anhydride 101 afforded crude phosphonate 118 which was deprotected by treatment with zinc dust to afford 119. The crude acid was then esterified with 2-trimethylsilylethanol and DCC to afford ester 120 as a 6:1 mixture of (E)- and (Z)-olefin isomers in 50% overall yield from 117. Finally, ester 120 was converted into the desired side chain 121 in 57% yield (6:1 (E):(Z) mixture) by application of the olefination sequence described previously.

With 121 and model acids 86 and 92 in hand we were ready to begin our studies aimed at completing the synthesis of verrucarin J. This work is the subject of the following chapter.
CHAPTER III

SYNTHESIS OF VERRUCARIN J
Having successfully developed methodology for constructing
the side chains of the verrucarins we turned our attention to
the esterification of these acids to the trichothecene nucleus.
We decided to concentrate initially on a synthesis of verrucarin
J (3)\textsuperscript{13} since we had the requisite side chains (i.e. \textsuperscript{86, 92, and}
121)\textsuperscript{67} in hand. Furthermore, we imagined that a synthesis of
verrucarin J would be relatively straightforward since the
potential epimerization problem\textsuperscript{37c,1} inherent in a verrucarin
A synthesis would be avoided.

Although several selective acylations of verrucarol C(4)-OH
have been reported\textsuperscript{14,30} numerous other examples suggest that
C(15)-OH is actually the more reactive of the two under a range
of acylation conditions.\textsuperscript{31-36,51} We therefore decided to perform
the initial coupling experiments with a C(15)-monoprotected
verrucarol derivative in order to avoid potential complications
from non-selective acylation. We felt that the known C(15)-
monoacetate \textsuperscript{58}\textsuperscript{28,32} would not be suitable since selective cleavage
of the acetate in the presence of a C(4)-muconate ester might

\begin{center}
\includegraphics[width=0.2\textwidth]{tikzexample}
\end{center}

not be possible.\textsuperscript{68,69} Hence, we decided to examine the use
of other protecting groups for C(15)-OH.

Treatment of verrucarol\textsuperscript{70} with carboxylic acid \textsuperscript{126,71}
DCC and catalytic 4-(dimethylamino)pyridine (DMAP)\textsuperscript{72,73} in
CH$_2$Cl$_2$ afforded ester 127 in 70% yield. The γ-tert-butyldimethylsilyloxybutyryl residue is a convenient protecting group for the C(15)-OH of verrucarol and is easily removed by treatment with n-Bu$_4$NF in THF (23°C, 10 min). This group was developed as an alternative to the levulinic ester protecting group after discovering that NaBH$_4$ reduction of ester 128 did not result in spontaneous liberation of the C(15)-hydroxyl group. Indeed, it was necessary to treat alcohol 129 with 1.1 equivalents of DBU for 61 h (23°C) to complete the deprotection sequence.

With suitably differentiated subunits in hand, we turned to an examination of the coupling sequence which we imagined would complete the synthesis of verrucarin J. Unfortunately, however, all attempts to couple 86, 92, or other simple (Z,E)-
muconate half-esters to trichothecenes 127 or 130 were accompanied with substantial isomerization to (E,E)-muconate diesters. Best results were obtained by using DCC and 4-pyrrolidinopyridine (4-PP) in CH$_2$Cl$_2$ but up to 50% of (E,E)-muconates were obtained under these conditions. For example, when levulinate 130 was treated in this manner with acid 86, ester 131 was obtained in 81% yield as a 60:40 mixture of (E,Z)- and (E,E)-muconate esters (inseparable). In addition, treatment of verrucarol derivative 132 (prepared as described subsequently) with acid 133 under the same conditions afforded predominantly the (E,E)-isomer of 134. Similar results were realized by Tamm in his verrucarin A synthesis.
Attempts to generate and esterify other active ester intermediates were also plagued by the olefin isomerization problem. Treatment of 86 with dipyridyl disulfide and triphenylphosphine in toluene\(^77\) afforded exclusively the (E,E)-pyridinethiol ester 135 in 56% yield. Esterification of acid 133 with cyclohexanol by using N,N-bis[2-oxo-2-oxazolidinyl]-phosphorodiamidic chloride (BOP-Cl) (136)\(^78\) afforded ester 137 in low (32%) yield as a 1:1 mixture of (E,Z)-, and (E,E)-isomers. Similarly, treatment of cyclohexanol with the mixed anhydride generated in situ from acid 92 and pivaloyl chloride afforded cyclohexyl ester 138 as 1:1 mixture of isomers.
Finally, an attempt to prepare acid chloride 139 by using oxalyl chloride was a complete failure. None of the desired acid chloride 139 was detectable by 270 MHz NMR analysis of the crude product.

These disappointing results prompted us to explore an alternative strategy in which the muconate esterification would be accomplished intramolecularly.43 We assumed that any acid (or the active ester intermediates) which might isomerize to the (E,E)-series would not undergo macrocyclization. This hypothesis was supported by the earlier observations of Still and Tamm that only (Z)-140 and (Z)-51 cyclized when the respective (Z,E)-muconate mixtures were subjected to the Mitsunobu (140)31,79 or the Yamaguchi mixed anhydride protocols (51).33,80
The key intermediate of this revised approach to verrucarin J thus became seco-acid 141. The most concise approach to 141, clearly, would involve the direct coupling of acid 142 to C(15)-OH of the trichothecene nucleus. A problem for which an immediate solution was not available, however, was the development of a mutually compatible protecting group scheme for the muconate and acrylate units suitable for use in a synthesis of 142. As will be shown subsequently a synthesis of 142 (R=CH₂CH₂SiMe₃) was eventually developed. First, however, we explored an indirect approach wherein most of the side chain, in the form of acid 119, was attached to the trichothecene before introduction
of the muconate by the Horner-Emmons reaction discussed previously.

Best results were obtained by esterification of verrucarol \textsuperscript{70} with 1.5 equivalents of acid \textsuperscript{119} (for preparation see Scheme XV, Chapter 2), DCC and DMAP in $\text{CH}_2\text{Cl}_2$ \textsuperscript{73} which afforded trichothecene monoester \textsuperscript{143} in 34-55\% yield as a 3:1 mixture of (E)- and (Z)-olefin isomers together with up to 19\% of diene \textsuperscript{144} (ca. 3:1 olefin mixture) and up to 19\% of phosphonoacetate \textsuperscript{145}. Diene \textsuperscript{144} undoubtedly arises from elimination of dimethylphosphonoacetic acid from \textsuperscript{143} or an activated form of \textsuperscript{119}, whereas \textsuperscript{145} is obviously the coupling product of verrucarol and the phosphonoacetic acid liberated in the aforementioned elimination reaction. Although a number of coupling methods (DCC, mixed anhydrides, etc.) proved to be highly selective for the primary hydroxyl group of 2, we were not able to eliminate the formation of \textsuperscript{144}, \textsuperscript{145}, or (Z)-\textsuperscript{143}. Moreover, we were unable to separate (E)-\textsuperscript{143} from its olefin isomer.

A parallel series of coupling experiments was performed by using acid \textsuperscript{146}. This intermediate was prepared initially
from 117, but a higher yielding sequence proceeded from 3-butyn-1-ol via the known vinyl iodide 147. Treatment of verrucarol with 1.5 equiv. of 146, DCC, and catalytic DMAP afforded ester 132 as a mixture of (E)- and (Z)-isomers in 82-88% yield. Careful separation of such mixtures by silica gel chromatography afforded pure (E)-132 in 56-60% overall yield along with 14-19% of (Z)-132. Condensation of 2 and 146 with Mukaiyama's salt afforded (E)-esters almost exclusively (>10:1), but in low yield (22%) and with poor regioselectivity (ca. 6:4 C(15) vs. C(4) monoesters). Several other methods (mixed anhydride prepared from CH₃COCl, Et₃N and DMAP; DCC, Bu₃N, HOBT) also afforded mixtures of olefin isomers. Similarly, an attempt to prepare the pyridine thiol ester of 146 afforded a 4:1 mixture of the (E)- and (Z)-isomers of thioester 148.
In addition, the Mitsunobu method as well as the mixed anhydride procedure developed by Roush and Spada in their synthesis of trichovertrol B\textsuperscript{35} also failed when applied to \textsuperscript{146}.\textsuperscript{83} All things considered, the DCC method discussed originally gave the best yield of (E)-\textsuperscript{132} and was used for all preparative scale experiments.

Deprotection of (E)-\textsuperscript{132} by treatment with aqueous acetic acid in THF (25°C, 5 h)\textsuperscript{84} smoothly provided (E)-\textsuperscript{11} in 96% yield (Scheme XVI). This compound is a known degradation product of verrucarin J\textsuperscript{13} and, interestingly, was recently isolated as a minor metabolite of \textit{M. verrucaria} and designated "verrol" by Jarvis.\textsuperscript{6} Deprotection of (E)-\textsuperscript{132} could also be accomplished by treatment with nBu\textsubscript{4}NF in THF\textsuperscript{84} but this procedure afforded verrol in lower yield (52-79%) and was less reproducible. Acylation of verrol with 1.1 equivalents of dimethylphosphonoacetic acid, DCC and DMAP afforded (E)-\textsuperscript{143} in 53% yield; 33% of \textsuperscript{11} was recovered. The use of larger excesses of carboxylic acid did not improve the yield of \textsuperscript{143} since diacylation (C(4) and C(5')) was a serious problem under such conditions. Finally, condensation of \textsuperscript{143} with malealdehydic acid by using the
procedure outlined previously afforded verrucarin J seco acid 141 in 57-58% yield.

Although the quantities of seco acid 141 prepared by the above sequence were sufficient to complete the synthesis of verrucarin J, we were disappointed with the inefficiency of the sequence (17% overall yield for the four steps from verrucarol). Accordingly, we sought an alternative method for introducing the muconate residue. We reasoned that an appropriately differentiated (Z,E)-muconate half acid could be coupled without complication to C(5')-OH of 11 by the Mitsonubu procedure since C(4)-OH is a rather hindered secondary alcohol. This, indeed, proved to be the case.
Muconate 154 was synthesized as outlined in Scheme XVII. Acylation of p-methoxybenzyl alcohol (149) with dimethylphosphonoacetic acid, DCC, and DMAP afforded phosphonate 150 in excellent yield. Condensation of 150 with malealdehydic

Scheme XVII
acid afforded isomerically pure muconate 151 in 71-76% yield, which was smoothly esterified with 2-trimethylsilylethanol (152) by using the Mitsunobu procedure.\textsuperscript{79} Note that the olefin isomerization problems which plagued our earlier attempts to prepare esters of muconic acids were, as expected, not encountered under these conditions. Finally, deprotection\textsuperscript{85} of 153 with formic acid afforded the desired muconate 154 in 72-83% yield.

Coupling of (E)-11 with 154 was smoothly accomplished by using the Mitsunobu procedure. The resulting seco acid ethyl ester 155 (87% from 11) was then deprotected by treatment with KF in wet DMSO.\textsuperscript{86} In this manner 141 was now available in 39% overall yield from verrucarol. In addition, this sequence afforded isomerically pure 141, whereas 141 prepared from phosphonate (E)-143 contained approximately 10% of the (Z,Z)-muconate isomer.

The observation that the muconate unit is stable under acidic reaction conditions (e.g., 153 + 154) provided the key to the development of a synthesis of acid 142 (Scheme XVIII). Unfortunately, however, we have not been able to separate the mixture of olefin isomers 155 obtained from the coupling of 142 and verrucarol. Even though this sequence constitutes the most direct route to seco acid 141 from verrucarol\textsuperscript{1} this approach is not preparatively useful in the absence of a convenient means of separating the (E,Z)-155 mixture.\textsuperscript{87} As a consequence, the transformations summarized in Scheme XVIII have not been optimized; the yields reported are for initial trials only.
A number of conditions for macrolactonization of seco acid 141 were explored. We were delighted, initially, with the observation that treatment of 141 with DCC and 4-PP effected cyclization without any olefin isomerization. Unfortunately, verrucarin J was isolated in only 33% yield, together with substantial quantities of the N-acyl urea derived from N-acylation of DCC. An attempt to suppress the formation of this by-product by performing the reaction in the presence of pyridinium p-toluenesulfonate led to extensive decomposition. A number of other methods (Mukaiyama salt; mesitylene sulfonyl chloride, Et3N, 4-PP) were also unsuccessful. In contrast to these previous results, the mixed anhydride 157 prepared from 141, pivaloyl chloride and triethylamine efficiently cyclized
to verrucarin J (55-60%) when treated with 4-pyrrolidinopyridine. Under these conditions, however, an isomer (158) possessing an (E,E)-muconate linkage was also obtained in 25-30% yield. Although we have not been successful in attempts to increase the yield of 3 by suppressing the formation of 158 (vide infra), the latter could be isomerized to verrucarin J (61%) when treated with I₂ in benzene. Interestingly, a new
isomer, (E,Z,E)-verrucarin 159, was also obtained under these conditions (31%). Nonetheless, the overall yield of verrucarin J from seco acid 141 was increased to 70-75% by virtue of the facile isomerization of 158.89

The latter results were most surprising. Prior to our first isolation51a of 158 we were unaware of any precedent in macrolide chemistry which suggested that isomers of a natural system with unnatural olefin configurations could be formed. The examples cited above (51 and 140) from the Still and Tamm laboratories31,33 certainly supported our (mistaken) assumption that such systems would not be easily produced. Verrucarin 158 is clearly less stable than the natural product, since no 158 remained in the I2 isomerization experiment (TLC and NMR analysis); verrucarin J did not isomerize when subjected to identical reaction conditions. In addition, 158 undergoes rapid (\(t_{1/2} \sim 3\)h) and clean solvolysis in ethanol to (E,E,E)-seco acid ethyl ester 160.90 The strain inherent in this ring system, however, is clearly insufficient to prevent the formation of

158 in the macrocyclization step.
Although the aforementioned isomerization of 158 to 3 constitutes compelling evidence of structure, additional evidence is provided by the independent synthesis outlined in Scheme XIX. Acylation of verrol (11) with (E,E)-acid 161\textsuperscript{91} by using the Mitsunobu procedure afforded seco-acid ester 162,

Scheme XIX

\[
\begin{align*}
\text{(E)-11} & \xrightarrow{\text{HO}_2C\text{C} \xrightarrow{\text{TMS}} \text{CO}_2 \xrightarrow{\text{TMS}} \text{KO} \cdot 2\text{H}_2\text{O}, \text{DMSO}, 70\%} \text{162} \\
163 & \xrightarrow{\text{pivaloyl chloride, Et}_3\text{N, CH}_2\text{Cl}_2, 4-\text{PP}} \frac{\text{50}\%}{\text{plus 14% of Verrucarin J}} \\
\end{align*}
\]

deprotection of which led smoothly to (E,E)-seco acid 163\textsuperscript{92}.

Finally, treatment of 163 with pivaloyl chloride and triethylamine followed by 4-pyrrolidinopyridine afforded 50\% of 158 together with 14\% of verrucarin J.

We believe that the isomerization observed in the cyclizations of seco acids 141 and 163 occurs at the stage of the active ester intermediate. This conclusion is necessitated
by the following evidence. First, control experiments established that verrucarin J (3) and isomer 158 do not equilibrate when treated with 4-pyrrolidinopyridine. Second, the mixed anhydride generation step (e.g. 141 + 157) was followed by 250 MHz NMR spectroscopy in two different solvents (CDCl₃ and d₆-benzene). In both instances it was possible to establish that mixed anhydride 157 was generated without detectable olefin isomerization. Moreover, no macrocyclization occurred at 23°C until an acylation catalyst, such as 4-PP, was introduced. Addition of 4-PP initiated a rapid ring closure (~1 h) reaction with the results cited previously.

Several mechanisms for the isomerization of mixed anhydride 157 are possible. One likely candidate is the reversible Michael addition of the acylation catalyst to 157, or to the N-acylpyridinium salt 73a derived from 157. If so, it should be possible to suppress the deleterious olefin isomerization by performing the macrocyclization step in the absence of nucleophilic acylation catalysts. This hypothesis led to a highly selective synthesis of trichoverrol B (10) by Roush and Spada. Unfortunately, however, attempts to extend this protocol to the synthesis of 3 have thus far met with limited success. For example, treatment of mixed anhydride 157 (generated in benzene) with DBU afforded a complex mixture of products containing, at best, only a trace of verrucarin J. The culprit here is probably the C(2')-C(3') double bond which facilitates the elimination of the muconic acid unit from C(4')-C(5').
(cf, 143 + 144). On the other hand, a solution of 157 in CHCl₃ maintained at reflux for 27 h in the presence of excess triethylamine afforded verrucarin J in 30% yield; isomer 158 was not detected under these conditions.

We were intrigued by the possibility that other isomers of verrucarin J could also be synthesized. Indeed, isomers 19 and 165 were prepared starting from (Z)-132 which, originally, had been produced as the minor product of the esterification of (E)-146 and verrucarol (see Scheme XX).²¹ Treatment of (Z)-132 with aqueous acetic acid in THF led smoothly to the diol (Z)-11 in 91% yield. It is interesting to note that treatment of (Z)-132 with nBu₄NF afforded verrucarol (2) in essentially quantitative yield, probably due to elimination of anhydromevalono-

Scheme XX

[Diagram showing chemical reactions and structures]
lactone from the initially generated alkoxide. This observation, along with the observed stability of (Z,E,Z)-verrucarin isomer 19 (vide infra) leads us to suspect that Tamm's isolation of only (E)-28 from the cyclization of a mixture of (E)- and (Z)-27 is due to selective destruction of (Z)-27 via thermal elimination of anhydromevalonolactone (see Scheme III, Chapter I).14

Mitsunobu coupling of (Z)-11 with acid 154, followed by deprotection of the resulting seco acid ester, afforded the (Z,E,Z)-seco acid 16495 in 46% overall yield from (Z)-11. Macrolactonization of 164 by using the procedure developed for verrucarin J afforded, as expected, the (Z,E,Z)-verrucarin isomer 19 in 52-56% yield as well as the (Z,E,E)-isomer 165 in 33-37% yield.

Several observations are noteworthy. First of all, isomer 19 possesses the structure originally proposed for verrucarin J by Tamm.13 Although verrucarin J and 19 are not distinguishable by TLC, the two structures are easily differentiated by 1H NMR analysis (see Table IX and Figures I and III).37e,f,96 Second, isomers 19, 158, and 165 all have relatively low melting points (<200°C) rather than the high melting points (>315°) which are typical of most of the naturally occurring verrucarins. Third, isomer 165, but not 19, shares with 158 the property of undergoing rapid transesterification in ethanol.97 Finally, 19 was recovered completely unchanged when exposed to iodine in benzene under conditions which completely isomerized 158. These data suggest that the verrucarin ring system is more tolerant of structural variation in the acrylic acid terminus
Figure 1. 270 MHz $^1$H NMR spectrum of synthetic verrucarin J (3)
Figure II. 250 MHz $^1$H NMR spectrum of natural verrucarin J (3)
Figure IV. 250 MHz $^1$H NMR spectrum of (E,E,E)-verrucaricin 158
Figure VI. 250 MHz 1H NMR spectrum of (E,2,E)-verrucarin 159
Table IXa
Selected $^1$H Chemical Shift Data for Verrucarin J Isomers

<table>
<thead>
<tr>
<th>Compound</th>
<th>C(4)-H</th>
<th>C(14)-H</th>
<th>C(15)-H$_a$</th>
<th>C(15)-H$_b$</th>
<th>C(6')-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>verrucarin J (3)</td>
<td>6.01</td>
<td>0.84</td>
<td>4.44</td>
<td>3.97</td>
<td>2.29</td>
</tr>
<tr>
<td>(Z,E,Z)-isomer 19</td>
<td>5.97</td>
<td>0.65</td>
<td>5.05</td>
<td>3.65</td>
<td>1.89</td>
</tr>
<tr>
<td>(E,E,E)-isomer 158</td>
<td>5.39</td>
<td>0.94</td>
<td>4.44</td>
<td>3.95</td>
<td>2.29</td>
</tr>
<tr>
<td>(Z,E,E)-isomer 165</td>
<td>5.27</td>
<td>0.88</td>
<td>4.29</td>
<td>3.94</td>
<td>1.94</td>
</tr>
<tr>
<td>(E,Z,E)-isomer 159</td>
<td>6.33</td>
<td>0.75</td>
<td>4.22</td>
<td>4.02</td>
<td>2.23</td>
</tr>
</tbody>
</table>

Chemical shifts are reported in $\delta$ units. The complete spectra are tabulated in the experimental section.

than in the muconate region, an observation which is born out in nature.$^{1,4}$

The biological properties of these verrucarin isomers are also sensitive to the nature of the macrocyclic ring system (see Table X). It is noteworthy that the in vitro activities of 3 and (Z,E,Z)-isomer 19 in the L1210 mouse leukemia assay are nearly equivalent whereas the two (E,E)-muconate isomers (158 and 165, respectively) are less active by an order of magnitude. The lower activity of 158 and 165 may reflect the solvolytic sensitivity of these systems, since the expected solvolysis products (e.g., seco acid 163 in the case of 158) would be expected to be essentially biologically inactive based on the very low activity measured for seco-acid 141.$^{98}$
Table X\textsuperscript{a}

<table>
<thead>
<tr>
<th>Compound</th>
<th>ID\textsubscript{50} vs. L1210 Cells (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>verrucarin J (3)</td>
<td>2.7\textsuperscript{b}</td>
</tr>
<tr>
<td>(Z,E,Z)-isomer 19</td>
<td>3.1\textsuperscript{b}</td>
</tr>
<tr>
<td>(E,E,E)-isomer 158</td>
<td>35</td>
</tr>
<tr>
<td>(Z,E,E)-isomer 165</td>
<td>26</td>
</tr>
<tr>
<td>seco acid 141</td>
<td>247</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The in vitro L1210 mouse leukemia assays were performed at the Warner-Lambert/Parke-Davis Laboratories by K. Hamelehle and M. Havlick.
\textsuperscript{b}Average of two runs.

With the completion of the synthesis of verrucarin J and several isomers we had accomplished our initial goal of developing methodology for the conversion of verrucarol to the macrocyclic verrucarins. We were, however, disappointed with the length of the sequence (5 steps) and our inability to suppress olefin isomerization in the final macrocyclization step. The development of solutions to these problems was thus central to our decision to undertake the synthesis of verrucarin B, which is described in the next chapter.
CHAPTER IV

SYNTHESIS OF VERRUCARIN B
The synthesis of verrucarin J and several isomers described in the previous chapter demonstrated the potential utility of our basic strategy for the synthesis of the verrucarins. There were, however, two specific points about this methodology which we felt could be improved. First, we wished to develop a more convergent synthesis in which the entire side chain would be attached to verrucarol. Second, we hoped to find a means of suppressing olefin isomerization in the final macrocyclization step. Successful solutions to either or both of these problems would improve the efficiency of the verrucarin synthesis from verrucarol. We decided, therefore, to focus on these problems by using verrucarin B (4)⁸,¹² as a synthetic target. Whereas we had initially planned to synthesize verrucarin A, we selected verrucarin B for these studies since Still had already accomplished a synthesis of our original target by using methodology which overlapped substantially with our intended route.³¹

Based on our experience with verrucarin J we decided to pursue a strategy in which verrucarol C(15)-OH would be selectively esterified with a monoacid such as 167. Deprotection of the resulting triester would then afford seco acid 166 which would be cyclized to give verrucarin B in the final step in the synthesis.

With this in mind we developed the synthesis of acid 167 which is outlined in Scheme XXI. Silylation of the known
alcohol \(^{48}\) followed by reduction of the ester functionality with DIBAL-H smoothly afforded the allylic alcohol \(^{168}\) in

\[ \text{Scheme XXI} \]

\[ \text{R} = \text{TBDMS} \]
excellent yield. Enantioselective epoxidation of 168 by using the extremely useful Sharpless procedure\textsuperscript{99} afforded optically active epoxyalcohol 169 which proved to be >95\% optically pure as determined by Mosher ester analysis.\textsuperscript{100} The next two steps of the synthesis (oxidation of 169 and esterification of the resulting epoxyacid) proved, however, to be rather troublesome. Best results were obtained when 169 was oxidized with permanganate in a benzene-water mixture in the presence of tetrabutylammonium bromide,\textsuperscript{101} followed immediately by esterification of the crude acid with 2-(p-toluenesulfonyl)ethanol,\textsuperscript{102} \(\text{Et}_3\text{N},\) BOP-Cl (136)\textsuperscript{78} and DMAP. This procedure afforded ester 170 in 56\% overall yield from 169. Purification of the intermediate acid led to a considerable decrease in the overall yield of this two-step sequence since the epoxyacid proved to be unstable to chromatography and was obtained in only 36-49\% yield after purification. In addition, attempts to prepare 170 from the crude acid by using several other esterification methods (DCC, DMAP; DCC, pyridine, TsOH; DCC, HOBT; mixed anhydride prepared with pivaloyl chloride) afforded 170 in much lower yields and the Mitsunobu\textsuperscript{79,103} and CDI\textsuperscript{104} procedures failed altogether.

When small scale (0.1 mmol) oxidations of 169 were performed by using catalytic \(\text{RuCl}_3\) in the presence of excess (3 equivalents) \(\text{NaIO}_4\textsuperscript{71b}\) and the crude acid esterified as before by using the BOP-Cl procedure, ester 170 was obtained in up to 55\% yield. Attempts to perform this procedure on larger scales (1.0 mmol), however, were less successful, affording ester 170 in only 31-37\% yield. All things considered the permanganate oxidation
followed by BOP-Cl mediated esterification of the crude acid
gave the best yield of 170 and was used for all preparative
scale experiments.

Hydrolysis of the TBDMS ether of 170 was smoothly accomplished
by exposure to aqueous acetic acid in THF\(^84\) (95% yield).
Treatment of 171 with mixed anhydride 172, generated in situ
from acid 154, Et\(_3\)N and pivaloyl chloride, led to triester 173
in 81% yield without olefin isomerization. Alternatively, 173
could also be prepared from 171 and 154 via the Mitsunobu
procedure but the yield of 173 was lower in this case (61%)
owing to material losses resulting from the repeated chromatog-
raphy required to obtain product of satisfactory purity.

With triester 173 in hand we next turned our attention to
removal of the 2-p-toluenesulfonylethyl ester protecting group
which would then complete the synthesis of acid 167. We were
delighted when our initial attempts to effect this deprotection
by treatment of 173 with DBU in benzene\(^{105}\) smoothly afforded
167 in 77% yield after chromatography. We were unable to
reproduce this result on a consistent basis, however, in spite
of the fact that in each case TLC analysis of the reaction
mixture showed that the deprotection had occurred cleanly.
Since 167 was obviously decomposing during the isolation and
purification steps we decided to circumvent this problem by
esterifying verrucarol (2) with crude 167, or its salts, gener-
at ed in situ. Thus, a mixture of 173 and DBU in benzene was
monitored by analytical TLC. When the deprotection was judged
complete BOP-Cl (136, 1.25-1.5 equivalents), triethylamine,
verrucarol (2) (1.0 equivalents) and catalytic 4-PP were added. This procedure afforded the C(15)-monoester 174 in 25-30% yield (49-53% based on unrecovered verrucarol).

Although 174 obtained in this manner could be smoothly deprotected to afford seco acid 166, we were somewhat disappointed in the low yield of the deprotection-acylation sequence. The low yield of 174 was due in part to relatively modest selectivity (ca. 3:1 C(15)-OH vs. C(4)-OH) in the acylation step\(^\text{106}\). In addition, a portion of 167 was consumed in an unproductive pathway resulting in the formation of a by-product, tentatively identified as having structure 175, resulting from acylation of DBU.
Attempts to avoid the formation of 175 by using triethylamine or 1,8-bisdimethylaminonapthalene (Proton Sponge®) in the deprotection step were unsuccessful (no deprotection of 173 by TLC analysis) as was the use of potassium tert-butoxide (extensive decomposition). We were therefore delighted, initially, when treatment of 173 with sodium hydride (NaH) in THF led to smooth elimination of the aryl vinyl sulfone. Subsequent esterification of the resulting sodium salt of 167, as before, afforded 174 in 41% yield (53% based on unrecovered verrucarol). However, this procedure could not be reproduced consistently as the desired deprotection step did not occur in some instances, possibly due to the absence of protic impurities which may have assisted the successful experiments. We reasoned that this problem could be circumvented by adding a catalytic amount of DBU to the reaction mixture. Indeed, treatment of 173 with excess NaH in the presence of 0.1 equivalent of DBU smoothly effected deprotection. Subsequent esterification of the intermediate sodium carboxylate afforded 174
in 35% yield (58% based on unrecovered verrucarol) with only a trace of 175 being detected by TLC.

This result, although slightly better than initial experiments involving DBU alone, was still unsatisfactory since a substantial amount of material (20-25%) was lost via acylation of verrucarol C(4)-OH. Attempts to suppress C(4)-acylation by using weaker acylation catalysts (e.g. 4-piperidino-pyridine, N-methylimidazole)73a were unsuccessful, as the use of these progressively less reactive catalysts led only to the formation of the various products in lower yield without significantly changing the ratio in which they were formed.107

Other esterification methods (DCC; mixed anhydride with pivaloyl chloride) were more selective for C(15)-OH but afforded 174 in much lower absolute yield108 and were therefore also considered unsatisfactory.

In light of these results, we decided to protect C(4)-OH of the trichothecene nucleus before attaching 167 to C(15)-OH. Although several C(4)-protected verrucarol derivatives have been reported in the literature109 we desired a protecting group which would be removed under conditions (KF·2H2O, DMSO) suitable for deprotection of a 2-trimethylsilyl ethyl ester, which we were already using as the blocking group for the C(6')-acid. Since we had previously observed that the γ-tert-butyldimethylsilyloxybutyryl residue was a convenient protecting group for verrucarol C(15)-OH (see Chapter 3), and since we suspected that it would be easily removed by treatment with KF in DMSO, we
decided to use this group to protect C(4)-OH. Thus, treatment of verrucarol (2) with imidazolidine 176 (either preformed with thionyldiimidazole or generated in situ with CDI) afforded, as expected, predominantly the C(4)-monoacylated product 177 along with varying amounts of the C(15)-acylated and diacylated products. Although we were disappointed with the low yield of 177, we realized that the by-products could be recycled to verrucarol if desired. This plan was not pursued, however, for as will be seen, 177 proved to be unsuited as an intermediate for this synthesis.

Deprotection of 173 by using the NaH-catalytic DBU procedure followed by acylation of the resulting sodium carboxylate with BOP-Cl (136) (1.4 equivalents), Et₃N, and 177 (1 equivalent) afforded diester 178 in 63% yield. Although we were very pleased
with this result, we quickly discovered that the γ-tertbutyl-
dimethylsilyloxybutyryl residue was unsuited as a protecting
group for C(4)-OH. Thus, treatment of 178 with 10 equivalents
of potassium fluoride in wet DMSO effected cleavage of both
the 2-trimethylsilylethyl ester and the tert-butyldimethylsilyl
ether. Unfortunately, however, spontaneous loss of butyro-
lactone to liberate C(4)-OH did not occur under these conditions.
In addition, the γ-hydroxybutyrate residue remained attached to
C(4) even after treatment with DBU in THF. This result,
which was unexpected in light of our previous experiences
(see Chapter 3), may be due to the more hindered nature of C(4)-
OH relative to C(15)-OH (possibly steric deceleration of
tetrahedral intermediate formation).

In spite of the failure of this deprotection sequence we
still felt that the basic synthetic strategy was sound.
Obviously, though, a different protecting group would be
required for C(4)-OH. Because the 2-trimethylsilylethyl ester
used to protect the C(6")-carboxyl function was easily removed
by treatment with KF in wet DMSO, we reasoned that a 2-trimethyl-
silylethoxycarbonyl unit 112 would prove suitable for protection
of C(4)-OH.

Thus, treatment of verrucarol (2) with 2-trimethylsilyl-
ethoxycarbonylimidazolide (180) 113 and DBU in benzene smoothly
afforded C(4)-monoprotected derivative 181 in 54% yield (81% yield based on unrecovered verrucarol after recycle of the
other reaction products).\textsuperscript{114} Esterification of 181 and in situ generated 167 by using the sequence described earlier smoothly afforded di-ester 182 in 64\% yield. Finally, deprotection of 182 by treatment with potassium fluoride in wet DMSO completed the synthesis of seco acid 166.\textsuperscript{115} Seco acid 166 was thus available in 46\% overall yield from verrucarol.\textsuperscript{116}

With a convenient synthesis of the seco acid in hand we turned to the final remaining problem, the macrolactonization of 166 which would complete the synthesis of verrucarin B. We decided to perform the initial cyclization by using the conditions worked out in our verrucarin J synthesis. Thus,
treatment of 166 with pivaloyl chloride and triethylamine followed by stoichiometric 4-pyrrolidinopyridine (4-PP) resulted in rapid macrocyclization and afforded verrucarin B (4) in 55% yield along with 34% of the (E,E)-muconate isomer 183. This result was essentially identical to that realized in the cyclization of verrucarin J seco acid 141. As with verrucarin J (E,E)-isomer 158, the verrucarin B (E,E)-isomer 183 could also be isomerized to verrucarin B (4) (60%) when treated with iodine in benzene. In addition, a new isomer, (Z,E)- verrucarin 184, was also obtained under these conditions (30%). Nonetheless, the overall yield of verrucarin B from seco acid 166 was increased to 75% by virtue of the isomerization of 183.
As with the isomers in the verrucarin J series, the isomers of verrucarin B are easily distinguished by $^1$H NMR analysis (see Figures VII through X). As before, the largest differences occur in the chemical shifts of C(4)-H, C(14)-H, and C(15)-H (see Table XI) since these are the protons which are most affected by changes in the orientation of the C(1')- and C(6")-carboxyl groups of the side chains.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C(4)-H</th>
<th>C(14)-H</th>
<th>C(15)-H&lt;sub&gt;a&lt;/sub&gt;</th>
<th>C(15)-H&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>verrucarin B (4)</td>
<td>5.85</td>
<td>0.89</td>
<td>4.51</td>
<td>4.35</td>
</tr>
<tr>
<td>(E,E)-isomer</td>
<td>5.29</td>
<td>1.02</td>
<td>5.14</td>
<td>3.90</td>
</tr>
<tr>
<td>(Z,E)-isomer</td>
<td>5.18</td>
<td>1.09</td>
<td>4.30</td>
<td>3.93</td>
</tr>
</tbody>
</table>

<sup>a</sup>Chemical shifts are reported in $\delta$ units. The complete spectra are tabulated in the experimental section.

In the previous chapter we speculated that the olefin isomerization observed in the macrocyclization might be promoted by reversible Michael addition of the acylation catalyst to the initially formed mixed anhydride or the corresponding N-acylpyridinium salt. We further hypothesized that this isomerization process might be suppressed if strong nucleophiles were omitted from the cyclization mixture. Table XII summarizes
Figure VII. 250 MHz $^1$H NMR spectrum of synthetic verrucarin B (4)
Figure VIII. 250 MHz $^1$H NMR spectrum of natural verrucarin B (4)
Figure IX. 250 MHz $^1$H NMR spectrum of (E,E)-verrucarin 183
<table>
<thead>
<tr>
<th>Cyclization Substrate</th>
<th>Cyclization Conditions</th>
<th>(\frac{3}{4})^a</th>
<th>(158/183)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>141</td>
<td>DCC, 4-PP(^b)</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>157(^c)</td>
<td>CH(_2)Cl(_2), 4-PP(^b)</td>
<td>55-60%</td>
<td>25-30%</td>
</tr>
<tr>
<td>157</td>
<td>DBU, benzene</td>
<td>(extensive decomposition)</td>
<td></td>
</tr>
<tr>
<td>157</td>
<td>Et(_3)N, CHCl(_3), reflux</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>185(^c)</td>
<td>CH(_2)Cl(_2), 4-PP(^d)</td>
<td>55%</td>
<td>34%</td>
</tr>
<tr>
<td>185</td>
<td>CH(_2)Cl(_2), 4-PP(^e)</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>185</td>
<td>CH(_2)Cl(_2), 4-PP(^f)</td>
<td>54%</td>
<td>10%</td>
</tr>
<tr>
<td>185</td>
<td>DBU, THF</td>
<td>24-58%</td>
<td>trace</td>
</tr>
<tr>
<td>185</td>
<td>KO(^t)Bu, THF</td>
<td>38%</td>
<td>trace</td>
</tr>
<tr>
<td>185</td>
<td>NaH, THF</td>
<td>20%(^g)</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\) verrucarins J (3) and B (4) are the desired products from cyclization of anhydrides 157 and 185 respectively, 158 and 183 are the corresponding (E,E)-muconate isomers

\(^b\) amount of catalyst not determined, at least one equivalent

\(^c\) mixed anhydrides 157 and 185 were generated in situ by treatment of seco acids 141 and 166 respectively with excess pivaloyl chloride and triethylamine

\(^d\) 1.0 equivalent of catalyst used

\(^e\) initially 0.02 equivalents of catalyst, increased to 0.05 equivalents after 1.5 h

\(^f\) initially 0.10 equivalents of catalyst, increased to 0.15 equivalents after 2 h

\(^g\) TLC analysis indicated extensive hydrolysis to form verrucarol
our efforts to reduce this plan to practice. Although treatment of verrucarin J mixed anhydride 157 with DBU in benzene resulted in extensive decomposition, we were pleased to find that exposure of 185 to similar reaction conditions led to verrucarin B in

\[
\begin{align*}
157 & \quad (R=\text{COCH}_3) \\
141 & \quad (R=\text{H}) \\
185 & \quad (R=\text{COCH}_3) \\
166 & \quad (R=\text{H})
\end{align*}
\]

24-58% yield. Only a trace of (E,E)-isomer 183 was observed in these experiments (TLC analysis). Unfortunately, the lower yields were obtained from the larger scale experiments. Attempts to effect the cyclization of 185 by using other bases (e.g. Ko^tBu or NaH) afforded verrucarin B in yields no greater than 38% (see Table XII).

We next considered the possibility that the olefin isomerization could be controlled by using acylation catalysts less reactive than 4-pyrrolidinopyridine in the cyclization step. According to some TLC experiments were conducted in which 185 was treated with 0.1 equivalents of a series of progressively weaker catalysts (i.e. 4-pyrrolidinopyridine > 4-piperidinopyridine > N-methylimidazole). In contrast to all previous seco acid cyclizations of this type in which relatively large amounts of catalyst had been used and which had proceeded very rapidly,
these carefully designed reactions were extremely slow and
did not go to completion. It was very apparent, however,
that much less isomerization to the (E,E)-product had occurred.
The best selectivity was achieved with N-methylimidazole, which
caused no detectable isomerization. This reaction, however,
was also the slowest of the three and, indeed, appeared to
be too slow to be practical for preparative purposes. The
other two catalysts (4-pyrrolidinopyridine (4-PP) and 4-piper-
ridinopyridine) caused a small amount of isomerization but the
cyclizations were considerably more rapid. The 4-PP catalyzed
cyclization was performed on a larger scale to determine whether
controlling the amount of catalyst would lead to a viable
solution to the olefin isomerization problem. In one experiment,
185 was treated with a total of 0.05 equivalents of 4-PP.
The reaction time (65 h) was substantially longer in this case
than when stoichiometric catalyst was used (1.5 h). Verrucarin
B (4) was obtained in 40% yield along with only 6% of 183.
In the second experiment 185 was treated with a total of 0.15
equivalents of 4-PP over a 15 h reaction period. In this case
verrucarin B was obtained in 54% yield along with 10% of 183.
These data clearly show that the amount of acylation catalyst
used in the esterification reaction is a critical variable
which must be controlled in order to optimize the yield of
macrocycle while minimizing the production of the (E,E)-muconate
isomers. This is, then, a possible area for future work on
this problem. It may also prove worthwhile to reconsider the
use of N-methylimidazole, or other weak acylation catalysts,
in these experiments.

Although we have not yet developed an optimum solution to the problem of olefin isomerization in the macrocyclization step, the overall yields of verrucarin J (27-30% after recycle of 158) and verrucarin B (35% after recycle of 183) from verrucarol are comparable to, or better than, the yields obtained in other published verrucarin syntheses (see Chapter 1). Indeed, although a solution to the isomerization problem is desirable for aesthetic reasons, it may not be necessary in practical terms due to the easy separation of verrucarins J and B from the respective (E,E)-muconate isomers and the facile iodine catalyzed isomerization of the (E,E)-muconates.
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 \(\delta\) units using tetramethysilane or the 7.27 ppm resonance of residual chloroform as internal reference. Carbon (\(^{13}\)C) NMR spectra were measured at 67.9 MHz on a Bruker WM 270 instrument or at 22.6 MHz on a JEOL FX90Q instrument. Carbon chemical shifts are reported in \(\delta_c\) units using the 77.0 ppm resonance of CDCl\(_3\) 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 \(^R\) 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 (125°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, and DMSO (reduced pressure) 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 CaSO₄ then distilled from P₂O₅. Pyridine was distilled from sodium hydroxide. 4-Pyrrolidinopyridine (4-PP) was recrystallized from hexane. Pivaloyl chloride, (-)-diethyl tartrate ((-)-DET), titanium tetra-isopropoxide, and DBU were distilled.

Analytical 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 iodine vapor or by charring with ethanolic H₂SO₄. Compounds containing the trichothecene 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.¹¹⁷ All chromatography solvents were distilled prior to use. The verrucarin numbering system¹³ is used for all compounds.
Experimental Procedures for Chapter II.

Methyl 5-bromoacetyl-3-methyl-pentanoate (78).45

A solution of borane-THF complex (40 mL of 1.0 M THF solution, 40 mmol) was added slowly to a cooled (0°C) solution of 12.0 g (93 mmol) of olefin 7744 in 50 mL of THF. The solution was stirred for 1 h at 25°C then 12 mL of water was added to destroy the excess borane. The pH was raised to 8 by addition of 3N NaOH. The solution was refluxed as 15 mL of 30% H₂O₂ was added dropwise then cooled to 25°C and stirred for 2 h. The mixture was neutralized by careful addition of 6N HCl then saturated with NaCl and extracted with CH₂Cl₂ (5x50 mL). The extracts were dried (Na₂SO₄), filtered and evaporated to afford 11.8 g (86%) of crude alcohol. This material gradually lactonized to form 3-methyl-α-valerolactone upon storage. Bromoacetyl bromide (2.21 g, 11 mmol) and pyridine (0.90 mL, 11 mmol) were added to a solution of 1.46 g (10 mmol) of the above crude alcohol in 50 mL of CH₂Cl₂. The solution was stirred for 4 h at 25°C then diluted with 75 mL of CH₂Cl₂. The solution was washed with 1N HCl (2x20 mL), saturated NaCl (2x20 mL), and saturated NaHCO₃ (2x20 mL) then dried (MgSO₄), filtered and evaporated. The residue was purified by flash chromatography
(60 mm column, 9:1 hexane-ether, Rf 0.12) to afford 1.78 g (67%) of 78 as a clear liquid (58% overall yield from 77).

**Data for 78:** ¹H NMR (270 MHz, CDCl₃) δ 4.30-4.15 (m, 2 H, H₅'), 3.84 (s, 2 H, H₂''), 3.68 (s, 3 H, OCH₃), 2.35 (dd, J=6, 15 Hz, 1 H, H₂'a), 2.21 (dd, J=7, 15 Hz, 1 H, H₂'b), 2.2-2.05 (m, 1 H, H₃'), 1.82-1.69 (m, 1 H, H₄'a), 1.63-1.50 (m, 1 H, H₄'b), 1.00 (d, J=6 Hz, 3 H, H₆'); ¹³C NMR (22.6 MHz, CDCl₃) δ 172.6, 166.9, 63.9, 51.2, 40.9, 34.5, 27.1, 25.6, 19.3; IR (film) 2962, 1734, 1458, 1436, 1284, 1168, 1112, 1010 cm⁻¹; mass spectrum m/e 128 (M⁺ - BrCH₂CO₂H), 121, 123 (BrCH₂CeO⁺);

**Anal.** Calcd for C₉H₁₅BrO₄: C, 40.47; H, 5.66; Br, 29.91. Found C, 40.31; H, 5.69; Br, 30.21.

![Chemical structure of 78 and 79](image)

Methyl 5-[(dimethoxyphosphinylacetyl)oxy]-3-methyl-pentanoate (79).

Trimethylphosphite (0.50 mL, 4.2 mmol) was added to a solution of 753 mg (2.8 mmol) of 78 in 4 mL of toluene. The solution was stirred for 4 h at reflux then evaporated. The residue was purified by flash chromatography (40 mm column, ether, Rf 0.19) to afford 716 mg (85%) of pure phosphonate 79 as a clear, colorless liquid: ¹H NMR (270 MHz, CDCl₃) δ 4.24-4.14 (m, 2 H, H₅'), 3.81 (d, J=11 Hz, 6 H, POCH₃), 3.67 (s, 3 H, OCH₃), 2.98 (d, J=21 Hz, 2 H, H₂''), 2.34 (dd, J=6, 15 Hz, 1 H, H₂'a), 2.23-2.08 (m, 2 H, H₂'b + H₃'), 1.78-1.67 (m, 1 H, H₄'a),
1.61-1.49 (m, 1 H, H$_4'b$), 0.98 (d, J=6 Hz, 3 H, H$_6'$); $^{13}$C NMR (22.6 MHz, CDCl$_3$) $\delta$ 172.5, 165.2 (d, J=6 Hz), 63.1, 52.7 (d, J=6 Hz), 51.0, 40.8, 34.5, 32.9 (d, J=135 Hz), 26.8, 19.0; IR (film) 2960, 1734, 1458, 1438, 1372, 1116, 1030, 874, 848 cm$^{-1}$; mass spectrum m/e 151 ((CH$_3$O)$_2$POCH$_2$C=O$^+$), 128 (M$^+$ - (CH$_3$O)$_2$POCH$_2$CO$_2$H).

\[
\begin{align*}
\text{CO,Me} & \quad \text{O} \quad \text{OH} \\
\text{CO,Me} & \quad \text{O} \quad \text{OH}
\end{align*}
\]

2,4-Hexadienedioic acid mono-(5-methoxy-3-methyl-5-oxopentyl ester) (80).

Phosphonate 79 (150 mg, 0.51 mmol) was converted to mono-acid 80 by using the procedure described below for 86. The crude product was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 1:1 hexane-ether, 2 developments, $R_f$ 0.33) to afford 101 mg (73%) of 80 as a clear liquid. When the olefination was performed by using phosphorane 82, acid 80 was obtained in 30% yield.$^{45}$

Data for 80: $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 8.37 (dd, J=12, 15 Hz, 1 H, H$_3''$), 6.75 (dd, J=12, 12 Hz, 1 H, H$_4''$), 6.15 (d, J=15 Hz, 1 H, H$_2''$), 6.01 (d, J=12 Hz, 1 H, H$_5''$), 4.29-4.20 (m, 2 H, H$_5'$), 3.68 (s, 3 H, OCH$_3$), 2.38 (dd, J=6, 15 Hz, 1 H, H$_2'a$), 2.26-2.08 (m, 2 H, H$_2'b + H_3'$), 1.81-1.71 (m, 1 H, H$_4'a$), 1.66-1.55 (m, 1 H, H$_4'b$), 1.01 (d, J=6 Hz, 3 H, H$_6'$); $^{13}$C NMR (22.5 MHz, CDCl$_3$) $\delta$ 173.3, 170.1, 166.0, 142.4, 138.3, 129.5,
123.9, 62.8, 51.5, 41.2, 34.9, 27.4, 19.5; IR (film) 3500-2500 (acid OH), 2960, 1716, 1634, 1600, 1436, 1308, 1270, 1172 cm\(^{-1}\); mass spectrum m/e 113 (M\(^+\) - muconic acid-CH\(_3\));

high resolution mass spectrum, calcd for C\(_{13}\)H\(_{18}\)O\(_6\) 270.11034, found 270.11307.

Methyl-5-bromoacyloxy-3-methyl-2-(E)-pentenoate (84).

Bromoacetylbromide (0.30 mL, 3.44 mmol) was added dropwise to a cold (0°C) solution of 451 mg (3.13 mmol) of methyl-5-hydroxy-3-methyl-2-(E)-pentenoate (83)\(^{48}\) and 0.28 mL (3.44 mmol) of pyridine in 10 mL of CH\(_2\)Cl\(_2\). The mixture was stirred for 4 h at 25°C then 10 mL of 1N HCl was added. The organic layer was washed with 10 mL of 1N HCl and 10 mL of sat NaHCO\(_3\) then filtered through a cotton plug and evaporated. The residue was purified by flash chromatography (30 mm column, 2:1 hexane:ether, R\(_f\) 0.35) to afford 785 mg (94\%) of pure bromoacetate 84 as a clear colorless liquid: \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 5.72 (br s, 1 H, H\(_2\)), 4.33 (t, J=7 Hz, 2 H, H\(_5\)), 3.83 (s, 2 H, H\(_2\)), 3.70 (s, 3 H, OCH\(_3\)), 2.51 (t, J=7 Hz, 2 H, H\(_4\)), 2.20 (br s, 3 H, H\(_6\)); \(^{13}\)C NMR (22.6 MHz, CDCl\(_3\)) \(\delta\) 166.9, 166.4, 154.3, 117.6, 63.2, 50.8, 39.1, 25.4, 18.4; IR (film) 2948, 1732, 1714, 1650, 1434, 1356, 1280, 1224, 1148, 1032 cm\(^{-1}\);
mass spectrum m/e 126 (M⁺ – BrCH₂CO₂H), 121, 123 (BrCH₂C≡O⁺), high resolution mass spectrum –M⁺ not observed (calcd for C₇H₁₀O₂, loss of bromoacetic acid) 126.06815 (found: 126.0604).

Methyl-5-[(dimethoxyphosphinyl)acetyl]oxy]-3-methyl-2-(E)-pentenoate (85).

Trimethyl phosphite (0.45 mL, 3.8 mmol) was added to a solution of 675 mg (2.55 mmol) of 84 in 4 mL of toluene. The solution was stirred for 10 h at reflux then the solvent was evaporated. The residue was purified by flash chromatography (30 mm column, 1:1 ether:CH₂Cl₂, Rf 0.23) to afford 736 mg (98%) of pure phosphonate 85 as a clear, colorless liquid: ¹H NMR (270 MHz, CDCl₃) δ 5.71 (br s, 1 H, H₂), 4.29 (t, J=7 Hz, 2 H, H₅), 3.79 (d, J=11 Hz, 6 H, POCH₃), 3.69 (s, 3 H, OCH₃), 2.97 (d, J=22 Hz, 2 H, H₂\(^\text{"prime}\)), 2.49 (t, J=7 Hz, 2 H, H₄\(^\text{"prime}\)), 2.19 (br s, 3 H, H₆); ¹³C NMR (22.6 MHz, CDCl₃) δ 166.2, 165.0 (d, J=6 Hz), 154.5, 117.0, 62.3, 52.7, (d, J=6 Hz), 50.4, 38.9, 32.7 (d, J=135 Hz), 18.0; IR (CH₂Cl₂) 3038, 2946, 1734, 1714, 1650, 1244, 1150, 1110, 1054, 1032 cm⁻¹; mass spectrum m/e 151 ((CH₃O)₂POCH₂C≡O⁺), 126 (M⁺ – (CH₃O)₂POCH₂CO₂H); Anal. Calcd for C₆H₁₉O₇P: C, 44.90; H, 6.51. Found C, 44.91; H, 6.51.
2,4-Hexadienedioic acid mono(5-methoxy-3-methyl-5-oxo-3-pentenyl-ester) (E,E,Z) (86).

A solution of 36 mg (0.36 mmol) of malealdehydic acid in 3 mL of ether and a solution of 80 mg (0.71 mmol) of potassium t-butoxide in 3 mL of t-butanol were added (dropwise) simultaneously but separately to a solution of 100 mg (0.34 mmol) of phosphonate 85 in 5 mL of ether. The mixture was stirred vigorously for 65 minutes at 25°C. Water (5 mL) was added and the mixture acidified to pH 2 by careful addition of 2N H₂SO₄ then extracted with ether (5x10 mL). The combined ether extracts were dried (Na₂SO₄), filtered and evaporated. The residue was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 1:1 hexane:ether, 2 developments, Rf 0.35-0.47) to afford 76 mg (83%) of pure 86 as a white crystalline solid.

Data for 86: mp 40-41°C; ¹H NMR (270 MHz, CDCl₃) δ 8.38 (dd, J=12, 15 Hz, 1 H, H₃"), 6.75 (dd, J=12, 12 Hz, 1 H, H₄"), 6.14 (d, J=15 Hz, 1 H, H₂"), 6.01 (d, J=12 Hz, 1 H, H₅"), 5.74 (br s, 1 H, H₂'), 4.34 (t, J=7 Hz, 2 H, H₅'), 3.69 (s, 3 H, OCH₃), 2.53 (t, J=7 Hz, 2 H, H₄'), 2.22 (br s, 3 H, H₆'); ¹³C NMR (22.6 MHz, CDCl₃) δ 169.9, 166.8, 165.8, 155.3, 142.1, 138.7, 129.1, 124.1, 117.4, 62.1, 50.9, 39.4, 18.7; IR (CH₂Cl₂)
3400-2500 (acid OH), 1714, 1652, 1600, 1416, 1224, 1168, 1152 cm$^{-1}$; mass spectrum m/e 126 (M$^+$ - muconic acid); UV (EtOH) 262 (ε 20,600), 217 (ε 21,000); Anal. Calcd for C$_{13}$H$_{16}$O$_6$: C, 58.20; H, 6.01. Found C, 58.31; H, 5.86.

Data for 87: R$_f$ 0.49-0.55 (1% formic acid in 1:1 hexane-ether, 2 developments); $^1$H NMR (270 MHz, CDCl$_3$) δ 8.00-7.81 (m, 2 H), 6.03-5.98 (m, 2 H), 5.73 (br s, 1 H, H$_{2}$), 4.32 (t, J=7 Hz, 2 H, H$_{5}$), 3.70 (ε, 3 H, OCH$_3$), 2.52 (t, J=7 Hz, 2 H, H$_{4}$), 2.21 (br s, 3 H, H$_{6}$).

Methyl-5-bromoacetyloxy-3-methyl-2-(Z)-pentenoate (90).45

Alcohol 89 (138 mg, 0.96 mmol, prepared from 88$^{49}$ immediately before use by using the literature procedure)$^{50}$ was converted into bromoacetate 90 by using the procedure described above for 84.

Data for 90: $^1$H NMR (270 MHz, CDCl$_3$) δ 5.79 (br s, 1 H, H$_{2}$), 4.34 (t, J=7 Hz, 2 H, H$_{5}$), 3.82 (s, 2 H, H$_{2''}$), 3.69 (s, 3 H, OCH$_3$), 3.00 (t, J=7 Hz, 2 H, H$_{4}$), 1.97 (br s, 3 H, H$_{6}$); $^{13}$C NMR (22.6 MHz, CDCl$_3$) δ 166.9, 166.2, 155.3, 118.0, 64.4, 50.9, 32.2, 25.6; IR (film) 2956, 1734, 1716, 1648, 1434, 1382, 1202, 1150, 1030, 858 cm$^{-1}$; mass spectrum m/e 126 (M$^+$ - BrCH$_2$(CH$_2$H), 121, 123 (BrCH$_2$C=O$^+$); Anal. Calcd for C$_9$H$_{13}$BrO$_4$: C, 40.78; H, 4.94; Br, 30.14. Found C, 40.96; H, 5.16; Br, 30.10.
Methyl 5-[(dimethoxyphosphinylacetyl)oxy]-3-methyl-2-[(Z)-pentenoate (91).

Trimethyl phosphite (0.23 mL, 1.93 mmol) was added to a solution of 340 mg (1.28 mmol) of (Z)-bromoacetate 90 in 4 mL of toluene. The solution was stirred for 4 h at reflux then concentrated in vacuo. The residue was purified by flash chromatography (30 mm column, 1:1 ether-CH₂Cl₂) to afford 262 mg (69%) of phosphonate 91 (Rᶠ 0.21) as a colorless liquid and 104 mg (30%) of recovered bromoacetate 90 (Rᶠ 0.88).

Data for 91: ¹H NMR (270 MHz, CDCl₃) δ 5.77 (br s, 1 H, H₂), 4.30 (t, J=7 Hz, 2 H, H₅), 3.81 (d, J=11 Hz, 6 H, POCH₃), 3.68 (s, 3 H, OCH₃), 2.97 (d, J=22 Hz, 2 H, H₂), 2.96 (t, J=7 Hz, 2 H, H₄), 1.96 (br s, 3 H, H₆); ¹³C NMR (22.6 MHz, CDCl₃) δ 166.0, 165.1 (d, J=5 Hz), 155.3, 117.7, 63.6, 52.7 (d, J=6 Hz), 50.6, 35.9, 30.1 (d, J=135 Hz), 25.3; IR (film) 2960, 2860, 1736, 1716, 1646, 1442, 1268, 1202, 1152, 1114, 1030, 850, 806 cm⁻¹; mass spectrum m/e 151 ((CH₃O)₂POCH₂C=O⁺), 126 (M⁺ - (CH₃O)₂POCH₂CO₂H).
2,4-Hexadienedioic acid mono-(5-methoxy-3-methyl-5-oxo-3-(Z)-pentenoate (92).  

Phosphonate 91 (123 mg, 0.42 mmol) was converted to monoacid 92 by using the olefination procedure described above for 86. The crude product was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 1:1 hexane-ether, Rf 0.27) to afford 66 mg (59%) of 92 as a white crystalline solid: mp 97.5-98.5°C; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 8.37 (dd, J=12, 16 Hz, 1 H, H$_3$'''), 6.75 (dd, J=12, 12 Hz, 1 H, H$_4$'''), 6.14 (d, J=16 Hz, 1 H, H$_2$'''), 6.01 (d, J=12 Hz, 1 H, H$_5$'''), 5.80 (br s, 1 H, H$_2$'), 4.36 (t, J=7 Hz, 2 H, H$_5$'), 3.69 (s, 3 H, OCH$_3$), 3.03 (t, J=7 Hz, 2 H, H$_4$'), 1.99 (br s, 3 H, H$_6$'); $^{13}$C NMR (22.6 MHz, CDCl$_3$) $\delta$ 170.4, 166.5, 165.9, 156.2, 142.6, 138.4, 129.6, 123.9, 118.0, 63.4, 51.0, 32.6, 25.9; IR (CH$_2$Cl$_2$) 3400-2500 (acid OH), 3046, 1714, 1648, 1602, 1432, 1202, 1168, 1150 cm$^{-1}$; mass spectrum m/e 126 (M$^+$ - muconic acid); UV (EtOH) 261 ($\varepsilon$ 21,100), 216 ($\varepsilon$ 16,100); Anal. Calcd for C$_{13}$H$_{16}$O$_6$: C, 58.20; H, 6.01. Found C, 58.21; H, 6.02.
Methyl 2-hydroxy-3-methyl-5-trimethylsilyl-4-pentyne 45

A solution of n-butyllithium (14.9 mL of 2.6 M hexane solution, 38.7 mmol) was added to a cooled (0°C) solution of 5.6 mL (40 mmol) of trimethylsilylacetylene 118 in 70 mL of toluene. The solution was stirred for 20 minutes at 0°C then a solution of diethylaluminum chloride (27 mL of 1.33 M hexane solution, 36 mmol) was added. The cloudy mixture was stirred for 2 h at 25°C then cooled to 0°C as a solution of 2.16 g (18.6 mmol) of racemic epoxide (±)-94 42 in 10 mL of toluene was added. The mixture was stirred for 2 h at 5-10°C then diluted with ether. Cold 1N HCl was added until all of the aluminum salts dissolved then the aqueous layer was extracted with CH₂Cl₂ (2x20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (60 mm column, 2:1 hexane-ether, Rf 0.38) to afford 3.49 g (87%) of 98 as a white crystalline solid: mp 33.5-35°C; ¹H NMR (270 MHz, CDCl₃) δ 4.18 (dd, J=4, 7 Hz, 1 H, H₂), 3.78 (s, 3 H, OCH₃), 3.01 (d, J=7 Hz, 1 H, OH), 2.90 (qd, J=4,7 Hz, 1 H, H₃), 1.19 (d, J=7 Hz, 3 H, H₆), 0.12 (s, 9 H, Si(CH₃)₃); ¹³C NMR (22.6 MHz, CDCl₃) δ 173.1, 106.1, 86.6,
73.5, 52.1, 32.1, 15.8, -0.15; IR (CH₂Cl₂) 3526, 2956, 2162, 1734, 1436, 1238, 1132, 1092, 842 cm⁻¹; mass spectrum m/e 214 (M⁺), 199 (M⁺ - CH₃).

![Chemical structure diagram]

Methyl 2-hydroxy-3-methyl-4-pentynoate (99).

Water (0.55 mL, 30.5 mmol) and potassium fluoride (880 mg, 15.1 mmol) were added to a solution of 1.62 g (7.56 mmol) of 98 in 12 mL of DMSO. The mixture was stirred vigorously for 5 h at 25°C then partitioned between water (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (2x50 mL) and the combined extracts dried (MgSO₄) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (30 mm column, ether, Rf 0.76) to afford 986 mg (92%) of acetylene 99 as a clear light yellow liquid.

Data for 99: ¹H NMR (270 MHz, CDCl₃) δ 4.27 (dd, J=4.6 Hz, 1 H, H₂), 3.82 (s, 3 H, OCH₃), 3.05 (d, J=6 Hz, 1 H, OH), 3.01-2.90 (m, 1 H, H₃), 2.16 (d, J=2 Hz, 1 H, H₅), 1.20 (d, J=7 Hz, 3 H, H₆); ¹³C NMR (22.6 MHz, CDCl₃) δ 172.9, 83.9, 73.1, 70.3, 52.2, 30.5, 15.2; IR (film) 3490, 3286, 2980, 2956, 2880, 2114, 1734, 1438, 1132, 1090, 1062, 996, 980 cm⁻¹; mass spectrum m/e 125 (M⁺ - OH); Anal. Calcd for C₇H₁₀O₃: C, 59.14; H, 7.09. Found C, 59.39; H, 7.09.
Methyl 2-tert-butyldimethylsilyloxy-3-methyl-4-pentenoate (100).

A solution of 801 mg (5.6 mmol) of 99, 950 mg (14 mmol) of imidazole, and 1.0 g (6.6 mmol) of tert-butyldimethylsilyl chloride in 2.5 mL of DMF was stirred for 15 h at 25°C. The mixture was diluted with 20 mL of water and extracted with hexane (7x100 mL). The combined extracts were washed with saturated NaCl, dried (Na$_2$SO$_4$), filtered and concentrated. The crude silyl ether was dissolved in 100 mL of CH$_2$Cl$_2$ then 128 mg of Lindlar catalyst$^{118}$ was added and the mixture stirred under an atmosphere of hydrogen for 35 h at 25°C. The catalyst was replaced twice during this time when the reaction appeared to have stopped short of completion (progress monitored by NMR of small aliquots). The reaction mixture was filtered through Celite and the filtrate concentrated to afford 1.24 g (85%) of essentially pure 100 as a clear liquid. Note: In the course of related experiments we have observed that Lindlar hydrogenation of a terminal acetylene occurs much more rapidly in methanol than in CH$_2$Cl$_2$.

Data for 100: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.84-5.69 (m, 1 H, H$_4$), 5.09-4.99 (m, 2 H, H$_5$), 4.07 (d, J=5 Hz, 1 H, H$_2$), 3.70
(s, 3 H, OMe), 2.63-2.53 (m, 1 H, H₃), 1.02 (d, J=7 Hz, 1 H, H₆), 0.90 (s, 3 H, CMe₃), 0.05 (s, 3 H, SiMe), 0.04 (s, 3 H, SiMe); ¹³C NMR (22.6 MHz, CDCl₃) δ 173.0, 140.0, 115.0, 76.2, 51.2, 42.6, 25.7, 18.2, 14.4, -5.0, -5.4; IR (film) 2946, 2924, 2860, 1756, 1738, 1636, 1472, 1460, 1254, 1140, 834, 774 cm⁻¹; mass spectrum m/e 201 (M⁺ - tBu); Anal. Calcd for C₁₃H₂₆O₃Si: C, 60.42; H, 10.14. Found C, 60.46; H, 10.34.

Methyl 2-tert-butyldimethylsilyloxy-5-dimethoxyphosphinylacetyloxy-3-methyl pentanoate (102).

A solution of 2-methyl-2-butene (0.50 mL of 4M THF solution, 2.0 mmol)¹¹⁸ was added slowly at -15°C to a solution of BH₃·THF (0.91 ml of 1.1 M THF solution, 1.0 mmol). The solution was left in a 0°C refrigerator for 2 h then cooled in an ice bath as a solution of 129 mg (0.50 mmol) of olefin 100 in 1 mL of THF was added dropwise. The solution was stirred for 10 minutes at 0°C then for 1.5 h at 25°C. The solution was then cooled in an ice bath as 1 mL of water was added cautiously (foaming). Solutions of H₂O₂ (0.50 mL of 30% aqueous H₂O₂) and NaOH (0.50 mL of 3M aqueous NaOH) were then added (dropwise) simultaneously but separately. The ice bath was removed and the mixture stirred for 5 minutes at 25°C then neutralized by careful
addition of 2N $\text{H}_2\text{SO}_4$. Water (5 mL) and 10 mL of ether were added, the layers separated, and the aqueous layer extracted with ether (2x10 mL). The combined organic layers were washed sequentially with 10 mL of saturated aqueous $\text{Na}_2\text{SO}_3$ and 5 mL of saturated aqueous $\text{NaCl}$ then dried ($\text{MgSO}_4$), filtered and evaporated. The crude alcohol was dissolved in 2 mL of $\text{CH}_2\text{Cl}_2$ then 0.061 mL (0.75 mmol) of pyridine was added. A solution of mixed anhydride 101 (prepared by stirring a solution of 101 mg (0.6 mmol) of dimethyl phosphonoacetic acid in 2 mL of trifluoroacetic anhydride for 4 h at 25°C then removing excess trifluoroacetic anhydride in vacuo)\textsuperscript{55} in 1 mL of $\text{CH}_2\text{Cl}_2$ was then added. The solution was stirred for 2 h at 25°C then 10 mL of $\text{CH}_2\text{Cl}_2$ and 5 mL of 1N HCl were added. After thorough mixing the layers were separated and the aqueous layer extracted with $\text{CH}_2\text{Cl}_2$ (2x10 mL). The combined organic extracts were washed with 5 mL of saturated aqueous NaHCO$_3$. The aqueous NaHCO$_3$ layer was then back-extracted with $\text{CH}_2\text{Cl}_2$ (2x10 mL). The combined organic layers were filtered through cotton and evaporated. The residue was purified by flash chromatography (30 mm column, 1:1 ether-$\text{CH}_2\text{Cl}_2$, $R_f$ 0.32) to afford 160 mg (75%) of pure phosphonate 102 as a clear, colorless liquid.

Data for 102: $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 4.25-4.14 (m, 2 H, H$_5$), 4.11 (d, J=4 Hz, 1 H, H$_2$), 3.80 (d, J=12 Hz, 6 H, POCH$_3$), 3.71 (s, 3 H, OCH$_3$), 2.98 (d, J=22 Hz, 2 H, H$_2$), 2.09-2.00 (m, 1 H, H$_3$), 1.85-1.73 (m, 1 H, H$_{4a}$), 1.61-1.48 (m, 1 H, H$_{4b}$), 1.24 (br s, 1 H, OH), 0.89 (s, 9 H, t-Bu), 0.88 (d, J=7 Hz, 3 H, H$_6$), 0.05 (s, 3 H, SiCH$_3$), 0.02 (s, 3 H, SiCH$_3$); $^{13}$C NMR
(22.6 MHz, CDCls) δ 173.3, 165.5 (d, J=6 Hz), 63.8, 53.1 (d, J=6 Hz), 51.4, 34.7, 33.5 (d, J=135 Hz), 32.1, 29.7, 25.8, 18.3, 14.0, -4.9, -5.3; IR (film) 2950, 2928, 2850, 1734, 1460, 1270, 1112, 1032, 834 cm⁻¹; mass spectrum m/e 151 ((CH₃)₂POCH₂C≡O⁺), 57 (tBu); Anal. Calcd for C₁₇H₃₅O₈PSi: C, 47.87; H, 8.27. Found C, 47.78; H, 8.22.

2,4-Hexadienedioic acid mono-(-4-tert-butyldimethylsilyloxy-5-methoxy-3-methyl-5-oxopentyl ester) (103).

Phosphonate 102 (160 mg, 0.375 mmol) was converted to mono-acid (±)-103 by using the olefination procedure described for 86. The crude product was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 3:1 hexane-ether, 3 developments, Rf 0.42) to afford 103 mg (68%) of acid (±)-103 as a clear, colorless syrup: ¹H NMR (270 MHz, CCl₃) δ 8.38 (dd, J=12, 16 Hz, 1 H, H₃"), 6.75 (dd, J=12, 12 Hz, 1 H, H₄"), 6.16 (d, J=16 Hz, 1 H, H₂"), 6.00 (d, J=12 Hz, 1 H, H₅"), 4.30-4.20 (m, 2 H, H₅'), 4.15 (d, J=3 Hz, 1 H, H₂'), 3.72 (s, 3 H, OCH₃), 2.10-2.00 (m, 1 H, H₃'), 1.90-1.78 (m, 1 H, H₄'a), 1.65-1.53 (m, 1 H, H₄'b), 0.92 (d, J=6 Hz, 3 H, H₆'), 0.91 (s, 9 H, t-Bu), 0.06 (s, 3 H, SiCH₃), 0.03 (s, 3 H, SiCH₃); ¹³C NMR (22.6 MHz, CCl₃) δ 173.7, 170.0, 166.1, 142.6, 138.4, 129.8, 123.9, 63.1, 51.7, 34.9, 32.2, 25.8, 18.4, 14.1, -4.8, -5.2;
IR (CH$_2$Cl$_2$) 2960, 2940, 2862, 1750, 1722, 1712, 1602, 1174, 1138, 840 cm$^{-1}$; mass spectrum m/e 125 (M$^+$ - muconic acid - TBDSMO); UV (EtOH) 261 ($\varepsilon$ 16,800); Anal. Calcd for C$_{19}$H$_{32}$O$_7$Si: C, 60.42; H, 10.14. Found C, 60.46; H, 10.34.

Verrucarinolactone (106).

Olefin 100 (258 mg, 1.0 mmol) was converted into the intermediate alcohol 105 by using the procedure described above for 102. The crude alcohol was dissolved in 10 mL of CH$_2$Cl$_2$ then a few crystals of p-toluenesulfonic acid were added. The solution was stirred for 14 h at 25°C then washed with saturated aqueous NaHCO$_3$ (aqueous layer back extracted with CH$_2$Cl$_2$). The combined organic layers were filtered through cotton and the filtrate concentrated. The residue was dissolved in 8 mL of acetonitrile then 2 mL of 2.4% HF in CH$_3$CN (prepared by diluting 1 mL of 48% aqueous HF to 20 mL with CH$_3$CN) was added. The solution was stirred for 4 h at 25°C then poured into 10 mL of saturated aqueous NaHCO$_3$. The mixture was extracted with ether (5x10 mL) and the extracts dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was chromatographed on a 0.5 mm silica gel plate (1:1 hexane-ether, R$_f$ 0.15) to afford 54 mg (41% overall yield from 100) of racemic verrucarino-
lactone (106) as a white crystalline solid: mp 71-72°C (lit\textsuperscript{56} mp 71-72.5°C); \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) \( \delta \) 4.38-4.30 (m, 2 H, H\textsubscript{5}), 3.84 (d, \( J=10 \text{ Hz} \), 1 H, H\textsubscript{1}), 3.28 (br s, 1 H, OH), 2.14-1.97 (m, 2 H, H\textsubscript{4}), 1.73-1.67 (m, 1 H, H\textsubscript{3}), 1.24 (d, \( J=6 \text{ Hz} \), 3 H, H\textsubscript{6}); IR (CH\textsubscript{2}Cl\textsubscript{2}) 3540, 2976, 2920, 1740, 1230, 1120, 1094, 1068 cm\textsuperscript{-1}; mass spectrum m/e 130 (M\textsuperscript{+}).

2,2,2-Trichloroethyl 5-hydroxy-3-methyl-2(E)-pentenoate (117).

Trimethylaluminum (7.5 mL of 2M toluene solution, 15 mmol) was added to a solution of 370 mg (1.27 mmol) of bis-(cyclopentadienyl)zirconium dichloride (Cp\textsubscript{2}ZrCl\textsubscript{2}). The yellow solution was cooled to 0°C then a solution of 350 mg (5 mmol) of 3-butyn-1-ol in 25 mL of CH\textsubscript{2}Cl\textsubscript{2} was added dropwise (gas evolution) at 0°C. The solution was stirred for 19.5 h at 25°C and then 0.75 mL (5.5 mmol) of 2,2,2-trichloroethyl chloroformate was added. The solution was stirred for 1.25 h at 25°C then cooled (10°C) as 10 mL of water was added very slowly dropwise (caution: vigorous reaction). Enough 6N HCl to dissolve the voluminous precipitate was then added. The aqueous layer was extracted with ether (3x15 mL) and the combined extracts dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and evaporated. The residue was purified by flash chromatography (60 mm column,
1:1 hexane:ether, Rf 0.28) to afford 273 mg (21%) of trichloroethyl ester 117. The yield of 117 was 32% when this procedure was performed on a 1 mmol scale.

Data for 117: $^1$H NMR (270 MHz, CDCl$_3$) δ 5.87 (br s, 1 H, H$_2$), 4.76 (s, 2 H, CH$_2$CCl$_3$), 3.83 (t, J=6 Hz, 2 H, H$_5$), 2.47 (t, J=6 Hz, 2 H, H$_4$), 2.24 (br s, 3 H, H$_6$), 1.75 (br s, 1 H, OH); IR (film) 3440, 2956, 1730, 1646, 1132, 1040 cm$^{-1}$.

\[
\begin{align*}
\text{CO}_2\text{CH}_2\text{CCl}_3 \quad &\xrightarrow{\text{HgCl}_2, \text{PhH, \Delta}}\quad \text{CO}_2\text{C}_2\text{H(CCl)}_3 \quad &\xrightarrow{\text{Zn}, \text{THF, KH}_2\text{PO}_4} \quad \text{CO}_2\text{PO}2\text{PO(O)}\text{Me}_3 \quad &\xrightarrow{\text{Zn}, \text{THF, KH}_2\text{PO}_4} \quad \text{CO}_3\text{H}
\end{align*}
\]

5-[[(dimethoxyphosphinyl)acetyl]oxy]-3-methyl-2-(E)-pentenoic acid (119).

Alcohol 117 was converted to phosphonate 118 by using the procedure described for conversion of 105 to 102. The crude phosphonate was purified by flash chromatography (25 mm column, 1:1 ether:CH$_2$Cl$_2$, Rf 0.35) to afford 459 mg (94%) of phosphonate 118 as a clear, colorless oil: $^1$H NMR (270 MHz, CDCl$_3$) δ 5.84 (br s, 1 H, H$_2$), 4.77 (s, 2 H, CH$_2$CCl$_3$), 4.33 (t, J=7 Hz, 2 H, H$_5$), 3.80 (d, J=12 Hz, 6 H, OCH$_3$), 2.98 (d, J=2 Hz, 2 H, CH$_2$P), 2.55 (t, J=7 Hz, 2 H, H$_4$), 2.25 (br s, 3 H, H$_6$).

Zinc dust (729 mg, 11 mmol) was added to a solution of 459 mg (1.1 mmol) of trichloroethyl ester 118 in 10 mL of THF then 2 mL of 1M aqueous KH$_2$PO$_4$ was added (note that the 5:1 THF:buffer ratio is important). The slurry was stirred for
18 h at 25°C then filtered. The filtrate was acidified to pH 1 by addition of 6N HCl then saturated with NaCl. The mixture was extracted with ethyl acetate (6x10 mL) and the combined extracts dried (MgSO₄), filtered and evaporated. The residue was purified by flash chromatography (25 mm column, 1% formic acid in 1:1 ether:CH₂Cl₂, Rf 0.26) to afford 239 mg (76%) of pure acid 119 as a clear, colorless liquid: $^1$H NMR (250 MHz, CDCl₃) δ 5.76 (br s, 1 H, H₂), 4.32 (t, J=6 Hz, 2 H, H₅), 3.85 (d, J=11 Hz, 6 H, OCH₃), 3.07 (d, J=22 Hz, 2 H, CH₂P), 2.52 (t, J=6 Hz, 2 H, H₄), 2.19 (br s, 3 H, H₆); IR (CH₂Cl₂) 3600-2500 (br OH), 2956, 1730, 1694, 1645, 1028, 850, 812; mass spectrum m/e 262 (M⁺ - H₂O), 248 (M⁺ - CH₃OH).

\[
\begin{align*}
\text{CO}_2\text{CH}_{2}\text{CCl}_2 & \quad \rightarrow \quad \text{CO}_2\text{CH}_2\text{CH}_2\text{TMS} \\
\text{117} & \quad \rightarrow \quad \text{120 (50% from 117)} \\
& \quad \rightarrow \quad \text{121 (R = CH}_2\text{Cl}_2\text{TMS)}
\end{align*}
\]

2,4-Hexadienedioic acid mono-[3-methyl-5-oxo-5-(β-trimethylsilyl-ethoxy)-3-(E)-pentenoate (121)

Alcohol 117 (83 mg, 0.32 mmol) was converted into phosphonate 118 by using the procedure described above. The crude phosphonate was deprotected with zinc dust as described above. The crude acid 119 was dissolved in 10 mL of ether then 45 mg (0.38 mmol) of 2-trimethylsilylethanol, 118 72 mg (0.35 mmol) of DCC, and a few crystals of 4-pyrrolidinopyridine were added. The mixture (white precipitate) was stirred for 20 h at 25°C, and then filtered. The filtrate was concentrated and the
residue chromatographed on a 1.5 mm silica gel plate (1:1
eraser-CH$_2$Cl$_2$, $R_f$ 0.54) to afford 60 mg (50% overall yield from
117) of ester 120 (ca. 6:1 (E):(Z) mixture) as a clear color-
less liquid: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.69 (br s, 1 H, H$_2^\prime$),
4.30 (t, $J$=7 Hz, 2 H, H$_5^\prime$), 4.22-4.15 (m, 2 H, OCH$_2$), 3.81 (d,
$J$=11 Hz, 6 H, OMe), 2.49 (t, $J$=7 Hz, 2 H, H$_4^\prime$), 2.20 (br s,
3 H, H$_6^\prime$), 1.04-0.97 (m, 2 H, CH$_2$Si), 0.05 (s, 9 H, SiMe$_3$).

Ester 120 (60 mg, 0.16 mmol), prepared as described in
the preceding paragraph, was converted into acid 121 by using
the olefination procedure described for 86. The crude product
was chromatographed on a 0.5 mm silica gel plate (1% formic acid
in 1:1 hexane-ether, 3 developments, $R_f$ 0.40) to afford 32 mg
(57%) of 121 (ca. 6:1 (E):(Z) mixture) as a clear liquid: $^1$H
NMR (250 MHz, CDCl$_3$) $\delta$ 8.39 (dd, $J$=11, 16 Hz, 1 H, H$_3^\prime$), 6.74
(t, $J$=11 Hz, 1 H, H$_4^\prime$), 6.13 (d, $J$=16 Hz, 1 H, H$_2^\prime$), 6.01 (d,
$J$=11 Hz, 1 H, H$_5^\prime$), 5.71 (br s, 1 H, H$_2^\prime$), 4.34 (t, $J$=7 Hz,
2 H, H$_5^\prime$), 4.22-4.14 (m, 2 H, OCH$_2$), 2.52 (t, $J$=7 Hz, 2 H, H$_4^\prime$),
2.21 (br s, 3 H, H$_6^\prime$), 1.03-0.96 (m, 2 H, CH$_2$Si), 0.04 (s, 9 H,
SiMe$_3$).
Experimental Procedures for Chapter III.

\[
\begin{align*}
\text{CO}_2\text{CH}_2\text{CCl}_4 & \quad 1) \quad \text{THF}:\text{HCl} \\
\text{OH} & \quad 2) \quad \text{Zn}, \text{H}_2\text{N}, \text{HCl}_2, \text{PO}_4 \\
117 & \quad 12-15 \text{ from butynol} \\
\text{CO}_2\text{H} & \quad 1) \quad \text{THF}:\text{HCl} \\
\text{OH} & \quad 2) \quad \text{BuLi}, \text{H}_2\text{O}, -60^\circ\text{C} \\
141 & \quad 3) \quad \text{H}_2, -78^\circ\text{C} \\
\text{OTBDMS} & \quad 46\% \text{ from butynol} \\
147 &
\end{align*}
\]

5-(tert-Butyldimethylsilyl)oxy-3-methyl-2-(E)-pentenoic acid ((E)-146).

**Method A:** Imidazole (137 mg, 2.0 mmol) and 145 mg (0.96 mmol) of tert-butyldimethylsilyl chloride\(^{118}\) were added to a solution of 210 mg (0.80 mmol) of \textbf{16} in 1 mL of DMF. The solution was stirred for 22 h at 25\(^\circ\)C, then diluted with 20 mL of water and extracted with hexane (8x50 mL). The combined extracts were washed with saturated aqueous NaCl, dried (MgSO\(_4\)), filtered, and evaporated. The crude silyl ether was dissolved in 10 mL of THF and treated with zinc dust (523 mg, 8.0 mmol) and 2 mL of 1M aqueous KH\(_2\)PO\(_4\) (note that the 5:1 THF:buffer ratio is important).\(^63\) The resulting slurry was stirred for 16 h at 25\(^\circ\)C. The mixture was then filtered and the filtrate acidified to pH 1 by addition of 6N HCl saturated with NaCl. The mixture was extracted with ethyl acetate (6x10 mL) and the combined extracts dried (Na\(_2\)SO\(_4\)), filtered, and evaporated. The residue was chromatographed on a 1.5-mm silica gel plate (1\% formic acid in 3:1 hexane:ether, R\(_f\) 0.43) to afford 115 mg (59\%) of pure (E)-146 as a clear, colorless liquid.
Method B: n-Butyllithium (0.53 mL of 2.9 M hexane solution, 1.54 mmol) was added dropwise to a solution of 4-(tert-butyldimethylsilyl)oxy-2-methyl-(E)-butenyl iodide (500 mg, 1.53 mmol) in 20 mL of ether at -78°C. The solution was allowed to warm to -60°C, stirred for 1.25 h at -60°C, and then recooled to -78°C. A stream of dry CO₂ gas was passed over the solution for 1 h at -78°C. The solution was then allowed to warm to 0°C with the CO₂ gas flow being continued for another 1 h at 0°C. Ether (10 mL) and water (5 mL) were added and the mixture acidified to pH 2 by careful addition of 3N HCl. The layers were separated and the aqueous layer extracted with ether (7x10 mL). The combined extracts were dried (MgSO₄), filtered and evaporated to afford 403 mg of crude acid. The crude product was purified by flash chromatography (30 mm column, 1% formic acid in 3:1 hexane-ether) to give 281 mg (75%) of pure (E) \[^1\text{H NMR (250 MHz, CDC}_{13}\text{)} \delta 5.72 \text{ (br s, 1 H, H}_2\text{), 3.77 (t, J=6 Hz, 2 H, H}_5\text{), 2.38 (t, J=6 Hz, 2 H, H}_4\text{), 2.20 (d, J=1 Hz, 3 H, H}_6\text{), 0.89 (s, 9 H, t-Bu), 0.05 (s, 6 H, SiMe}_2\text{); IR (film) 3400-2500 (br OH), 2954, 2926, 2860, 1692, 1640, 1250, 1100, 832, 772 cm}^{-1}\text{; mass spectrum m/e 229 (M}^+\text{-CH}_3\text{), 187 (M}^+\text{-t-Bu). Anal. Calcd for C}_{12}\text{H}_{24}\text{O}_3\text{Si: C, 58.97; H, 9.90. Found: C, 58.74; H, 9.87.}
5-\{(tert-Butyldimethylsilyl)oxy\}-3-methyl-2-(Z)-pentenoic acid \((Z)-146\).

Anhydromevalonolactone \((88, 143 \text{ mg}, 1.28 \text{ mmol})\)\(^{49}\) was hydrolyzed by using the literature procedure.\(^{50}\) A solution of the crude hydroxy-acid and 0.6 mL (5.12 mmol) of 2,6-lutidine in 5 mL of \(\text{CH}_2\text{Cl}_2\) was stirred for 5 minutes at 25°C then 0.88 mL (3.84 mmol) of tert-butyldimethylsilyl triflate\(^{118}\) was added dropwise. The solution was stirred for 10 minutes at 25°C then poured into 10 mL of saturated aqueous \(\text{NH}_4\text{Cl}\). The mixture was extracted with \(\text{CH}_2\text{Cl}_2\) (3x10 mL) and the combined extracts dried (\(\text{MgSO}_4\)), filtered and evaporated. The crude disilylated material was dissolved in 6 mL of DME and 2 mL of \(\text{H}_2\text{O}\) then 184 mg (7.68 mmol) of \(\text{LiOH}\) was added. The mixture was stirred vigorously for 20 minutes at 25°C then diluted with 10 mL of water and acidified to pH 2 by careful addition of 3N HCl. The mixture was extracted with ether (3x20 mL) and the combined extracts dried (\(\text{MgSO}_4\)), filtered and evaporated to afford 525 mg of light yellow liquid. A portion (190 mg) of this crude material was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 6:1 hexane-ethyl acetate, \(R_f\) 0.53) to afford 43 mg (38% based on percentage of crude product chromatographed).
of pure (Z)-146 as a clear, colorless liquid.

Data for (Z)-146: $^1$H NMR (250, CDCl₃) δ 5.83 (br s, 1 H, H₂), 3.82 (t, J=6 Hz, 2 H, H₅), 2.76 (t, J=6 Hz, 2 H, H₄), 1.96 (br s, 3 H, H₆), 0.90 (s, 9 H, tBu), 0.09 (s, 6 H, SiMe₂); IR (CH₂Cl₂) 3400–2500 (acid OH), 2954, 2936, 2860, 1724, 1690, 1638, 1092, 1078, 834 cm⁻¹; mass spectrum m/e 229 (M⁺-CH₃), 187 (M⁺-tBu).

\[
\begin{align*}
\text{DCC, CH₂Cl₂, DMAP} & \quad \rightarrow \quad \text{(E)-132 (56-60%) + (Z)-132 (14-19%)}
\end{align*}
\]


A solution of 112 mg (0.55 mmol) of dicyclohexylcarbodiimide (DCC) and 10 mg (0.08 mmol) of 4-dimethylaminopyridine (DMAP) in 0.40 mL of CH₂Cl₂ was added to a solution of 58 mg (0.22 mmol) of verrucarol and 75 mg (0.31 mmol) of (E)-146 in 0.40 mL of CH₂Cl₂. The resulting mixture (white precipitate) was stirred for 6 h at 25°C. The mixture was then filtered and the filtrate chromatographed on a 1.5-mm silica gel plate (1:1 ether:CH₂Cl₂, Rf 0.51) to give 88 mg (82%) of a 3:1 mixture of product isomers. This mixture was separated by careful chromatography on a 1.5-mm silica gel plate (1:1 hexane:ether, 8 developments) to give 64 mg (60%) of (E)-132 from the band centered at Rf 0.53 and 22 mg (19%) of Z-132.
from the faster moving band (Rf 0.62). Esterification of verrucarol with \(\text{(Z)-146}\) under analogous conditions afforded 41% of (Z)-132 and 28% of (E)-132 as waxy white solids.

**Data for (E)-132:** \([\alpha]_{D}^{22} = -42^\circ\) (c 1.4, CHCl\(_3\))

\(1^H\) NMR

(270 MHz, CDC\(_3\)) \(\delta\) 5.70 (br s, 1 H, H\(_2\)), 5.41 (br d, J=5 Hz, 1 H, H\(_{10}\)), 4.50 (m, 1 H, H\(_4\)), 4.17 (d, J=12 Hz, 1 H, H\(_{15a}\)), 3.90 (d, J=12 Hz, 1 H, H\(_{15b}\)), 3.84 (d, J=5 Hz, 1 H, H\(_2\)), 3.76 (t, J=6 Hz, 2 H, H\(_5\)), 3.61 (br d, J=5 Hz, 1 H, H\(_{11}\)), 3.12 (d, J=4 Hz, H\(_{13a}\)), 2.82 (d, J=4 Hz, 1 H, H\(_{13b}\)), 2.59 (dd, J=8, 16 Hz, 1 H, H\(_3\)), 2.35 (t, J=6 Hz, 2 H, H\(_4\)), 2.20 (d, J=1 Hz, 3 H, H\(_6\)), 2.05-1.75 (m, 6 H, H\(_7\), H\(_8\), H\(_{3\beta}\), and OH), 1.65 (br s, 3 H, H\(_{16}\)), 0.89 (s, 9 H, t-Bu), 0.87 (s, 3 H, H\(_{14}\)), 0.05 (s, 6 H, SiMe\(_2\))

\(13^C\) NMR (22.6 MHz, CDC\(_3\)) \(\delta\) 166.1, 158.2, 140.8, 118.2, 116.5, 74.2, 66.5, 65.4, 62.4, 60.8, 48.9, 47.3, 43.8, 42.6, 39.7, 27.9, 25.8, 23.1, 21.0, 19.1, 18.1, 7.0, -5.5; IR (CHCl\(_3\)) 3580, 3004, 2952, 2930, 2860, 1709, 1648, 1146, 1060, 962, 832 cm\(^{-1}\); mass spectrum m/e 492 (M\(^+\)), 435 (M\(^+\)-t-Bu), 265 (M\(^+\)-side chain).

**Data for (Z)-132:** \([\alpha]_{D}^{22} = -37^\circ\) (c 2.0, CHCl\(_3\))

\(1^H\) NMR (270 MHz, CDC\(_3\)) \(\delta\) 5.70 (br s, 1 H, H\(_2\)), 5.42 (br d, J=5 Hz, 1 H, H\(_{10}\)), 4.53 (m, 1 H, H\(_4\)), 4.14 (d, J=12 Hz, 1 H, H\(_{15a}\)), 3.90 (d, J=12 Hz, 1 H, H\(_{15b}\)), 3.84 (d, J=5 Hz, 1 H, H\(_2\)), 3.78 (t, J=7 Hz, 2 H, H\(_5\)), 3.62 (br d, J=5 Hz, 2 H, H\(_{11}\)), 3.12 (d, J=4 Hz, 1 H, H\(_{13a}\)), 2.85 (t, J=7 Hz, 2 H, H\(_4\)), 2.81 (d, J=4 Hz, 1 H, H\(_{13b}\)), 2.60 (dd, J=8, 16 Hz, 1 H, H\(_3\)), 1.98 (br s, 3 H, H\(_6\)), 1.95-1.75 (m, 6 H, H\(_7\), H\(_8\), H\(_{3\beta}\), and OH),
1.70 (br s, 3 H, H₁₆), 0.88 (br s, 12 H, t-Bu and H₁₄), 0.05 (s, 6 H, SiMe₂); IR (CH₂Cl₂) cm⁻¹ 3576, 2934, 2858, 1710, 1642, 1142, 1070, 832.

![Chemical Structure](image)

**Trichothec-9-ene-4β,15-diol-12,13-epoxy-15-(5′-hydroxy-3′-methyl-2′(E)pentenoate ((E)-11)).**

A solution of 86.0 mg (0.17 mmol) of (E)-132 in 5 mL of 3:1:1 acetic acid-water-THF was stirred for 5 h at 25°C. Heptane (20 mL, MCB reagent grade) was then added, and the mixture concentrated in vacuo. This procedure was repeated several times until the azeotropic removal of acetic acid and water was complete. The residue was purified by chromatography on a 1.5-mm silica gel plate (ethyl acetate, Rf 0.35) to give 64.1 mg (97%) of (E)-11 (verrol): 6 mp 55-60°C; [α]²⁰_D - 42° (c 0.29, CHCl₃) (lit.¹³ [α]D - 41°); ¹H NMR (250 MHz, CDCl₃) δ 5.74 (br s, 1 H, H₂.), 5.42 (br d, J=5 Hz, 1 H, H₁₀), 4.54 (m, 1 H, H₄), 4.16 (d, J=12 Hz, 1 H, H₁₅a⁻¹), 3.94 (d, J=12 Hz, 1 H, H₁₅b), 3.87-3.77 (br s, 2 H, H₅⁻¹), 3.84 (d, J=5 Hz, 1 H, H₂), 3.65 (br d, J=5 Hz, 1 H, H₁₁), 3.12 (d, J=4 Hz, 1 H, H₁₃a⁻¹), 2.82 (d, J=4 Hz, 1 H, H₁₃b), 2.60 (dd, J=8, 16 Hz, 1 H, H₃⁻¹), 2.43 (t, J=6 Hz, 2 H, H₄⁻¹), 2.21 (br s, 3 H, H₆⁻¹), 2.10-1.75 (m, 5 H, H₇⁻¹, H₈⁻¹ and H₁₀⁻¹), 1.71 (br s, 3 H, H₁₆⁻¹), 0.88 (s, 3 H, H₁₄⁻¹).
$^{13}$C NMR (22.6 MHz, CDCl$_3$) δ 166.0, 157.4, 140.7, 118.3, 116.9, 74.1, 66.5, 65.4, 62.7, 59.9, 48.8, 47.4, 43.6, 42.6, 39.5, 27.9, 23.1, 21.1, 18.7, 7.0; IR (CH$_2$Cl$_2$) 3600, 3060, 2960, 1712, 1650, 1224, 1150, 1074, 966, 690 cm$^{-1}$; mass spectrum m/e 378 (M$^+$), 265 (M$^+$ - side chain), 113 (side chain).

![Chemical Structure](image)


Silyl ether (Z)-132 (19.0 mg, 0.039 mmol) was deprotected by using the procedure described above for the preparation of (E)-II. The crude product was chromatographed on a 0.5 mm silica gel plate (ethyl acetate, R$_f$ 0.34) to give 13.3 mg (91%) of pure (Z)-II: m.p. 128.5-130°C (recrystallized from 1:1 benzene-hexane); [α]$_D^{22}$ = -49° (c 1.33, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ 5.82 (br s, 1 H, H$_2$), 5.41 (br 3, J=5 Hz, 1 H, H$_{10}$), 4.52 (br s, 1 H, H$_4$), 4.16 (d, J=12 Hz, 1 H, H$_{15a}$), 3.93 (d, J=12 Hz, 1 H, H$_{15b}$), 3.83 (d, J=6 Hz, 1 H, H$_2$), 3.82 (t, J=6 Hz, 2 H, H$_5$), 3.63 (br d, J=5 Hz, 1 H, H$_{11}$), 3.12 (d, J=4 Hz, 1 H, H$_{13a}$), 2.87 (t, J=6 Hz, 2 H, H$_4$), 2.81 (d, J=4 Hz, 1 H, H$_{13b}$), 2.59 (dd, J=8, 16 Hz, 1 H, H$_{3a}$), 2.1-1.8 (m, 7 H, H$_7$, H$_8$, H$_{38}$, and 2-OH's), 1.97 (d, J=1 Hz,
3 H, H₆'), 1.71 (br s, 3 H, H₁₆), 0.87 (s, 3 H, H₁₄); IR (CHCl₃) 3580, 3460, 3006, 2974, 1700, 1648, 1168, 1070, 964 cm⁻¹; mass spectrum m/e 348 (M⁺ - CH₂OH).

\[ \text{(E)-11} \xrightarrow{\text{DCC, CH₂Cl₂, (HCO)₂POCH₃CO₂H (68)}} \text{(E)-143} \]


A solution of 26.2 mg (0.13 mmol) of dicyclohexylcarbodiimide and several small crystals of 4-dimethylaminopyridine (DMAP) in 0.60 mL of CH₂Cl₂ was added to a solution of 23 mg (0.061 mmol) of (E)-11 and 11.2 mg (0.067 mmol) of dimethylphosphonoacetic acid in 0.40 mL of CH₂Cl₂. The mixture was stirred for 5 h at 25°C and then filtered. The filtrate was concentrated and chromatographed on a 0.5 mm silica gel plate (97:3 ethyl acetate-methanol, Rf 0.25) to give 17.1 mg (53%) of phosphonate (E)-143 as a colorless syrup and 7.5 mg (33%) of recovered (E)-11 (Rf 0.50).

**Data for (E)-143:** [α]D⁰²¹ = 33° (c 0.32, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 5.73 (br s, 1 H, H₂), 5.43 (br d, J=5 Hz, 1 H, H₁₀), 4.63 (m, 1 H, H₄), 4.33 (t, J=6 Hz, 2 H, H₅'), 4.15 (d, J=12 Hz, 1 H, H₁₅a'), 3.96 (d, J=12 Hz, 1 H, H₁₅b'), 3.84 (d, J=5 Hz, 1 H, H₂), 3.81 (d, J=11 Hz, 3 H, -OME), 3.80 (d, J=11 Hz, 3 H, -OME), 3.70 (br d, J=5 Hz, 1 H, H₁₄),
3.12 (d, J=4 Hz, 1 H, H₁₃a), 2.98 (d, J=21 Hz, 2 H, H₂w),
2.81 (d, J=4 Hz, 1 H, H₁₃b), 2.59 (dd, J=8, 16 Hz, 1 H, H₃α),
2.52 (t, J=6 Hz, 2 H, H₅1), 2.26 (d, J=9 Hz, 1 H, OH), 2.21
(d, J=2 Hz, 3 H, H₆), 2.15-1.75 (m, 5 H, H₇, H₈, and H₃β),
1.71 (br s, 3 H, H₁₆), 0.88 (s, 3 H, H₁₄); IR (CH₂Cl₂) 3580,
2964, 1738, 1714, 1650, 1260, 1040, 690 cm⁻¹; mass spectrum
m/e 528 (M⁺).

Trichothec-9-ene-4β,15-diol-12,13-epoxy-15[5′-([dimethoxy-
phosphinylacetyl]oxyl)-3′-methyl-2′(Z)-pentenoate], (Z)-143.

Diol (Z)-11 (8.0 mg, 0.021 mmol) was acylated using the
procedure described above for (E)-11. The crude product was
chromatographed on a 0.25 mm silica gel plate (97:3 ethyl
acetate:methanol, Rₚ 0.25) to afford 6.5 mg (58%) of phosphonate
(Z)-143 as a colorless syrup.

Data for (Z)-143: [α]D⁻¹⁹ - 35° (c 0.92 in CHCl₃); ¹H NMR
(250, CDCl₃) δ 5.77 (br s, 1 H, H₂), 5.41 (br d, J=5 Hz, 1 H,
H₁₀), 4.53 (m, 1 H, H₄), 4.31 (m, 2 H, H₅), 4.16 (d, J=12 Hz,
1 H, H₁₅a), 3.90 (d, J=12 Hz, 1 H, H₁₅b), 3.81 (d, J=11 Hz,
3 H, OMe), 3.80 (d, J=11 Hz, 3 H, OMe), 3.78 (d, J=5 Hz, 1 H,
H₂), 3.63 (d, J=5 Hz, 1 H, H₁₁), 3.11 (d, J=4 Hz, 1 H, H₁₃a),
3.1-2.9 (m, 2 H, H₄), 2.97 (d, J=22 Hz, 2 H, CH₂P), 2.80 (d,
J=4 Hz, 1 H, H₁₃b), 2.58 (dd, J=8, 16 Hz, 1 H, H₃α), 2.2-1.7
(m, 6 H, H₈ + H₇ + H₃β + OH), 1.98 (br s, 3 H, H₆), 1.71
(br s, 3 H, H₁₆), 0.88 (s, 3 H, H₁₄); IR (CH₂Cl₂) 3570, 3420,
3050, 2955, 1736, 1710, 1650, 1145, 1035, 962 cm⁻¹; mass
spectrum m/e 510 (M⁺ - H₂O).
p-Methoxybenzyl Dimethyl Phosphonoacetate (150).

A solution of 1.85 g (9.0 mmol) of dicyclohexylcarbodiimide in 5 mL of CH₂Cl₂ was added to a cooled (ice bath) solution of 1.00 g (5.95 mmol) of dimethylphosphonoacetic acid, 0.82 mL (6.5 mmol) of p-methoxybenzyl alcohol, and 75 mg (0.61 mmol) of 4-dimethylaminopyridine in 7 mL of CH₂Cl₂. The mixture (white precipitate) was stirred for 17 h at 25°C and then filtered. The filtrate was concentrated and the residue purified by flash chromatography (50 mm column, 1:1 ether-CH₂Cl₂, Rf 0.36) to afford 1.63 g (95%) of pure 150 as a colorless liquid: ¹H NMR (250 MHz, CDCl₃) δ 7.32 (d, J=9 Hz, 2 H), 6.89 (d, J=9 Hz, 2 H), 5.12 (br s, 2 H, benzylic), 3.81 (s, 3 H, ArOCH₃), 3.76 (d, J=11 Hz, 6 H, -POCH₃), 3.01 (d, J=21 Hz, 2 H); ¹³C NMR (22.6 MHz, CDCl₃) δ 165.2, (d, J=6 Hz), 159.5 (s), 129.9 (s), 127.1 (s), 113.6 (s), 66.9 (s), 55.0 (s), 52.8 (d, J=6 Hz, 2 C, POCH₃), 33.1 (d, J=135 Hz, CH₂P); IR (film) 2960, 2840, 1734, 1614, 1586, 1516, 1250, 1030 cm⁻¹; mass spectrum m/e 288 (M⁺). Anal. Calcd. for C₁₂H₁₄O₆P: C, 50.00; H, 5.94. Found C, 50.23; H, 6.04.
mono-(p-Methoxybenzyl)(E,Z)-Muconate (151).

A solution of 586 mg (5.85 mmol) of malealdehydic acid\(^{46}\) in 40 mL of ether and a solution of 1.29 g (11.5 mmol) of potassium tert-butoxide in 40 mL of tert-butanol were added dropwise via separate addition funnels to a cooled (ice bath) solution of 1.58 g (5.47 mmol) of phosphonate \(^{150}\) in 50 mL of ether. The mixture (white precipitate) was stirred for 3 h at 25° and then poured into 50 mL of water. Ether (100 mL) was added and the cooled (ice bath) mixture acidified to pH 2 by careful addition of 3N HCl. The layers were separated and the aqueous phase extracted with ether (5×100 mL). The combined extracts were dried (Na\(_2\)SO\(_4\)), filtered, and evaporated to give 1.82 g of white solid. The crude muconate was purified by flash chromatography (60 mm column, 1% formic acid in 2:1 hexane:ether, \(R_f\) 0.21 for \(^{151}\) and \(R_f\) 0.3 for the (Z,Z)-isomer; mixed fractions were rechromatographed) to give 0.10 g (7%) of the (Z,Z)-isomer and 1.1 g (76%) of \(^{151}\): mp 118.5-120°C; \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 8.42 (dd, \(J=12, 16\) Hz, 1 H), 7.35 (d, \(J=9\) Hz, 2 H, aromatic), 6.91 (d, \(J=9\) Hz, 2 H, aromatic), 6.75 (t, \(J=12\) Hz, 1 H), 6.18 (d, \(J=16\) Hz, 1 H), 6.00 (d, \(J=12\) Hz, 1 H).
Hz, 1 H), 5.18 (br s, 2 H, benzylic), 3.82 (s, 3 H, OMe);
13C NMR (22.6 MHz, CDCl₃) δ 170.4, 165.8, 159.6, 142.5, 138.5,
130.1, 129.5, 127.8, 123.8, 113.9, 66.4, 55.1; IR (CH₂Cl₂)
3500-2400 (br OH), 1716, 1696, 1612, 1602, 1514, 1230 cm⁻¹;
mass spectrum m/e 262 (M⁺): UV (EtOH) 262 (ε = 21,600), 227
Found C, 63.96; H, 5.68.

p-Methoxybenzyl 2'-Trimethylsilylethylene (E,Z)-Muconate (153).

Diethyl azodicarboxylate (0.19 mL, 1.21 mmol) was added
to a cooled (10-15°C) solution of 161 mg (0.61 mmol) of 151,
0.11 mL (0.77 mmol) of 2-trimethylsilyl ethanol, 118 and 322
mg (1.22 mmol) of triphenylphosphine in 10 mL of THF. The
yellow solution was stirred for 2.5 h at 25°C and then the
solvent was removed in vacuo. The crude product was purified
by flash chromatography (60 mm column, 10:1 hexane:ethyl
acetate; Rf 0.24; mixed fractions were rechromatographed) to
give 185 mg (83%) of pure diester 153: mp 42-43°C; 1H NMR
(250 MHz, CDCl₃) δ 8.42 (dd, J=12, 16 Hz, 1 H), 7.34 (d, J=
9 Hz, 2 H, aromatic), 6.90 (d, J=9 Hz, 2 H, aromatic), 6.61
(t, J=12 Hz, 1 H), 6.12 (d, J=16 Hz, 1 H), 5.95 (d, J=12 Hz,
1 H), 5.16 (s, 2 H, benzylic), 4.30-4.24 (m, 2 H, OCH₂),
3.82 (s, 3 H, -OCH₃), 1.08-1.02 (m, 2 H, CH₂Si), 0.06 (s, 9 H, SiMe₃); IR (CH₂Cl₂) 2960, 2900, 2840, 1710, 1612, 1602, 1516, 1242, 1162, 836 cm⁻¹; mass spectrum m/e 362 (M⁺); UV (EtOH) 264 (ε = 30,500), 227 (ε = 17,400). Anal. Calcd for C₁₉H₂₆O₅Si: C, 62.95; H, 7.23. Found: C, 62.84; H, 7.05.

mono-2-Trimethylsilylethyl (E,Z)-Muconate (154)

A solution of 490 mg (1.35 mmol) of diester 153 in 3 mL of formic acid was stirred for 2 h at 25°C. Carbon tetrachloride was added and the solution concentrated in vacuo. This procedure was repeated several times to remove the formic acid (HCO₂H-CCl₄ azoetope). Purification of the resulting white solid by flash chromatography (50 mm column, 1% formic acid in 3:1 hexane ether, Rₑ 0.21; mixed fractions were rechromatographed) afforded 251 mg (76%) of pure 154:

mp 70-72°C (recrystallized from CH₂Cl₂-hexane); ¹H NMR (250 MHz, CDCl₃) δ 8.52 (dd, J=12, 16 Hz, 1 H), 6.62 (t, J=12 Hz, 1 H), 6.11 (d, J=16 Hz, 1 H), 6.00 (d, J=12 Hz, 1 H), 4.32-4.25 (m, 2 H, OCH₂), 1.10-1.03 (m, 2 H, CH₂Si), 0.07 (s, 9 H, SiMe₃); IR (CH₂Cl₂) 3300-2500 (br OH), 3050, 2958, 2900, 1712, 1696, 1682, 1646, 1602, 1254, 1176, 858, 836 cm⁻¹; mass
spectrum 242 (M⁺); UV (EtOH) 261 (ε = 21,600); Anal. Calcd
for C₁₁H₁₈O₄Si: C, 54.52; H, 7.49. Found: C, 54.29; H,
7.48.

Verrucarin J Seco Acid 2-Trimethylsilyl ethyl Ester (155).

Diethyl azodicarboxylate (0.025 mL, 0.158 mmol) was
added to a solution of 42 mg (0.158 mmol) of triphenylphosphate,
22 mg (0.091 mmol) of acid 154 and 30.0 mg (0.079 mmol) of
(E)-11 in 1.5 mL of THF. The light yellow solution was
stirred for 1 h at 25°C. The solvent was evaporated leaving
148 mg of clear yellow syrup which was chromatographed on a
1.5-mm silica gel plate (1% HCO₂H in 1:1 hexane:ether, 3
developments, R_f 0.09-0.18) to give 42 mg (87%) of pure 155:
mp 42-46°C; [α]D²⁰ - 28° (c 4.2, CHCl₃); ¹H NMR (250 MHz, CDCl₃)
δ 8.41 (dd, J=11, 16 Hz, 1 H, H₃‴), 6.61 (t, J=11 Hz, 1 H, H₄‴),
6.07 (d, J=16 Hz, 1 H, H₂‴), 5.95 (d, J=11 Hz, 1 H, H₅‴),
5.68 (br s, 1 H, H₂), 5.39 (br d, J=5 Hz, 1 H, H₁₀), 4.48
(m, 1 H, H₄), 4.33 (t, J=7 Hz, 2 H, H₅′), 4.26 (m, 2 H, -OCH₂),
4.15 (d, J=12 Hz, 1 H, H₁₅a), 3.90 (d, J=12 Hz, 1 H, H₁₅b), 3.81
(d, J=5 Hz, 1 H, H₂), 3.60 (br d, J=5 Hz, 1 H, H₁₁), 3.09 (d,
J=4 Hz, 1 H, H₁₃a), 2.79 (d, J=4 Hz, 1 H, H₁₃b), 2.57 (dd,
J=8, 16 Hz, 1 H, H₃α), 2.52 (t, J=7 Hz, 2 H, H₄), 2.21 (d, J=1 Hz, 3 H, H₆'), 2.0-1.7 (m, 6 H, H₇, H₈, H₃β, and OH), 1.69 (br s, 3 H, H₁₆), 1.04 (m, 2 H, CH₂Si), 0.84 (s, 3 H, H₁₄), 0.05 (s, 9 H, SiMe₃); IR (CHCl₃) 3580, 3004, 2960, 1712, 1650, 1602, 1171, 1148 cm⁻¹; UV (EtOH) 263 nm (ε = 24,800), 218 nm (ε = 18,800).

Verrucarin J Seco Acid (141).

Method A: A solution of potassium tert-butoxide in tert-butanol (0.30 mL of 0.265 M solution, 0.080 mmol) was added dropwise to a solution of 5.0 mg (0.05 mmol) of malealdehydic acid and 13.0 mg (0.025 mmol) of phosphonate (E)-143 in 0.40 mL of tert-butanol. The solution was stirred for 3 h at 25°C. Analytical TLC still showed some starting material remaining so an additional 0.050 mL (0.015 mmol) of potassium tert-butoxide solution was added. A few minutes later a considerable amount of yellow precipitate began to form. The reaction was then quenched by addition of 1 mL of water and 3 mL of ether. The pH was adjusted to 2 by careful addition of 1N HCl. The layers were separated and the aqueous phase extracted with ether (3x3 mL) and ethyl acetate (4x3 mL). The combined extracts
were dried (MgSO₄), filtered, and evaporated to give 14.5 mg of a colorless syrup. This crude product was chromatographed on a 0.25-mm silica gel plate (1% HCO₂H in 1:1 ether:CH₂Cl₂, Rf 0.37) to give 8.1 mg (57%) of verrucarin J seco acid 141 which contained approximately 10% of a muconate isomer.

Method B: Water (0.016 mL, 0.98 mmol) was added to a solution of 27 mg (0.46 mmol) of anhydrous potassium fluoride and 39.5 mg (0.0655 mmol) of ester 155 in 3 mL of Me₂SO. The resulting mixture was stirred for 42.5 h at 25°C. The reaction mixture (white precipitate) was then cooled in an ice bath as 25 mL of water and 15 mL of ethyl acetate were added. The pH was lowered to 1.5 careful addition of 3N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (5x15 mL) and CH₂Cl₂ (2x15 mL). The combined extracts were dried (MgSO₄), filtered and evaporated to give 398 mg of yellow liquid. The crude product (containing a large amount of Me₂SO) was chromatographed on a 1.5-mm silica gel plate (1% formic acid in 1:1 ether-CH₂Cl₂) to give 30 mg of impure product. This material was rechromatographed on a 0.25 mm silica gel plate (1% formic acid in 1:1 ether:CH₂Cl₂, Rf 0.42) to afford 26.8 mg (81%) of isomerically pure seco acid 141: mp 63-66°C; [α]D²⁰ 26° (c 0.81, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 8.35 (dd, J=11, 16 Hz, 1 H, H₃"), 6.64 (t, J=11 Hz, 1 H, H₄"), 6.02 (d, J=16 Hz, 1 H, H₂"), 5.97 (d, J=11 Hz, 1 H, H₅"), 5.87 (br s, 1 H, H₂'), 5.43
(br d, J=6 Hz, 1 H, H₁₀), 4.84 (dd, J=2, 8 Hz, 1 H, H₄),
4.34 (m, 2 H, H₅), 4.07 (m, 2 H, H₁₅), 3.87 (d, J=6 Hz, 1 H,
H₂), 3.78 (br d, J=6 Hz, 1 H, H₁₁), 3.16 (d, J=4 Hz, 1 H,
H₁₃a), 2.85 (d, J=4 Hz, 1 H, H₁₃b), 2.68 (dd, J=8, 16 Hz, 1 H,
H₃a), 2.57 (t, J=6 Hz, 2 H, H₄), 2.21 (d, J=2 Hz, 3 H, H₆),
2.1-1.8 (m, 5 H, H₇, H₈, and H₃b), 1.72 (br s, 3 H, H₁₆),
0.98 (s, 3 H, H₁₄); ¹³C NMR (67.9 MHz, CDCl₃) δ 167.3, 166.0,
165.8, 156.2, 141.1, 140.7, 139.0, 128.4, 124.9, 118.3, 117.6,
78.5, 74.7, 66.3, 65.7, 62.9, 61.3, 49.1, 47.7, 42.4, 39.7,
39.4, 27.8, 23.2, 21.2, 18.0, 7.1; IR (CHCl₃) 3004, 2974, 1710,
1650, 1601, 1438, 1148 cm⁻¹; mass spectrum m/e 360 (M⁺-muconic
acid); UV (EtOH) 263 (ε = 33,500), 221 (ε = 29,100).

![Chemical structure](image)

Verrucarin J (3) and (E,E,E)-Verrucarin (158).

Pivaloyl chloride (0.0048 mL, 0.039 mmol) was added to
a solution of triethylamine (0.009 mL, 0.065 mmol) and 12.9 mg
(0.026 mmol) of verrucarin J seco acid 141 in 30 mL of CH₂Cl₂.¹²⁰
The solution was stirred for a few minutes at 25°C and then
two small crystals of 4-pyrrolidinopyridine were added. The
solution was stirred for 2.5 h at 25°C. Analytical TLC still
showed some seco acid remaining so an additional 0.009 mL
(0.065 mmol) of triethylamine was added followed by 0.0048 mL
(0.039 mmol) of pivaloyl chloride. The solution was stirred
for an additional 1.5 h at 25°C then the solvent was evaporated.
The residue was chromatographed on a 0.5-mm silica gel plate
(1:1 ether-CH₂Cl₂) to afford 6.7 mg (54%) of synthetic
verrucarin J (Rf 0.70) and 4.0 mg (32%) of (E,E,E)-isomer 158
(Rf 0.53). The cyclization was complete within 1 h at 25°C
when 141 was treated 3-4 equiv. of pivaloyl chloride and 5
equiv. of Et₃N at the start of the reaction.

Synthetic verrucarin J so obtained¹²⁰ was identical in
all respects with an authentic sample provided by Professor
B. Jarvis: mp > 290°C; lit.¹³ mp > 315°C; [α]₂₀º + 40° (c 0.33,
C₆H₆); lit.¹³ [α]₂³³ + 41°; ¹H NMR (270 MHz, CDCl₃) δ 8.07
(dd, J=11, 16 Hz, 1 H, H₃α'), 6.63 (t, J=11 Hz, 1 H, H₄α''),
6.11 (dt, J=11 Hz, 1 H, H₅α''), 6.01 (d, J=16 Hz, 1 H, H₂α''),
6.01 (dd, J=4, 8 Hz, 1 H, H₄), 5.84 (br s, 1 H, H₂α'), 5.46
(br d, J=5 Hz, 1 H, H₁₀), 4.47 (m, 1 H, H₅α'), 4.44 (d, J=13
Hz, 1 H, H₁₅α'), 4.15 (m, 1 H, H₅β'), 3.97 (d, J=13 Hz, 1 H,
H₁₅β'), 3.86 (d, J=5 Hz, 1 H, H₂), 3.76 (br d, J=5 Hz, 1 H, H₁₁),
3.15 (d, J=4 Hz, 1 H, H₁₃α'), 2.84 (d, J=4 Hz, 1 H, H₁₃β'),
2.53 (m, 3 H, H₄α'), and H₃α), 2.29 (br s, 3 H, H₆'), 2.2-1.8
(m, 5 H, H₇, H₈, and H₃β), 1.72 (br s, 3 H, H₁₆'), 0.84 (s, 3 H,
H₁₄); IR (CH₂Cl₂) 3022, 2962, 1712, 1650, 1224, 1182 cm⁻¹;
mass spectrum m/e 484 (M⁺); UV (EtOH) 262 (ε = 20,400), 218
(ε = 27,600).
Data for 158: mp 136-142°C; $[\alpha]_D^{20} + 64^\circ$ (c 0.36, C$_6$H$_5$); $^1$H NMR (270, CDCl$_3$) $\delta$ 7.41 (dd, J=12, 14 Hz, 1 H, H$_3''$ or H$_4''$), 7.26 (dd, J=12, 15 Hz, 1 H, H$_4''$ or H$_3''$), 6.46 (d, J=14 Hz, 1 H, H$_2''$ or H$_5''$), 6.16 (d, J=15 Hz, 1 H, H$_5''$ or H$_2''$), 5.78 (br s, 1 H, H$_2$), 5.43 (br d, J=6 Hz, 1 H, H$_{10}$), 5.39 (dd, J=3, 7 Hz, 1 H, H$_4$), 4.57-4.47 (m, 1 H, H$_{5'a}$), 4.44 (d, J=13 Hz, 1 H, H$_{15a}$), 4.34-4.25 (m, 1 H, H$_{5'b}$), 3.95 (d, J=13 Hz, 1 H, H$_{15b}$), 3.89 (d, J=6 Hz, 1 H, H$_2$), 3.70 (br d, J=6 Hz, 1 H, H$_{11}$), 3.12 (d, J=4 Hz, 1 H, H$_{13a}$), 2.83 (d, J=4 Hz, 1 H, H$_{13b}$), 2.68 (dd, J=8, 16 Hz, 1 H, H$_{3a}$), 2.5-2.3 (m, 3 H, H$_4$ and H$_{3b}$), 2.29 (d, J=1 Hz, 3 H, H$_6$), 2.10-1.90 (m, 4 H, H$_7$ and H$_8$), 1.74 (br s, 3 H, H$_{16}$), 0.94 (s, 3 H, H$_{14}$); IR (CH$_2$Cl$_2$) 3060, 2980, 1720, 1650, 1228, 1144, 1080, 690 cm$^{-1}$; mass spectrum m/e 484 (M$^+$); UV (decomposes in EtOH to give 34); high resolution mass spectrum, calcd for C$_{27}$H$_{32}$O$_8$ m/e 484.210, found m/e 484.210.

Data for 160: Prepared by ethanolysis of 158 (t$_{1/2}$ ~ 3 h; TLC analysis); R$_f$ 0.45 (1:1 ether-CH$_2$Cl$_2$); $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 7.4-7.2 (m, 2 H, H$_3''$ and H$_4''$), 6.3-6.15 (m, 2 H, H$_2''$ and H$_5''$), 5.70 (br s, 1 H, H$_2$), 5.41 (br d, J=5 Hz, 1 H, H$_{10}$), 4.50 (m, 1 H, H$_4$), 4.35 (t, J=7 Hz, 2 H, H$_5$), 4.25 (q, J=7 Hz,
2H, OCH₂CH₃), 4.17 (d, J=13 Hz, 1H, H₁₅a), 3.93 (d, J=13 Hz, 1H, H₁₅b), 3.84 (d, J=5 Hz, 1H, H₂), 3.65 (br s, 1H, OH), 3.62 (br d, J=5 Hz, 1H, H₁₁), 3.12 (d, J=4 Hz, 1H, H₁₃a), 2.81 (d, J=4 Hz, 1H, H₁₃b), 2.57 (dd, J=8, 16 Hz, 1H, H₃a), 2.54 (t, J=7 Hz, 2H, H₄), 2.22 (br s, 3H, H₆'), 2.1-1.8 (m, 5H, H₇, H₈, and H₃b), 1.71 (br s, 3H, H₁₆), 1.32 (t, J=7 Hz, 3H, OCH₂CH₃), 0.87 (s, 3H, H₁₄); UV (EtOH) 263 (ε = 24,500), 217 (ε = 20,700).

Data for 157: Generated in situ by addition of excess pivaloyl chloride and Et₃N to a dilute (ca. 2 mM) solution of 141 in an NMR tube: Rf 0.5 (1% formic acid in 1:1 ether-CH₂Cl₂); ¹H NMR (250 MHz, CDCl₃) δ 8.36 (dd, J=12, 15 Hz, 1H, H₃'), 6.85 (dd, J=12, 12 Hz, 1H, H₄'), 6.18 (d, J=15 Hz, 1H, H₂'), 5.98 (d, J=12 Hz, 1H, H₅'), 5.70 (br s, 1H, H₂'), 5.41 (br d, J=5 Hz, 1H, H₁₀), 4.52-4.47 (m, 1H, H₄'), 4.35 (t, J=7 Hz, 2H, H₅'), 4.16 (d, J=13 Hz, 1H, H₁₅a), 3.92 (d, J=13 Hz, 1H, H₁₅b), 3.84 (d, J=5 Hz, 1H, H₂), 3.62 (br d, J=5 Hz, 1H, H₁₁), 3.12 (d, J=4 Hz, 1H, H₁₃a), 2.81 (d, J=4 Hz, 1H, H₁₃b), 2.54 (t, J=7 Hz, 2H, H₄'), 2.22 (br s, 3H, H₆'), 2.2-1.8 (m, 6H, H₇ + H₈ + H₃b + OH), 1.70 (br s,
3 H, H_{16}'), 0.86 (s, 3 H, H_{14}), signals due to H_{3a} and CMe_{3} were obscured by signals from Et_{3}N and pivaloyl chloride.

Isomerization of 158 to Verrucarin J and (E,Z,E)-Isomer 159.

One small crystal of I_{2} was added to a solution of 1.3 mg of 158 in 1 mL of dry benzene. The resulting red solution was stirred at 25°C for 90 minutes and then was diluted with 10 mL of dry benzene. Solid sodium sulfite (Na_{2}SO_{3}) was added and the mixture stirred at 25°C until the iodine color had disappeared. The mixture was chromatographed on a 0.25 mm silica gel plate (1% methanol in CH_{2}Cl_{2}; 5 developments) to afford 0.8 mg (61%) of verrucarin J (R_{f} 0.60) and 0.4 mg (31%) of the (E,Z,E)-isomer 159 (R_{f} 0.63).

Data for 159: \textsuperscript{1}H NMR (250 MHz, CDCl_{3}) \delta 8.08 (dd, J=12, 16 Hz, 1 H, H_{4''}), 6.71 (t, J=12 Hz, 1 H, H_{3''}), 6.33 (dd, J=5, 8 Hz, 1 H, H_{4}), 6.20 (d, J=16 Hz, 1 H, H_{5''}), 5.93 (d, J=12 Hz, 1 H, H_{2''}), 5.90 (br s, 1 H, H_{2''}), 5.52 (br d, J=5 Hz, 1 H, H_{10}), 4.39-4.43 (m, 2 H, H_{5}), 4.22 (d, J=13 Hz, 1 H, H_{15a}), 4.11 (d, J=5 Hz, 1 H, H_{11}), 4.02 (d, J=13 Hz, 1 H, H_{15b}), 3.88 (d, J=5 Hz, 1 H, H_{2}), 3.19 (d, J=4 Hz, 1 H, H_{13a}), 2.86 (d, J=4 Hz, 1 H, H_{13b}), 2.8-2.5
(m, 3 H, H₄, and H₃α), 2.23 (br s, 3 H, H₆'), 2.2-1.8 (m, 5 H, H₇, H₈, and H₃β), 1.72 (br s, 3 H, H₁₆), 0.75 (s, 3 H, H₁₄); mass spectrum m/e 484 (M⁺); UV (EtOH) 263 (ε=11,400), 218 (ε=17,000).

\[ \text{O} \text{O} \text{O} \text{OH} \rightarrow \text{I₂, reflux} \rightarrow \text{HO} \text{C} \text{CHO} \]

**Fumaraldehydic Acid (186).**

One crystal of iodine was added to a solution of 208 mg (2.08 mmol) of malealdehydic acid (39) in 10 mL of benzene. The deep red solution was refluxed for 13.5 h then (after cooling to 25°C) a spatula tip full of solid sodium sulfite (Na₂SO₃) was added. The mixture was stirred at 25°C until the red color disappeared (ca. 25 minutes) then filtered. The filtrate was concentrated in vacuo and the residue chromatographed on a 1.5 mm silica gel plate (85:10:5 chloroform-acetone-acetic acid) to give 27 mg (13%) of fumaraldehydic acid (186, Rₕ 0.45) and 140 mg (67%) of recovered malealdehydic acid (39, Rₕ 0.35).

**Data for 186: mp 122-125°C (recrystallized from acetone-CHCl₃) (lit²ᵇ mp 125-126°C); \(^1\)H NMR (250 MHz, CD₃COCD₃) δ 9.85 (d, J=7 Hz, 1 H, H₄), 6.97-6.79 (m, 2 H, H₂ and H₃).**
mono-2-Trimethylsilylethyl (E,E)-muconate (161).

A solution of 479 mg (2.3 mmol) of dicyclohexylcarbodiimide in 1 mL of CH₂Cl₂ was added to a cooled (10°C) solution of 260 mg (1.55 mmol) of dimethylphosphonoacetic acid, 0.24 mL (1.7 mmol) of 2-trimethylsilylethanol and 19 mg (0.155 mmol) of 4-dimethylaminopyridine in 1 mL of CH₂Cl₂. The mixture (white precipitate) was stirred for 16 h at 25°C and then filtered. The crude product was purified by flash chromatography (50 mm column, 1:1 ether-CH₂Cl₂, Rf 0.45) to give 429 mg of crude phosphonate ester which was distilled (Kugelrohr, 160-163°C at 0.35 mm Hg) to afford 381 mg (92%) of pure phosphonate: ¹H NMR (250 MHz, CDCl₃) δ 4.25-4.21 (m, 2 H, OCH₂), 3.80 (d, J=11 Hz, 6 H, OMe), 2.96 (d, J=21 Hz, 2 H, CH₂P), 1.05-0.98 (m, 2 H, CH₂Si), 0.03 (s, 9 H, SiMe₃): IR (film) 2954, 2900, 2856, 1732, 1450, 1400, 1260, 1054, 1030, 834 cm⁻¹; mass spectrum m/e 268 (M⁺). Anal. Calcd for C₉H₂₁O₅PSi: C, 40.29; H, 7.89. Found C, 40.68; H, 8.09.

A solution of 22.0 mg (0.22 mmol) of fumaraldehydic acid (186) in 3 mL of ether and a solution of potassium tert-butoxide in tert-butanol (1.65 mL of 0.28 M solution, 0.46 mmol) were added dropwise simultaneously, but separately, to a solution
of 59 mg (0.22 mmol) of the above phosphonate in 3 mL of ether. The cloudy yellow mixture was stirred for 6 h at 25°C and then 5 mL of water was added. The mixture was acidified to pH 1.5 by slow addition of 3N HCl and then extracted with ether (5 x 100 mL). The combined extracts were dried (MgSO₄), filtered, and evaporated to afford 65 mg of crude product. The crude material was chromatographed on a 0.5-mm silica gel plate (1% formic acid in 3:1 hexane-ether, Rf 0.22) to afford 35 mg (66%) of a 5:1 mixture of 161 and its (Z,E)-isomer. Recrystallization of this mixture from hexane-CH₂Cl₂ afforded pure (E,E)-161: mp 135.5-137°C; H NMR (250 MHz, CDCl₃) 7.47-7.30 (m, 2 H), 6.26-6.18 (m, 2 H), 4.32-4.25 (m, 2 H, OCH₂), 1.09-1.02 (m, 2 H, CH₂Si), 0.07 (s, 9 H, SiMe₃); IR (CH₂Cl₂) 3400-2400 (br OH), 2958, 2900, 1708, 1695, 1612, 1002, 908, 856, 836 cm⁻¹; mass spectrum m/e 227 (M⁺-CH₃), 199 (M⁺-CH₃-C₂H₄); UV (EtOH) 261 (ε = 24,500).

(E,E,E)-Verrucarin J Seco Acid 2-Trimethylsilylethyl ester (162).

Diethyl azodicarboxylate (0.015 mL, 0.095 mmol) was added to a solution of 25.0 mg (0.095 mmol) of triphenylphosphine, 15.0 mg
(0.062 mmol) of acid 161, and 18.0 mg (0.0475 mmol) of (E)-11 in 1 mL of THF. The solution was stirred for 1.5 h at 25°C, and then all volatile components were removed in vacuo. The residue was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 1:1 hexane-ether, 3 developments, Rf 0.15-0.25) to afford 23 mg (80%) of the seco acid β-trimethylsilylethyl ester 162 as a waxy white solid: mp 28-33°C; [α]D²⁰ - 31° (c 1.89, CHCl₃); H NMR (250 MHz, CDCl₃) δ 7.35-7.2 (m, 2 H, H₃" and H₄"), 6.25-6.15 (m, 2 H, H₂" and H₅"), 5.69 (br s, 1 H, H₂'), 5.4 (br d, J=5 Hz, 1 H, H₁₀), 4.49 (m, 1 H, H₄), 4.34 (t, J=7 Hz, 2 H, H₅'), 4.27 (m, 2 H, OCH₂), 4.16 (d, J=12 Hz, 1 H, H₁₅a'), 3.91 (d, J=12 Hz, 1 H, H₁₅b), 3.83 (d, J=5 Hz, 1 H, H₁'), 3.61 (br d, J=5 Hz, 1 H, H₁₁), 3.11 (d, J=4 Hz, 1 H, H₁₃a), 2.80 (d, J=4 Hz, 1 H, H₁₃b), 2.59 (dd, J=8, 16 Hz, 1 H, H₃a), 2.53 (t, J=7 Hz, 2 H, H₄'), 2.21 (br s, 3 H, H₆'), 2.05-1.7 (m, 6 H, H₈ + H₇ + H₃β and OH), 1.70 (br s, 3 H, H₁₆), 1.04 (m, 2 H, CH₂Si), 0.85 (s, 3 H, H₁₄), 0.04 (s, 9 H, SiMe₃); IR (CHCl₃) 3580, 3480, 3010, 2958, 2904, 1710, 1242, 1150, 1072 cm⁻¹; UV (EtOH) 264 (ε = 32,800), 219 (ε = 19,700).
(E, E, E)-Verrucarin J Seco Acid (163).

Water (0.0095 mL, 0.528 mmol) was added to a solution of 15.4 mg (0.264 mmol) of potassium fluoride and 20.0 mg (0.033 mmol) of 162 in 2 mL of DMSO. The mixture was stirred for 44 h at 25°C. The reaction mixture (white precipitate) was cooled in an ice bath as 25 mL of water and 15 mL of ethyl acetate were added. The pH was lowered to 1.5 by careful addition of 3N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (5x15 mL) and CH₂Cl₂ (2x15 mL). The combined extracts were dried (MgSO₄), filtered and evaporated to give 33 mg of a yellow residue. The crude product was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 ether-CH₂Cl₂, Rf 0.30) to give 11.7 mg (70%) of (E, E, E)-secosteroid 163 as a waxy white solid: mp 59-62°C; [α]D¹⁹ - 19° (c 0.80, CHCl₃); ¹H NMR (270 MHz, CDCl₃) δ 7.4-7.25 (m, 2 H, H₃" and H₄"), 6.3-6.15 (m, 2 H, H₂" and H₅"), 5.70 (br s, 1 H, H₂), 5.41 (br d, J=5 Hz, 1 H, H₁₀), 4.52 (br d, 1 H, H₄), 4.35 (t, J=6 Hz, 2 H, H₅), 4.17 (d, J=13 Hz, 1 H, H₁₅a), 3.92 (d, J=13 Hz, 1 H, H₁₅b), 3.84 (d, J=5 Hz, 1 H, H₂), 3.62 (d, J=5 Hz, 1 H, H₁₁), 3.13 (d, J=4 Hz, 1 H, H₁₃a), 2.81 (d, J=4 Hz, 1 H, H₁₃b), 2.57 (dd,
J = 9, 16 Hz, 1 H, H_{3α}), 2.54 (t, J = 6 Hz, 2 H, H_{4}), 2.22 (br s, 3 H, H_{6}), 2.1-1.75 (m, 5 H, H_{8}, H_{7}, and H_{3β}), 1.70 (br s, 3 H, H_{16}), 0.86 (s, 3 H, H_{14}); IR (CH_{2}Cl_{2}) 3570, 3480, 3400-2500 (acid OH), 2980, 1715, 1695, 1648, 1612, 1220, 1142, 1070 cm^{-1}; mass spectrum m/e 360 (M^{+} - muconic acid), 265 (M^{+} - side chain); UV (EtOH) 262 (ε = 21,700), 219 (ε = 15,800).

\[
\begin{align*}
\text{pivaloyl chloride} & \quad \rightarrow \\
\text{(E,E,E)-Verrucarin 158 from Seco Acid 163.} \\

\text{Pivaloyl chloride (0.0060 mL, 0.048 mmol) was added to a} \\
solution of 0.0112 mL (0.080 mmol) of triethylamine and 8.1 mg \\
(0.016 mmol) of seco acid 163 in 5 mL of CH}_{2}Cl_{2}. \text{ The solution} \\
was stirred for 30 minutes at 25^\circ C then 25 mL of CH}_{2}Cl_{2} \text{ and two} \\
small crystals of 4-pyrrolidinopyridine were added. \text{ The} \\
solution was stirred for 3.5 h at 25^\circ C. \text{ Analytical TLC still} \\
showed some seco acid remaining so additional quantities of \\
triethylamine (0.011 mL, 0.079 mmol) and pivaloyl chloride (0.006 \\
ml, 0.048 mmol) were added. \text{ The solution was stirred for an} \\
additional 2.5 h at 25^\circ C then the solvent was evaporated. \text{ The} \\
residue was chromatographed on a 0.5 mm silica gel plate (1:1 \\
ether-CH}_{2}Cl_{2}) \text{ to afford 3.9 mg (50%) of (E,E,E)-isomer 158 (R}_f \\
0.53) \text{ and 1.1 mg (14%) of synthetic verrucarin J (R}_f 0.70).}
\end{align*}
\]
(Z,E,Z)-Verrucarin J Seco Acid (164).

Diethyl azodicarboxylate (0.011 mL, 0.066 mmol) was added to a solution of 17.3 mg (0.066 mmol) of triphenylphosphine, 9.0 mg (0.036 mmol) of acid 154, and 12.5 mg (0.033 mmol) of (Z)-11 in 1 mL of THF. The solution was stirred for 35 minutes at 25°C, and then the solvent was evaporated leaving a residual yellow liquid. This material was chromatographed on a 0.5 mm silica gel plate (ethyl acetate, Rf 0.63) to give 26 mg of impure product. This impure material was rechromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 hexane-ether, 2 developments, Rf 0.09) to afford 13.3 mg (66%) of pure seco acid ester as a waxy white solid: mp 30-35°C; [α]D22 36° (c 1.33, CHCl₃); 1H NMR (250 MHz, CDCl₃) δ 8.40 (dd, J=12, 16 Hz, 1 H, H₃n), 6.62 (t, J=12 Hz, 1 H, H₄n), 6.08 (d, J=16 Hz, 1 H, H₂n), 5.95 (d, J=12 Hz, 1 H, H₅n), 5.76 (br s, 1 H, H₂), 5.40 (br d, J=5 Hz, 1 H, H₁₀), 4.51 (br s, 1 H, H₄), 4.34 (t, J=7 Hz, 2 H, H₅), 4.27 (m, 2 H, OCH₂), 4.15 (d, J=12 Hz, 1 H, H₁₅), 3.92 (d, J=12 Hz, 1 H, H₁₅), 3.83 (d, J=5 Hz, 1 H, H₂), 3.63 (br d, J=5 Hz, 1 H, H₁₁), 3.11 (d, J=4 Hz, 1 H, H₁₃), 3.02 (t, J=7 Hz, 2 H, H₄).
2.81 (d, J=4 Hz, 1 H, H$_{13b}$), 2.59 (dd, J=8, 16 Hz, 1 H, H$_{3a}$), 1.99 (br s, 3 H, H$_6$), 2.0-1.7 (m, 6 H, H$_7$, H$_8$, H$_{3b}$, and OH), 1.71 (br s, 3 H, H$_{16}$), 1.05 (m, 2 H, CH$_2$Si), 0.87 (s, 3 H, H$_{14}$), 0.06 (s, 9 H, SiMe$_3$); IR (CH$_2$Cl$_2$) 3580, 3050, 2955, 1712, 1648, 1602, 1170, 1146, 1072, 964 cm$^{-1}$; mass spectrum m/e 585 (M$^+$ - H$_2$O), 484 (M$^+$ - Me$_3$SiCH$_2$OH); UV (EtOH) 263 (ε = 23,100), 218 (ε = 16,800).

The (Z,E,Z)-ester prepared as described in the preceding paragraph (12.3 mg, 0.0204 mmol) was deprotected by using a procedure analogous to the one described for the synthesis of 141. The crude product was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 ether-CH$_2$Cl$_2$, R$_f$ 0.42) to afford 7.2 mg (70%) of seco acid 164: mp 90-93°C (with softening at 40-45°C); [α]$^2_1$D + 32° (c 0.72, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ 8.33 (dd, J=12, 16 Hz, 1 H, H$_{3''}$), 6.63 (t, J=12 Hz, 1 H, H$_{4''}$), 6.03 (d, J=16 Hz, 1 H, H$_2''$), 5.96 (d, J=12 Hz, 1 H, H$_5''$), 5.86 (br s, 1 H, H$_2'$), 5.35 (br d, J=5 Hz, 1 H, H$_{10}$), 4.67 (m, 1 H, H$_4$), 4.34 (m, 2 H, H$_5$), 4.20 (d, J=12 Hz, 1 H, H$_{15a}$), 3.98 (d, J=12 Hz, 1 H, H$_{15b}$), 3.86 (d, J=5 Hz, 1 H, H$_2$), 3.85-3.65 (m, 1 H, H$_{4'a}$), 3.62 (br d, J=5 Hz, 1 H, H$_{11}$), 3.16 (d, J=4 Hz, 1 H, H$_{13a}$), 2.87 (d, J=4 Hz, 1 H, H$_{13b}$), 2.7-2.55 (m, H$_{4'b}$ and H$_{3a}$), 2.1-1.7 (m, 5 H, H$_8$, H$_7$, and H$_{3b}$), 1.95 (br s, 3 H, H$_6$), 1.71 (br s, 3 H, H$_{16}$), 0.99 (s, 3 H, H$_{14}$); IR (CH$_2$Cl$_2$) 3560, 3400-2800 (acid OH), 2970, 1712, 1650, 1194, 1148, 1072 cm$^{-1}$; mass spectrum m/e 265 (M$^+$ - side chain); UV (EtOH) 261 (ε = 18,600), 220 (ε = 17,600).
(Z,E,Z)-Verrucarin Isomer 19 and (Z,E,E)-Verrucarin Isomer 165.

Pivaloyl chloride (0.0061 mL, 0.049 mmol) was added to a solution of 0.0086 mL (0.061 mmol) of triethylamine and 6.2 mg (0.0123 mmol) of seco acid 164 in 7 mL of CH₂Cl₂. The solution was stirred for 35 minutes at 25°C. Two crystals of 4-pyrrrolidinopyridine were then added and the solution stirred for an additional 70 minutes at 25°C. The solvent was evaporated and the residue chromatographed on a 0.25 mm silica gel plate (1:1 ether-CH₂Cl₂) to give 3.1 mg (52%) of (Z,E,Z)-isomer 19 (Rf 0.70) and 2.2 mg (37%) of (Z,E,E)-isomer 165 (Rf 0.54).

Data for 19: mp 118-121°C; [α]²¹_D +124° (c 0.31, C₆H₆); ¹H NMR (250 MHz, CDCl₃) δ 8.22 (dd, J=12, 16 Hz, 1 H, H₃a), 6.66 (t, J=12 Hz, 1 H, H₄a), 6.10 (d, J=12 Hz, 1 H, H₅a), 6.02-5.94 (m, 2 H, H₂b and H₄b), 5.78 (br s, 1 H, H₂c), 5.44 (br d, J=5 Hz, 1 H, H₁₀), 5.05 (d, J=12 Hz, 1 H, H₁₅a), 4.66-4.46 (m, 2 H, H₅c), 4.18-4.12 (m, 1 H, H₄a), 3.87 (d, J=5 Hz, 1 H, H₂c), 3.65 (d, J=12 Hz, 1 H, H₁₅b), 3.65 (d, J=5 Hz, 1 H, H₁₁), 3.15 (d, J=4 Hz, 1 H, H₁₃a), 2.84 (d, J=4 Hz, 1 H, H₁₃b), 2.45 (dd, J=8, 15 Hz, 1 H, H₃a), 2.35-1.7 (m, 6 H, H₄b, H₇, H₈, and H₃b), 1.89 (br s, 3 H, H₆c), 1.73 (br s, 3 H, H₁₆), 0.65 (s, 3 H, H₁₄); IR (CH₂Cl₂)
2960, 2920, 1712, 1650, 1188, 1148, 1080, 966 cm\(^{-1}\); mass spectrum m/e 484 (M\(^+\)); UV (EtOH) 262 (ε = 14,700), 217 (ε = 19,800); high resolution mass spectrum, calcd for C\(_{27}\)H\(_{32}\)O\(_8\), m/e 484.2097, found 484.2100.

**Data for 165:** mp 185-187°C; [α]\(_D\)\(^{21}\) + 110° (c 0.22, C\(_6\)H\(_6\));

\(^1\)H NMR (250 MHz, CDCl\(_3\)) δ 7.42 (dd, J=12, 14 Hz, 1 H, H\(_3\) or H\(_4\)); 7.25 (dd, J=12, 15 Hz, 1 H, H\(_4\) or H\(_3\)); 6.43 (d, J=14 Hz, 1 H, H\(_2\) or H\(_5\)); 6.08 (d, J=15 Hz, 1 H, H\(_5\) or H\(_2\)); 5.83 (br s, 1 H, H\(_2\)); 5.42 (br d, J=5 Hz, 1 H, H\(_10\)); 5.27 (dd, J=3, 8 Hz, 1 H, H\(_4\)); 4.61-4.56 (m, 1 H, H\(_5\), a), 4.4-4.2 (m, 2 H, H\(_5\), b and H\(_4\), a), 4.29 (d, J=13 Hz, 1 H, H\(_{15}\)), 3.94 (d, J=13 Hz, 1 H, H\(_{15}\)), 3.89 (d, J=5 Hz, 1 H, H\(_2\)), 3.55 (br d, J=5 Hz, 1 H, H\(_11\)), 3.12 (d, J=4 Hz, 1 H, H\(_{13}\)), 2.84 (d, J=4 Hz, 1 H, H\(_{13}\)), 2.63 (dd, J=8, 16 Hz, 1 H, H\(_3\)), 2.46-2.36 (m, 1 H, H\(_4\), b), 2.2-1.8 (m, 5 H, H\(_8\), H\(_7\), and H\(_3\)), 1.94 (br s, 3 H, H\(_6\)), 1.73 (br s, 3 H, H\(_{16}\)), 0.88 (s, 3 H, H\(_{14}\)); IR (CH\(_2\)Cl\(_2\)) 2960, 2940, 1714, 1642, 1142, 1088, 910 cm\(^{-1}\); mass spectrum m/e 484 (M\(^+\)); UV (decomposes in EtOH to give the corresponding (E,E,E) seco acid ethyl ester); high resolution mass spectrum, calcd for C\(_{27}\)H\(_{32}\)O\(_8\), m/e 484.2097, found 484.211.
Experimental Procedures for Chapter IV.

\[ \text{CO}_2\text{Me} \quad 1) \text{TEMS-Cl} \quad \rightarrow \quad \text{OH} \quad 2) \text{DIBAL-H} \quad 92\% \quad \text{OTBDMS} \]

5-(tert-Butyldimethylsilyl)oxy-3-methyl-2-(E)-penten-1-ol (168).

Imidazole (2.60 g, 38.2 mmol) and 2.63 g (17.4 mmol) of tert-butyldimethylsilyl chloride were added to a solution of 2.19 g (15.2 mmol) of \( \text{B3} \) in 20 mL of DMF. The solution was stirred for 13 h at 25°C then diluted with 100 mL of water and extracted with hexane (8x100 mL). The combined hexane extracts were washed with saturated aqueous NaCl, dried (\( \text{Na}_2\text{SO}_4 \)), filtered and evaporated. The crude silyl ether was dissolved in 100 mL of ether and the solution cooled to -78°C. DIBAL-H (50 mL of 1M hexane solution, 50 mmol) was then added and the solution stirred at -78°C for 10 minutes then allowed to warm gradually to 25°C and stirred at 25°C for 90 minutes. The solution was cooled in an ice bath as 15 mL of water was added cautiously (white precipitate) followed by slow addition of 3N HCl to lower the pH to 4 (precipitate dissolved) (Note: important not to add too much acid). The layers were separated, and the aqueous layer extracted with ether (7x75 mL). The combined extracts were dried, filtered, and evaporated to afford 4.07 g of crude product. The crude alcohol was distilled (kugelrohr, oven temp 140-150°C at 10-15 mm Hg) to give
3.224 g (92%) of pure 168: $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.43 (br t, J=7 Hz, 1 H, H$_2$), 4.14 (br d, J=7 Hz, 2 H, H$_1$), 3.69 (t, J=7 Hz, 2 H, H$_5$), 2.24 (t, J=7 Hz, 2 H, H$_4$), 1.69 (br s, 3 H, H$_6$), 1.52 (br s, 1 H, OH), 0.88 (s, 9 H, H$_8$), 0.04 (s, 6 H, H$_7$); $^{13}$C NMR (22.6 MHz, CDCl$_3$) $\delta$ 135.6, 125.4, 62.0, 58.7, 42.6, 25.7, 18.0, 16.4, -5.5; IR (film) 3340, 2950, 2926, 2858, 1664, 1470, 1460, 1254, 1092, 832 cm$^{-1}$; mass spectrum m/e 213 (M$^+$ - OH); Anal. Calcd for C$_{12}$H$_{26}$O$_2$Si: C, 62.55; H, 11.37. Found C, 62.85; H, 11.49.

5- (tert-Butyldimethylsilyl)oxy-3-methyl-(2R,3R)-epoxy-pentan-1-ol (169).

Freshly distilled (−)-diethyl tartrate (3.6 mL, 20.6 mmol) was added to a −20°C solution of 4.13 mL (13.8 mmol) of titanium (IV) isopropoxide in 60 mL of CH$_2$Cl$_2$. The solution was stirred for 20 minutes at −20°C. A solution of 3.02 g (13.1 mmol) of olefin 168 in 50 mL of CH$_2$Cl$_2$ was then added dropwise at −20°C followed by tert-butyl hydroperoxide solution (6.6 mL of 3.98 M toluene solution, 26.2 mmol). The mixture was left in a −20°C freezer for 17 h then 5 mL of saturated aqueous Na$_2$SO$_4$ was added. The mixture was stirred vigorously then filtered through Celite. The filtrate was evaporated and the residue dissolved in a mixture of 80 mL of ether and 80 mL of saturated aqueous
NaCl. The mixture was cooled to 0°C then 10 mL of 5N aqueous NaOH was added and the mixture stirred vigorously for 1.5 h at 0°C. Analytical TLC showed complete disappearance of (-)-diethyl tartrate. The layers were separated and the aqueous layer washed with 50 mL of ether. The combined organic layers were dried (Na₂SO₄), filtered, and evaporated. The crude epoxide was purified by flash chromatography (50 mm column, 1:1 hexane-ether, Rₓ 0.26) to afford 2.63 g (81%) of pure epoxy alcohol \textbf{169} as a colorless liquid: [\alpha]_{D}^{19} +2.1^\circ$ (c 1.59, CHCl₃); $^1$H NMR (250 MHz, CDCl₃) δ 3.91-3.63 (m, 4 H, H₁, + H₅), 3.06 (dd, J=4.7 Hz, 1 H, H₂), 1.90 (dt, J=14, 6 Hz, 1 H, H₄'ₐ), 1.71 (t, J=7 Hz, 1 H, OH), 1.65 (dt, J=14, 16 Hz, 1 H, H₄'ₐ), 1.34 (s, 3 H, H₆'), 0.90 (s, 9 H, H₈'), 0.06 (s, 6 H, H₇'); $^{13}$C NMR (67.9 MHz, CDCl₃) δ 63.2, 61.3, 59.8, 59.5, 41.4, 25.8, 18.1, 17.2, -5.5; IR (film) 3340, 2950, 2926, 2858, 1470, 1256, 1098, 832, 772 cm$^{-1}$; mass spectrum m/e 246 (M$^+$); Anal. calcd for C₁₂H₂₆O₃Si: C, 58.49; H, 10.63. Found C, 58.28; H, 10.89.

\[
\begin{align*}
\text{OH} & \quad 1) \quad \text{KMnO}_4 \\
\text{OTBDMS} & \quad 2) \quad \text{HO-} \longrightarrow \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3 \\
\text{169} & \quad \text{BCl-Cl, Et}_3\text{N} \\
& \quad \text{OTBDMS} \\
\text{170}
\end{align*}
\]

2-p-Toluenesulfonylthethyl 5-(tert-butyldimethylsilyl)oxy-3-methyl-(2S,3R)-epoxy-pentanoate (170).

A mixture of 640 mg (4.0 mmol) of potassium permanganate and and 8 mL of water was stirred vigorously (mechanical stirrer) for 15 minutes at 25°C. The mixture was cooled (10-15°C)
as 200 mg (0.6 mmol) of tetrabutylammonium bromide was
added followed by a solution of 400 mg (1.6 mmol) of epoxy
alcohol (169) in 8 mL of benzene. The resulting purple
mixture was stirred vigorously for 28 h at 25°C. The brown
mixture was cooled in an ice bath as 10 mL of saturated aqueous
NaHSO₃ and 10 mL of benzene were added. The mixture was
stirred at 0°C until the color changed from brown to white
(~5 minutes) then the pH was lowered to 3 by careful addition
of 3N HCl. The layers were separated and the aqueous layer
was saturated with NaCl then extracted with ethyl acetate
(6x10 mL). The combined organic layers were dried (Na₂SO₄),
filtered, and concentrated to afford the crude epoxy acid:
[α]¹⁸_D + 14.4° (c 0.84, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ
3.74 (t, J=6 Hz, 2 H, H₅), 3.53 (s, 1 H, H₂), 1.98 (dt,
J=14, 6 Hz, 1 H, H₄a), 1.74 (dt, J=14, 6 Hz, 1 H, H₄b),
1.44 (s, 3 H, H₆), 0.89 (s, 9 H, H₈), 0.06 (s, 6 H, H₇); IR (film) 3600-2500 (acid OH), 2956, 2928, 2858, 1752, 1732,
1472, 1254, 1104, 832, 774 cm⁻¹.

The crude acid, prepared as described in the preceding
paragraph was dissolved in 10 mL of CH₂Cl₂ then 0.57 mL
(4.1 mmol) of triethylamine was added followed by 496 mg
(1.95 mmol) of N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic
chloride (BOP-Cl), 455 mg (2.3 mmol) of 2-p-toluenesulfonyl-
ethanol and 10 mg (0.08 mmol) of 4-dimethylaminopyridine. The
mixture (white precipitate) was stirred for 16 h at 25°C then
cooled in an ice bath as 10 mL of 0.5N HCl and 10 mL of CH₂Cl₂
were added. After thorough mixing the layers were separated
and the aqueous layer extracted with CH₂Cl₂ (3x15 mL). The combined organic layers were filtered through cotton and evaporated. The crude product was purified by flash chromatography (50 mm column, 1:1 hexane-ether, Rf 0.23) to afford 399 mg (56%) of pure **170** as a colorless liquid: [α]D²¹ + 17° (c 1.54, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 7.81 (d, J=8 Hz, 2 H, H₁₂, or H₁₃), 7.39 (d, J=8 Hz, 2 H, H₁₃, or H₁₂), 4.54 (dt, J=12, 6 Hz, 1 H, H₉ₐ), 4.42 (dt, J=12, 6 Hz, 1 H, H₉₉), 3.69 (t, J=6 Hz, 2 H, H₅), 3.47 (t, J=6 Hz, 1 H, H₁₀, 3.23 (s, 1 H, H₂), 2.46 (br s, 3 H, H₁₄), 1.89 (dt, J=14, 6 Hz, 1 H, H₄₉), 1.68 (dt, J=14, 6 Hz, 1 H, H₄₉), 1.33 (s, 3 H, H₆), 0.89 (s, 9 H, H₉), 0.05 (s, 6 H, H₇); ¹³C NMR (67.9 CDCl₃) δ 167.9, 145.2, 136.1, 130.0, 128.1, 61.5, 58.9, 58.2, 58.1, 54.8, 40.5, 25.8, 21.6, 18.1, 16.5, -5.5; IR (CHCl₃) 3020, 2958, 2936, 2870, 1754, 1652, 1600, 1324, 1142, 834 cm⁻¹; mass spectrum m/e 385 (M⁺ - t-Bu); Anal. calcd for C₂₁H₃₄O₆SSi: C, 56.98; H, 7.74. Found C, 57.00; H, 7.81.

![Chemical Structure](image)

**2-p-Toluenesulfonylethyl-5-hydroxy-3-methyl-(2S,3R)-epoxy-pentanoate (171).**

A solution of 250 mg (0.56 mmol) of silyl ether **170** in 5 mL of 3:1:1 acetic acid-water-THF was stirred for 5 h at 25°C. Heptane (20 mL, MCB reagent grade) was then added and the mixture concentrated in vacuo. This procedure was
repeated several times until the azeotropic removal of acetic acid and water was complete. The residue was purified by flash chromatography (30 mm column, ether, \(R_f\) 0.23) to afford 177 mg (95%) of pure 171 as a colorless syrup: \([\alpha]_{D}^{20} = -3^\circ\) (c 1.1, CHCl\(_3\)); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \& 7.80 (d, \(J=9\) Hz, 2 H, H\(_{12}\), or H\(_{13}\)), 7.32 (d, \(J=9\) Hz, 2 H, H\(_{13}\), or H\(_{12}\)), 4.61 (dt, \(J=12, 5\) Hz, 1 H, H\(_9\),\(_{a}\)), 4.45 (dt, \(J=12, 5\) Hz, 1 H, H\(_9\),\(_b\)), 3.75 (br t, \(J=6\) Hz, 2 H, H\(_5\)), 3.46 (t, \(J=6\) Hz, 2 H, H\(_{10}\)), 3.37 (s, 1 H, H\(_2\)), 2.47 (br s, 3 H, H\(_{14}\)), 2.09 (br s, 1 H, OH), 1.95 (dt, \(J=15, 5\) Hz, 1 H, H\(_4\),\(_a\)), 1.84 (dt, \(J=15, 5\) Hz, 1 H, H\(_4\),\(_b\)), 1.39 (s, 3 H, H\(_6\)); IR (CH\(_2\)Cl\(_2\)) cm\(^{-1}\) 3596, 3540, 3052, 2954, 2930, 1756, 1598, 1408, 1320, 1188, 1142, 1084 cm\(^{-1}\); mass spectrum m/e 310 (M\(^+\) - H\(_2\)O); Anal. calcd for C\(_{15}\)H\(_{20}\)O\(_6\): C, 54.86; H, 6.14. Found C, 54.99; H, 6.33.

\[
\begin{align*}
\text{O} & \text{O} & \text{Ts} \\
\text{O} & \text{O} & \text{OH} \\
\text{CH}_2\text{Cl}_2 & \text{Me,C} & \text{CH}_2\text{Cl}_2, \text{DPP, 81\%} \\
\text{171} & \xrightarrow{\text{(172)}} & \text{Ts} \\
\text{O} & \text{O} & \text{TMS} \\
\text{O} & \text{O} & \text{TMS} \\
\text{173}
\end{align*}
\]

**Verrucarin B Side Chain Triester (173).**

Triethylamine (0.18 mL, 1.29 mmol) and 0.078 mL (0.63 mmol) of pivaloyl chloride were added to a solution of 137 mg (0.57 mmol) acid 154 in 3 mL of CH\(_2\)Cl\(_2\). The mixture was stirred for 1.5 h at 25°C then transferred via syringe to another flask containing 158 mg (0.48 mmol) of alcohol 171 and 6 mg (0.049 mmol) of 4-dimethylaminopyridine (DMAP). The solution was stirred
for 13 h at 25°C. The solvent was evaporated and the residue dissolved in 20 mL of ethyl acetate and 10 mL of 0.1 N HCl. The aqueous layer was extracted with ethyl acetate (5x15 mL). The combined organic solutions were dried (Na₂SO₄), filtered and evaporated. The crude product was purified by flash chromatography (40 mm column, 2:1 ether-hexane, Rₐ 0.28) to afford 217 mg (81%) of pure triester as a colorless syrup: [α]^{20}_D + 22° (c 1.01, CHCl₃). ^{1}H NMR (270 MHz, CDCl₃) δ 8.44 (dd, J=12, 15 Hz, 1 H, H₃'ₚ), 7.80 (d, J=9 Hz, 2 H, H₁₃ or H₁', 7.38 (d, J=9 Hz, 2 H, H₁₃ or H₁₂), 6.66 (dd, J=12, 12 Hz, 1 H, H₄'ₚ), 6.13 (d, J=15 Hz, 1 H, H₂'ₚ), 5.98 (d, J=12 Hz, 1 H, H₅'ₚ), 4.55-4.44 (m, 2 H, H₅'ₚ + H₉'ₚ), 4.38-4.18 (m, 4 H, H₅'ₜ + H₉'ₜ + OCH₂), 3.45 (t, J=6 Hz, 2 H, H₁₀'), 3.18 (s, 1 H, H₂'), 2.46 (br s, 3 H, H₁₄'), 2.06 (dt, J=15, 6 Hz, 1 H, H₄'ₚ), 1.91 (dt, J=15, 6 Hz, 1 H, H₄'ₜ), 1.37 (s, 3 H, H₆'), 1.08-1.02 (m, 2 H, CH₂Si), 0.06 (s, 9 H, SiMe₃); ^{13}C NMR (67.9, CDCl₃) δ 167.4, 165.7, 165.3, 145.1 140.0, 139.1, 130.0, 128.1, 128.0, 125.2, 62.8, 60.7, 60.4, 58.3, 57.7, 54.7, 36.6, 21.5, 17.3, 16.2, -1.6; IR (CHCl₃) 3018, 2958, 1756, 1712, 1684, 1598, 1174, 858, 834 cm⁻¹; mass spectrum m/e 552 (M⁺); UV (EtOH) 263 (ε = 26, 0), 226 (ε = 17,650); Anal. calcd for C₂₆H₃₆O₈SSi: C, 56.50; H, 6.57. Found C, 56.33; H, 6.64.
Verrucarin B side chain mono-2-trimethylsilyl ethyl ester (167).

A solution of 16.0 mg (0.029 mmol) of triester 173 and 0.0052 mL (0.0348 mmol) of DBU in 1 mL of benzene was stirred for 1 h at 25°C. A small amount of 173 remained (TLC analysis) so an additional 0.0025 mL (0.017 mmol) of DBU was added and the solution stirred for 1 h at 25°C. The reaction was quenched by the addition of 1 mL of acidic (pH 2) saturated aqueous NaCl. The pH of the mixture was adjusted to 2 by careful addition of 3N HCl. The mixture was extracted with ethyl acetate (7x2 mL) and the combined extracts dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed on a 0.25 mm silica gel plate (1% formic acid in 1:1 hexane-ethyl acetate, Rf 0.39) to afford 8.3 mg (77%) of acid 167 as a colorless syrup (decomposes slowly upon storage). Note that we were unable to consistently reproduce this result (see text).

**Data for 167:** $^1$H NMR (250 MHz, CDCl₃) δ 8.46 (dd, J=12, 16 Hz, 1 H, H₃'''), 6.64 (dd, J=12, 12 Hz, 1 H, H₄''), 6.12 (d, J=16 Hz, 1 H, H₂''), 5.98 (d, J=12 Hz, 1 H, H₅''), 4.40-4.24 (m, 4 H, H₅, + OCH₂).
3.47 (s, 1 H, H_2), 2.19-1.98 (m, 2 H, H_4), 1.48 (s, 3 H, H_6), 1.09-1.02 (m, 2 H, CH_2Si), 0.06 (s, 9 H, SiMe_3).

Verrucarin B seco acid-2-trimethylsilylethyl ester (174).

Verrucarol (52.0 mg, 0.195 mmol) was acylated with the sodium salt of 167 (generated in situ from 72 mg (0.13 mmol) of triester 173) by using the procedure described for the preparation of 182. The crude product was chromatographed on a 1.5-mm silica gel plate (1% formic acid in 1:1 ether-CH_2Cl_2, R_f 0.51) to afford 28.5 mg (35% based on 173) of pure 174 as a colorless syrup along with 32 mg of recovered verrucarol (2).

Data for 174: [α]_D^20 - 8.5° (c 2.4, CHCl_3); ^1H NMR (250 MHz, CDCl_3) δ 8.45 (dd, J=11, 16 Hz, 1 H, H_3), 6.64 (dd, J=11, 11 Hz, 1 H, H_4), 6.11 (d, J=16 Hz, 1 H, H_2), 5.98 (d, J=11 Hz, 1 H, H_5), 5.40 (br d, J=5 Hz, 1 H, H_10), 4.48-4.40 (m, 1 H, H_4), 4.38-4.22 (m, 4 H, H_5, + OCH_2), 4.27 (d, J=12 Hz, 1 H, H_15), 4.02 (d, J=12 Hz, 1 H, H_15b), 3.83 (d, J=5 Hz, 1 H, H_2), 3.57 (d, J=5 Hz, 1 H, H_11), 3.41 (s, 1 H, H_2), 3.11 (d, J=4 Hz, 1 H, H_13), 2.79 (d, J=4 Hz, 1 H, H_13b), 2.58 (dd, J=7, 16 Hz, 1 H, H_3), 2.2-1.7 (m, 8 H, H_4, + H_7 +
+ H₈ + H₃β + OH), 1.71 (br s, 3 H, H₁₆), 1.44 (s, 3 H, H₆'),
1.09-1.02 (m, 2 H, CH₂Si), 0.85 (s, 3 H, H₁₄), 0.06 (s, 9 H,
SiMe₃); IR (CHCl₃) 3570, 3006, 2954, 1744, 1714, 1600, 1412,
1172, 1070, 964 cm⁻¹; mass spectrum m/e 618 (M⁺); UV (EtOH)
263 (ε = 21,800).

1-(2-trimethylsilylethoxycarbonyl)-imidazolide (180).

Carbonyldiimidazole (CDI, 195 mg, 1.2 mmol)¹¹₈ was
added to a solution of 118 mg (1 mmol) of 2-trimethylsilyl-
ethanol¹¹₈ in 2 mL of benzene. The resulting mixture (white
precipitate) was stirred for 1 h at 25°C then diluted with
20 mL of CH₂Cl₂. The solution was washed quickly with ice
cold water then filtered through a cotton plug and evaporated.
The crude product was chromatographed on a 1.5 mm silica gel
plate (1:1 hexane-ether, Rf 0.35) to give 205 mg (97%) of
imidazolide ¹⁸₀ as a white crystalline solid: mp 29-30.5°C;
¹H NMR (250 MHz, CDCl₃) δ 8.11 (s, 1 H), 7.40 (br s, 1 H),
7.05 (br s, 1 H), 4.52-4.46 (m, 2 H), 1.20-1.13 (m, 2 H),
0.08 (s, 9 H); IR (CH₂Cl₂) 2966, 1760, 1472, 1400, 1322, 1294,
1242, 1172, 1004, 862, 842 cm⁻¹; mass spectrum m/e 212 (M⁺);
Anal. calcd for $C_{9}H_{16}N_{2}O_{2}$Si: C, 50.91; H, 7.50. Found C, 50.62; H, 7.46.

4-(2-Trimethylsilylethoxycarbonyl)-verrucarol (181).

Verrucarol (50 mg, 0.188 mmol) was added to a solution of 39.9 mg (0.188 mmol) of imidazolide 180 in 1 mL of benzene then DBU (0.0056 mL, 0.0375 mmol) was added. The mixture was stirred for 22 h at 25°C then cooled in an ice bath as 1 mL of 0.1 N HCl was added followed by 1 mL of ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate (7x3 mL). The combined extracts were dried (Na$_2$SO$_4$), filtered and evaporated. The crude product was chromatographed on a 0.5 mm silica gel plate (2:1 ether-hexane, $R_f$ 0.45) to afford 41.6 mg (54%) of 181 as a white crystalline solid. The rest of the silica gel plate was extracted to afford 29.4 mg of a colorless syrup which was dissolved in 20 mL of saturated methanolic K$_2$CO$_3$. The solution was stirred for 24 h at 25°C then most of the solvent was evaporated. The residue was dissolved in 10 mL of water and 20 mL of ether. The mixture was neutralized by careful addition
of 3N HCl. The layers were separated and the aqueous layer extracted with ethyl acetate (2x15 mL) and CH₂Cl₂ (6x15 mL). The combined extracts were dried (Na₂SO₄), filtered, and evaporated. The crude verrucarol was chromatographed on a 0.25 mm silica gel plate (ethyl acetate, Rf 0.26) to afford 16.5 mg (33%) of recovered verrucarol. The yield of 181 based on unrecovered verrucarol was therefore 81%.

In a second experiment, conducted on the same scale but with a reaction time of 18 h, all of the products were isolated separately. This experiment afforded 34 mg (44%) of 181 along with 11 mg (10%) of the di-acylated product (Rf 0.55), 4 mg (5%) of the C-15 mono-acylated product (Rf 0.19) and 9 mg (18%) of recovered verrucarol.

Data for 181: mp 128.5-129°C (recrystallized from hexane-CH₂Cl₂); [a]_D^20 + 10° (c 3.3, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 5.90 (dd, J=4, 8 Hz, 1 H, H₄), 5.48 (br d, J=5 Hz, 1 H, H₁₀), 4.25-4.18 (m, 2 H, OCH₂), 3.87 (br d, J=5 Hz, 1 H, H₁₁), 3.82 (d, J=5 Hz, 1 H, H₂), 3.81 (d, J=12 Hz, 1 H, H₁₅a), 3.66 (d, J=12 Hz, 1 H, H₁₅b), 3.12 (d, J=4 Hz, 1 H, H₁₃a), 2.81 (d, J=4 Hz, 1 H, H₁₃b), 2.51 (dd, J=8, 15 Hz, 1 H, H₃a), 2.15-1.95 (m, 5 H, H₃β + H₇ + H₈), 1.71 (br s, 3 H, H₁₆), 1.57 (br s, 1 H, OH), 1.09-1.02 (m, 2 H, CH₂Si), 0.88 (s, 3 H, H₁₄), 0.04 (s, 9 H, SiMe₃); IR (CHCl₃) 3630, 3500, 3016, 2960, 2910, 1728, 1275, 1086, 962, 862, 840 cm⁻¹; mass spectrum m/e 392 (M⁺ - H₂O); Anal. Calcd for C₂₁H₃₄O₆Si: C, 61.43; H, 8.35. Found C, 61.22; H, 8.62.
4-(2-Trimethylsilylethoxycarbonyl)-Verrucarin B Seco Acid-(2-Trimethylsilyl)ethyl Ester (182).

Sodium hydride (4.7 mg of 60% oil dispersion, 0.117 mmol) and 0.0012 mL (0.0078 mmol) of DBU were added to a solution of 43 mg (0.078 mmol) of side chain triester 173 in 1.2 mL of THF. The mixture was stirred for 6.5 h at 25°C after which analytical TLC showed complete deprotection (ester-Rf 0.50, acid Rf 0.40 with 1% formic acid in 1:1 hexane-ethyl acetate). Triethylamine (0.0163 mL, 0.117 mmol) was added, followed by 27.7 mg (0.109 mmol) of N,N-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl) and a solution of 32 mg (0.078 mmol) of alcohol 181 in 1.5 mL of THF. Dimethylaminopyridine (DMAP, 0.10 mL of a solution containing 24 mg of DMAP in 1.0 mL of THF, 0.019 mmol) was then added and the mixture stirred for 16 h at 25°C. The mixture was cooled in an ice bath as 1 mL of 0.1 N HCl was added followed by 0.5 mL of ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate (7x2 mL). The combined extracts were dried (Na₂SO₄), filtered, and evaporated. The crude
product was chromatographed on a 0.5 mm silica gel plate (1:1 hexane-ether, 2 developments, Rf 0.37) to afford 38 mg (64%) of 182 as a clear colorless syrup: [α]D\textsuperscript{20} = +8.2° (c 3.8, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}) δ 8.46 (dd, J=12, 16 Hz, 1 H, H\textsubscript{3}'''), 6.63 (dd, J=12, 12 Hz, 1 H, H\textsubscript{4}''), 6.09 (d, J=16 Hz, 1 H, H\textsubscript{2}'''), 5.97 (d, J=12 Hz, 1 H, H\textsubscript{5}'''), 5.51 (dd, J=4,8 Hz, 1 H, H\textsubscript{4}), 5.43 (br d, J=5 Hz, 1 H, H\textsubscript{10}), 4.37-4.10 (m, 8 H, H\textsubscript{15} + H\textsubscript{5}, + OCH\textsubscript{2}), 3.84 (d, J=5 Hz, 1 H, H\textsubscript{2}), 3.67 (br d, J=5 Hz, 1 H, H\textsubscript{11}), 3.47 (s, 1 H, H\textsubscript{2}'), 3.12 (d, J=4 Hz, 1 H, H\textsubscript{13a}), 2.79 (d, J=4 Hz, 1 H, H\textsubscript{13b}), 2.55 (dd, J=8,16 Hz, 1 H, H\textsubscript{3a}), 2.14-1.90 (m, 7 H, H\textsubscript{4}, + H\textsubscript{7} + H\textsubscript{8} + H\textsubscript{3b}), 1.72 (br s, 3 H, H\textsubscript{16}), 1.42 (s, 3 H, H\textsubscript{6}), 1.09-1.00 (m, 4 H, CH\textsubscript{2}Si), 0.82 (s, 3 H, H\textsubscript{14}), 0.06 (s, 9 H, SiMe\textsubscript{3}), 0.04 (s, 9 H, SiMe\textsubscript{3}; IR (CHCl\textsubscript{3}) 3040, 3018, 2964, 2910, 1724, 1604, 910, 860, 840 cm\textsuperscript{-1}; mass spectrum m/e 762 (M\textsuperscript{+}); UV (EtOH) 263 (ε = 24,100).

![Chemical Structure](image)

**Verrucarin B Seco Acid (166).**

**Method A:** Water (0.0156 mL, 0.86 mmol) was added to a suspension of 25.1 mg (0.43 mmol) of potassium fluoride (KF) and 33 mg (0.043 mmol) of 182 in 2.4 mL of DMSO. The mixture was stirred for 36 h at 25°C then cooled in an ice bath as
30 mL of water and 25 mL of ethyl acetate were added. The pH was adjusted to 2 by careful addition of 3N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (7x25 mL). The combined extracts were dried (Na₂SO₄), filtered, and evaporated. The residue was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 ether-CH₂Cl₂, Rf 0.31) to afford 20 mg (89%) of pure seco acid 166 as a white solid.

Method B: Trimethylsilyl ethyl ester 174 (40 mg, 0.065 mmol) was deprotected by using the procedure described in the preceding paragraph (reaction time 66 h). The crude product was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 ether-CH₂Cl₂; Rf 0.31) to afford 23.5 mg (70%) of seco acid 166.

Data for 166: mp 75-78°C; [α]ᵢ²⁰ₒ - 16° (c 1.27, CHCl₃);
¹H NMR (250 MHz, CDCl₃) δ 8.43 (dd, J=12, 16 Hz, 1 H, H₃ᵣ), 6.71 (dd, J=12, 12 Hz, 1 H, H₄ᵣ), 6.12 (d, J=16 Hz, 1 H, H₂ᵣ), 6.02 (d, J=12 Hz, 1 H, H₅ᵣ), 5.42 (br d, J=5 Hz, 1 H, H₁₀ᵣ), 4.61-4.56 (m, 1 H, H₄), 4.38-4.29 (m, 2 H, H₅), 4.32 (d, J=12 Hz, 1 H, H₁₅ᵣ), 3.98 (d, J=12 Hz, 1 H, H₁₅ᵣ), 3.86 (d, J=5 Hz, 1 H, H₂), 3.62 (d, J=5 Hz, 1 H, H₁₁), 3.52 (s, 1 H, H₂ᵣ), 3.14 (d, J=4 Hz, 1 H, H₁₃ᵣ), 2.83 (d, J=4 Hz, 1 H, H₁₃ᵣ), 2.62 (dd, J=8, 16 Hz, 1 H, H₃ᵣ), 2.2-1.75 (m, 7 H, H₄, + H₇ + H₈ + H₁₃), 1.72 (br s, 3 H, H₁₆), 1.45 (s, 3 H, H₆), 0.92 (s, 3 H, H₁₄); IR (CHCl₃) 3400-2800 (acid OH) 3016, 2976, 1746, 1718, 1700, 1602, 1272, 1204, 1072, 962 cm⁻¹; mass spectrum m/e 500 (M⁺ - H₂O); UV (EtOH) 262 (ε = 18,300).
Verrucarin B(4) and (E,E)-Verrucarin (183).

Method A: Pivaloyl chloride (0.0095 mL, 0.077 mmol) was added to a solution of 0.0134 mL (0.096 mmol) of triethylamine and 10.0 mg (0.019 mmol) of seco acid 166 in 10 mL of CH₂Cl₂. The solution was stirred for 15 minutes at 25°C then 4-pyrrolidinopyridine (4-PP, 0.050 mL of 0.39 M CH₂Cl₂ solution, 0.019 mmol) was added. The solution was stirred for 90 minutes at 25°C then concentrated. The residue was chromatographed on a 0.5 mm silica gel plate (1:1 ether-CH₂Cl₂) to give 5.3 mg (55%) of verrucarin B (R₇ 0.61) and 3.3 mg (34%) of (E,E)-isomer 183 (R₇ 0.44).

Method B: A solution of mixed anhydride 185 (generated in situ from 7.0 mg (0.013 mmol) of seco acid 166 as described in the preceding paragraph) in 7 mL of CH₂Cl₂ was treated with 4-PP (0.020 mL of 0.067 M CH₂Cl₂ solution, 0.0013 mmol). The solution was stirred for 2 h at 25°C then additional 4-PP was added (0.010 mL of 0.067 M CH₂Cl₂ solution, 0.00065 mmol). The solution was stirred for 17 h at 25°C. Some mixed anhydride and seco acid still remained (TLC analysis). In an attempt
to force the reaction to completion, additional pivaloyl chloride (0.0017 mL, 0.013 mmol) and triethylamine (0.0019 mL, 0.013 mmol) were added. The solution was stirred for 3 h at 25°C (TLC analysis showed no change) then concentrated to ca. 2 mL volume. Ethyl acetate (2 mL) and 1 mL of 0.1 N HCl were added and the layers separated. The aqueous layer was extracted with ethyl acetate (7x2 mL) and the combined extracts dried (Na$_2$SO$_4$), filtered and concentrated. The crude product was chromatographed on a 0.25 mm silica gel plate (1% formic acid in 1:1 ether-CH$_2$Cl$_2$) to afford 3.7 mg (54%) of verrucarin B (R$_f$ 0.74) and 0.7 mg (10%) of (E,E)-isomer 183 (R$_f$ 0.55).

**Method C:** A solution of mixed anhydride 185 (generated in situ from 9.5 mg (0.018 mmol) of seco acid 166 as described above) in 9.5 mL of THF was cooled in an ice bath as 0.016 mL (0.11 mmol) of DBU was added. The red solution was stirred for 75 minutes at 25°C (reaction clean and complete by TLC analysis). The mixture was cooled in an ice bath as 2.5 mL of 0.1 N HCl was added (color changed immediately from red to yellow). The mixture was extracted with ethyl acetate (8x5 mL) and the combined extracts dried (Na$_2$SO$_4$), filtered and concentrated. The residue was chromatographed on a 0.25 mm silica gel plate (1% formic acid in 1:1 ether-CH$_2$Cl$_2$) to give 2.2 mg (24%) of verrucarin B (R$_f$ 0.74). Only a trace of (E,E)-isomer 183 was present by TLC analysis. The yield of verrucarin B was 58% when this procedure was performed on 2.5 mg (0.0048 mmol) of 166.
Synthetic verrucarin B obtained by these methods was identical with an authentic sample provided by Professor C. Tamm: mp >300°C; lit$^{121}$ mp>330°C; [α]$^{20}_D$ + 94° (c 1.2, CHCl$_3$); lit$^{121}$ [α]$^{23}_D$ + 94° (c 0.99, CHCl$_3$); $^1$H NMR (250 MHz, CDCl$_3$) δ 7.90 (dd, J=11, 16 Hz, 1 H, H$_3''$), 6.64 (dd, J=11, 11 Hz, 1 H, H$_4''$), 6.18 (d, J=11 Hz, 1 H, H$_5''$), 6.07 (d, J=16 Hz, 1 H, H$_2''$), 5.85 (dd, J=4, 8 Hz, 1 H, H$_4$), 5.44 (br d, J=5 Hz, 1 H, H$_{10}$), 4.51 (d, J=12 Hz, 1 H, H$_{15a}$), 4.42-4.28 (m, 2 H, H$_5$), 4.35 (d, J=12 Hz, 1 H, H$_{15b}$), 3.87 (d, J=5 Hz, 1 H, H$_2$), 3.60 (d, J=5 Hz, 1 H, H$_{11}$), 3.40 (s, 1 H, H$_2$), 3.15 (d, J=4 Hz, 1 H, H$_{13a}$), 2.84 (d, J=4 Hz, 1 H, H$_{13b}$), 2.53 (dd, J=8, 15 Hz, 1 H, H$_{3a}$), 2.32 (ddd, J=15, 6, 3 Hz, 1 H, H$_4'a$), 2.21 (ddc, J=15, 5, 5 Hz, 1 H, H$_{3b}$), 2.1-1.7 (m, 5 H, H$_7$ + H$_8$ + H$_4'a$), 1.74 (br s, 3 H, H$_{16}$), 1.57 (s, 3 H, H$_6$), 0.89 (s, 3 H, H$_{14}$); IR (CHCl$_3$) 3040, 2980, 1750, 1710, 1190, 1080, 1040, 965, 980 cm$^{-1}$; UV (EtOH) 258.5 (ε = 22,400).

Data for 183: mp 170-175°C; [α]$^{20}_D$ + 145° (c 0.19, CHCl$_3$); $^1$H NMR (250, CDCl$_3$) δ 7.52 (dd, J=14, 15 Hz, 1 H, H$_3''$ or H$_4''$), 7.24 (dd, J=14, 15 Hz, 1 H, H$_4''$ or H$_3''$), 6.54 (d, J=14 Hz, 1 H, H$_2''$ or H$_5''$), 6.22 (d, J=15 Hz, 1 H, H$_5''$ or H$_2''$), 5.42 (br d, J=5 Hz, 1 H, H$_{10}$), 5.29 (dd, J=3, 8 Hz, 1 H, H$_4$), 5.14 (d, J=13 Hz, 1 H, H$_{15a}$), 4.75-4.68 (ddd, J=12, 4, 2 Hz, 1 H, H$_{5'a}$), 4.11-4.00 (m, 1 H, H$_{5'b}$), 3.90 (d, J=13 Hz, 1 H, H$_{15b}$), 3.88 (d, J=5 Hz, 1 H, H$_2$), 3.48 (br d, J=5 Hz, 1 H, H$_{11}$), 3.34 (s, 1 H, H$_2$), 3.12 (d, J=4 Hz, 1 H, H$_{13a}$), 2.86 (d, J=4 Hz, 1 H, H$_{13b}$), 2.68 (dd, J=16, 8 Hz, 1 H, H$_3a$), 2.46 (ddd,
J=16, 5, 3 Hz, 1 H, H3β), 2.34-1.95 (m, 6 H, H4', H7 + H8), 1.76 (br s, 3 H, H16'), 1.62 (s, 3 H, H6'), 1.02 (s, 3 H, H14'); IR (CH2Cl2) 2980, 2940, 1755, 1720, 1600, 1320, 1174, 1082, 1000, 970 cm⁻¹.

Isomerization of 183 to Verrucarin B and (Z,E)-Isomer 184.

One crystal of iodine was added to a solution of 2.0 mg (0.0040 mmol) of (E,E)-isomer 183 in 1 mL of toluene (note: benzene is the preferred solvent for this reaction). The red solution was stirred for 90 minutes at 25°C. A small amount of 183 remained (TLC analysis) so an additional small crystal of iodine was added. The solution was stirred for 1 h at 25°C then diluted with 10 mL of toluene. Solid sodium sulfite (Na2SO3) was added and the mixture stirred until the red color had disappeared then filtered. The filtrate was concentrated to a dark yellow liquid residue which was a 2:1 mixture of verrucarin B and 184 (250 MHz NMR analysis). The crude product was chromatographed on a 0.25 mm silica gel plate (1:2 hexane-ether; 2 developments) to afford 1.2 mg (60%) of verrucarin B (Rf 0.44) and 0.6 mg (30%) of the (Z,E)-isomer 184 (Rf 0.34).
Data for 184: $^1$H NMR (250 MHz, CDCl$_3$) ð 8.02 (dd, J=12, 15 Hz, 1 H, $H_4''$), 6.72 (dd, J=12, 12 Hz, 1 H, $H_3''$), 6.11 (d, J=15 Hz, 1 H, $H_5''$), 5.97 (d, J=12 Hz, 1 H, $H_2''$), 5.47 (br d, J=5 Hz, 1 H, $H_{10}$), 5.18 (dd, J=4, 8 Hz, 1 H, $H_4$), 5.02-4.95 (m, 1 H, $H_{5'a}$), 4.30 (d, J=13 Hz, 1 H, $H_{15a}$), 4.00-3.91 (m, 1 H, $H_{5'b}$), 3.93 (d, J=13 Hz, 1 H, $H_{15b}$), 3.86 (d, J=5 Hz, 1 H, $H_2$), 3.63 (br d, J=5 Hz, 1 H, $H_{11}$), 3.45 (s, 1 H, $H_1$), 3.21 (d, J=4 Hz, 1 H, $H_{13a}$), 2.87 (d, J=4 Hz, 1 H, $H_{13b}$), 2.76 (dd, J=8, 16 Hz, 1 H, $H_3$), 2.46-2.35 (m, 1 H, $H_3'$), 2.18-1.81 (m, 6 H, $H_7 + H_8 + H_4$), 1.75 (br s, 3 H, $H_{16}$), 1.36 (s, 3 H, $H_6'$), 1.09 (s, 3 H, $H_{14}'$); UV (EtOH) 260 (ε = 18,500).
REFERENCES
References


28. Verrucarol, which is the trichothece nucleus present in most of the macrocyclic epoxytrichotheccenes, is easily prepared from anguidine: Tulshian, D.B.; Fraser-Reid, B. Tetrahedron Lett. 1980, 4549.

29. Note that it is the (E)-isomer of 26 that ultimately leads to tetrahydroverrucarin J. It was in connection with this work that Tamm re-assigned the C(2')-C(3') olefinic geometry of verrucarin J (see reference 14).


32. The first selective acylation of verrucarol C(15)-OH was reported by Fraser-Reid and Tulshian (reference 28), as outlined below.

\[
\begin{align*}
\text{HO} & \quad \text{O} \quad \text{Ac}_2\text{O, pyridine} \\
\text{OH} & \quad \text{2} \\
\text{AcO} & \quad \text{OH} \quad \text{70%}
\end{align*}
\]


45. We thank Dr. Fatima Z. Basha for performing this experiment.

46. (a) Doerr, I.L.; Willette, R.E. J. Org. Chem. 1973, 38, 3878; (b) For other syntheses of malealdehydic acid and alternative olefination procedures to give (Z,E)-muconate half esters, see references 31 and 37e; (c) we have found White's procedure for preparation of malealdehydic acid (ref. 37e) to be superior to the Doerr method (ref. 46a) and have adopted the former in all of our recent work.


49. (a) Moriconi, E.J.; Meyer, W.C. Ibid. 1971, 36, 2841; (b) Anhydromevalonolactone 88 is now commercially available (Aldrich Chemical Company).


60. Esters 110, 111, and 112 were prepared by DCC mediated esterification of epoxy crotonic acid (reference 61) with p-methoxybenzyl alcohol (58% yield), 2-trimethylsilyl-ethanol (47%), and 2,2,2-trichloroethanol (52%) respectively.


62. Ester 114 was prepared in 81% yield by DCC mediated esterification of the corresponding acid with trichloro-ethanol (4-PP catalyst). The acid was prepared by a modification of Ireland's preparation of 3-methyl-4-pentenoic acid (see Ireland, R.E.; Mueller, R.H.; Willard, A.K. J. Am. Chem. Soc. 1976, 98, 2868).


64. Prepared in 69% yield from acid 86 by DCC mediated esterification with 2-propanol.

![](image)

65. Interestingly, trichloroethyl sorbate (prepared in 67% yield from sorbic acid) is smoothly converted to sorbic acid (78%) under these conditions.

![](image)


67. Most of the initial esterification experiments in the verrucarin J work were performed with 86, 92, and 133 while the synthesis of 121 was still being developed.
Ironically, our inability to cleanly esterify these compounds ultimately meant that a synthesis of 121 was unnecessary.

68. Although selective deprotection of the acetate group in diester 59 was later accomplished in the Fraser-Reid/-Jarvis synthesis of trichoverrin B (9) (see Scheme VII, chapter I) it should be noted that a muconic acid residue would be much more sensitive to hydrolysis than the dienoic acid residue in 59.

69. TBDMS ether i, which has been described previously by Fraser-Reid (reference 28), might also have been useful for our purposes. We were not, however, able to prepare i by the literature procedure or by a number of alternative methods (including TBMDS-OTf, lutidine).

70. (a) Verrucarol used in these studies was prepared from natural anguidine by a method developed by Fraser-Reid (described in footnote 8 of ref. 34a) (see also ref. 28); (b) We thank Drs. T.W. Doyle and T. Kaneko of Bristol Laboratories for a generous supply of anguidine.

71. (a) Acid 126 was prepared from 1,4-dihydroxybutane by monosilylation (n-BuLi, TBDMS-Cl, 88%) followed by oxidation of the free hydroxyl group (catalytic RuCl₃, NaIO₄, CH₃CN, H₂O, CCl₄); (b) For details of the oxidation procedure, see: Carlson, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. 1981, 46, 3936. (c) For detailed experimental procedures for 126 and 127 see: Spada, A.P. Ph.D. Thesis, MIT, 1984.


75. Levulinate ester 130 was prepared in 73% yield by treatment of verrucarol with levulinic acid, DCC, and 4-PP in CH₂Cl₂.

76. In contrast, however, Still was able to esterify a (Z,E)-muconate derivative to a trichothecene C4-OH by using the DCC-DMAP procedure (see reference 31). In addition, we were able to esterify 86 with isopropanol without olefin isomerization in our preliminary studies (see reference 64). Nonetheless, we were unable to suppress the deleterious isomerization in the other DCC couplings which we performed.


81. (a) Coupling of verrucarol with (Z)-146 by using the DCC-DMAP procedure afforded 41% of (Z)-132 and 28% of (E)-132 after separation by chromatography. This sequence was used to prepare larger quantities of (Z)-132 required for the synthesis of verrucarin J isomers 19 and 165; (b) Acid (Z)-146 was prepared in 38% yield from anhydro-mevalonolactone by a three step sequence: (i) NaOH, H₂O; (ii) TBDMS-OTf (3 equiv.), lutidine, CH₂Cl₂; (iii) LiOH, 3:1 DME-H₂O.

83. No reaction was observed when verrucarol and the mixed anhydride prepared from 146 and pivaloyl chloride were treated with either n-BuLi-TMEDA (before addition of mixed anhydride), NaH, or KO-t-Bu in THF or DME. Both reaction components were recovered unchanged under these conditions. We thank Mr. A.P. Spada for performing these experiments.


87. We have also been unsuccessful in attempts to separate mixtures of seco acids 141/164 or of verrucarin J/19 which have been prepared from the (E,Z)-155 described in Scheme XVIII.


89. The overall yield of verrucarin J from verrucarol, after recycle of 158, was 27-30%.

90. The ethanolysis of 158 to 160 was discovered during our first attempt to measure the UV spectrum of 158.

91. Acid 161 was synthesized as shown below:

\[
\begin{align*}
\text{MeO}_2\text{POCH}_2\text{CO}_2\text{H} & \xrightarrow{1) \text{HO}} \text{TMS} \xrightarrow{2) \text{HO}_2\text{CCH}_2\text{CHO}} \text{KO-t-Bu} \\
& \xrightarrow{68} \text{HO}_2\text{CCH}_2\text{CH}_2\text{SiMe}_3
\end{align*}
\]

92. (a) Alternatively, seco acid 163 was prepared in 41% yield by treatment of (E)-phosphonate 143 with fumaraldehydeic acid (reference 92b) and potassium tert-butoxide in an ether/tert-butanol solvent mixture; (b) Fumaraldehydic acid was prepared by isomerization of malealdehydic acid (I\textsubscript{2}, C\textsubscript{6}H\textsubscript{6}, reflux, 12-40 h, 12-18% yield; 51-67% of malealdehydeic acid was recovered). For an alternative isomerization procedure, see Grove, M.D.; Weisleder, D. J. Org. Chem. 1973, 38, 815.
93. This conclusion was also reached by monitoring the cyclization mixture by TLC. No 3 or 158 was detected in the absence of acylation catalysts. All components of this reaction system are easily resolved in 1:1 ether-
CH2Cl2 containing 1% HCO2H: 141, Rf 0.4; 157, Rf 0.5; 
158, Rf 0.65; 3, Rf 0.8.

94. Another possibility is that 157 or the derived N-acyl-
pyridinium salt eliminates reversibly to a methylene ketene intermediate. For a review of methyleneketenes, see Brown, R.F.C.; Eastwood, F.W. in "The Chemistry of Ketenes, Allenes, and Related Compounds", S. Patai, ed.; Wiley: New York, 1980, p. 757). Olefin isomerization, however, also occurs in the esterification of angelic acid derivatives for which the methylene ketene pathway is not possible (see, for example, Beeby, P.J. Tetra-
hedron Lett. 1977, 3379). Hence, we favor the reversible Michael addition mechanism discussed in text.

95. Alternatively, acylation of (Z)-11 with dimethylphosphono-
acetic acid (68), DCC and DMAP afforded phosphonate (Z)-143 which was then converted to 164 by using the olefination procedure discussed previously (39% overall yield from 
(Z)-11.


97. A UV-sample of 165 in absolute ethanol underwent clean, rapid transesterification to the 2'-3'-(Z)-isomer of seco acid ethyl ester 160. Isomer 19 was recovered unchanged after measurement of the UV spectrum in ethanol.

98. The ID50 values for several other trichotheccines in the LL210 in vitro assay are summarized in reference 4a. The low activity of seco acid 141 is fully consistent with previous observations that the intact macrocycle is essential for full biological activity (e.g., trichoverrins A,B).

99. (a) Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1980, 
102, 5974; (b) Sharpless, K.B.; Behrens, C.H.; Katsuki, 
T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; 
Walker, F.J.; Woodard, S.S. Pure Appl. Chem. 1983, 55, 
589; (c) Rossiter, D.E.; Katsuki, T.; Sharpless, K.B. J. 
Am. Chem. Soc. 1981, 103, 464; (d) Martin, V.S.; Woodard, 
S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. 
Ibid. 1981, 103, 6237.

2543.

102. Available from Kodak Laboratory Chemicals.

103. The Mitsunobu reaction failed in this instance due to facile decomposition of the activated intermediate generated from 2-(p-toluenesulfonyl)ethanol, leading to triphenylphosphine oxide and an arylvinylsulfone.


106. In an experiment in which verrucarol (2) was esterified with purified acid 167, (BOP-Cl, Et₃N, DMAP) ester 174 was obtained in 47% yield along with 9% of C(4)-monoacylated trichothecene, 8% of diacylated product, and 24% of recovered verrucarol.

107. These experiments are summarized in the table below:

<table>
<thead>
<tr>
<th>Acylation catalyst</th>
<th>174 (C(15)-acylated)</th>
<th>C(4)-acylated</th>
<th>diacylated</th>
<th>recovered verrucarol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-pyrrolidinopyridine⁷</td>
<td>47%</td>
<td>9%</td>
<td>8%</td>
<td>24%</td>
</tr>
<tr>
<td>4-dimethylaminopyridine</td>
<td>41%</td>
<td>4%</td>
<td>17%</td>
<td>28%</td>
</tr>
<tr>
<td>4-piperidinopyridine</td>
<td>30%</td>
<td>7%</td>
<td>17%</td>
<td>32%</td>
</tr>
<tr>
<td>1-methylimidazole</td>
<td>26%</td>
<td>6%</td>
<td>11%</td>
<td>44%</td>
</tr>
</tbody>
</table>

⁷This experiment performed using purified acid 167.

108. This result was not surprising based on our earlier observations regarding the oxidation-esterification of epoxy-alcohol 169 to afford ester 170 (see Scheme XXI).

109. Previously reported C(4)-protected verrucarol derivatives include the C(4)-acetate (references 14 and 28), the C(4)-trichloroethoxycarbonyl derivative (reference 30) and the C(4)-THP ether (reference 30). In addition, the C(4)-TBDMS ether (reference 28) could have been useful for our purposes but the preparation of this derivative requires three steps from verrucarol.

110. (a) Bast, S.; Andersen, K.K. J. Org. Chem. 1968, 33, 846; (b) Dodd, J.R.; Lewis, A.J. J.C.S. Chem. Comm. 1975, 520; (c) see also reference 104.
111. In a typical experiment, treatment of 0.1 mmol of verrucarol with 1 equivalent of imidazolidine 176 afforded 177 in 22% yield along with C(15)-monoacylated product (6%), diacylated product (7%) and recovered verrucarol (52%).


113. In principle, 181 might also have been prepared by treating verrucarol with 2-trimethylsilylthethyl chloroformate (124) (see reference 112). However, 124 is unstable and phosgene is used in its preparation (reference 66). In contrast, imidazolidine 180 is a crystalline, apparently stable compound which can be easily prepared from 2-trimethylsilylethanol and CDI (see experimental section), both of which are commercially available (Aldrich Chemical Company). It seems likely, therefore, that 180 could become a useful reagent for the protection of alcohols and possibly amines.

114. In one experiment, verrucarol (2) was treated with one equivalent of imidazolidine 180 and DBU in benzene for 18 h to afford 181 in 44% yield along with C(15)-monoacylated product (5%), diacylated product (10%) and recovered verrucarol (18%). In a second experiment (22 h) 181 was obtained in 54% yield. In this experiment the other products were combined and hydrolyzed to verrucarol. The yield of 181 based on unrecovered verrucarol in this experiment was 81% (see experimental section for details).

115. It is interesting to note that the deprotection of 182 with KF actually proceeds somewhat more rapidly than the deprotection of 174. Furthermore, although we have not actually isolated either intermediate in the deprotection of 182, it appears by TLC as if the C(4)-protecting group is cleaved faster than the C(6")-ester. Thus, it may be that the C(4)-alkoxide generated in the case of 182 somehow assists in the cleavage of the 2-trimethylsilyl-ethyl ester at C(6").

116. Yield based on unrecovered verrucarol in the preparation of 181.


118. Available from Aldrich Chemical Company.


120. Seco acid (141) from phosphonate (E)-143 contains approximately 10% of the (Z,Z)-muconate isomer. Macro-
cyclization of such mixtures afforded verrucarin J containing the corresponding amount of a verrucarin isomer (probably the \((Z,Z)\)-muconate derivative) which was removed by crystallization from CHCl\(_3\)-ether (see footnote 17a of ref. 51a). The latter isomer was not detected when isomerically pure 141 (prepared as outlined in Scheme XVII) served as the substrate for the macrocyclization step.