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

by

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

ABSTRACT

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

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

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

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

Thesis Supervisor: Dr. William R. Roush
Title: Roger and Georges Firmenich Career Development Associate Professor of Natural Products Chemistry

ABBREVIATIONS

BOP-Cl	N,N'-bis[2-oxo-2-oxazolidinyl]-phosphorodiamidic chloride
CDI	N,N'-carbonyldiimidazole
Cp	cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHP	dihydropyran
DIBAL-H	disobutylaluminum hydride
DIPT	diisopropyl tartrate
4-DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
HMPT	hexamethylphosphosphorictriamide
LDA	lithium diisopropylamide
NCS	N-chlorosuccinimide
PCC	pyridinium chlorochromate
4-PP	4-pyrrolidinopyridine
SEM	2-trimethylsilylethoxymethyl
TES	triethylsilyl
TBMDS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl

TBHP	tert-butylhydroperoxide
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	p-toluenesulfonyl
pTsCl	p-toluenesulfonylchloride
pTsOH	p-toluenesulfonic acid

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TABLE OF CONTENTS

To Barbara

CHAPTER I

INTRODUCTION

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

The trichothecenes possess common strucural features based on the trichothecane skeleton illustrated in Figure 1.[3]

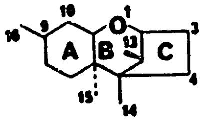

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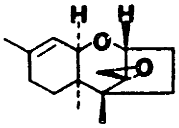
Figure 1

With very few exceptions, the naturally occurring trichothecenes contain an epoxide at C(12)-C(13) and an olefin at C(9)-C(10) (c.f., structure 2).



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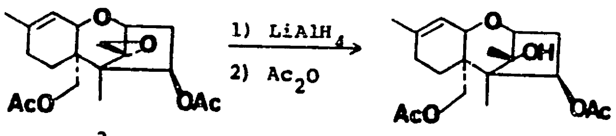
In addition, various levels of oxygenation are found at carbons 3, 4, 7, 8 and/or 15.[1g] Representative examples of the so-called simple trichothecenes are listed in Table I. Other trichothecenes contain macrocyclic ring systems. Representative examples of these compounds are listed in Tables III, IV and V.

Although the position and degree of hydroxylation of the trichothecene nucleus varies, it has been demonstrated that the presence of the 12,13-epoxide is essential for biological activity. Thus, reduction of diacetoxyverrucarol (3) with lithium aluminum hydride followed by acylation affords the tertiary alcohol 4, which is completely devoid of biological activity.[4] Similarly, acid-induced rearrangement of the 12,13-epoxy trichothecene nucleus affords the apotrichothecene skeleton 15, which also lacks biological activity.[4] In addition, catalytic hydrogenation of the C.9,10 olefin affords products



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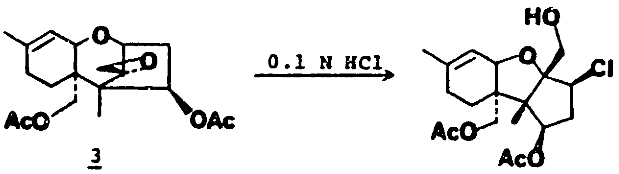

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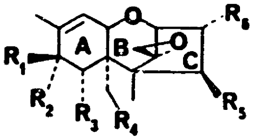
Table I



Structures of Selected Trichothecenes

Compound	R_1	R_2	R_3	R_4	R_5	R_6
Trichothecin <u>5</u>	0	0	H	H	$OCOCH=CHCH_3$	H
Trichothecolone <u>6</u>	0	0	H	H	OH	H
Diacetoxyscirpenol (anguidine) <u>7</u>	H	H	H	OAc	OAc	OH
Verrucarol <u>8</u>	H	H	H	OH	OH	H
T-2 Toxin <u>9</u>	H	$OCOCH_2CH(CH_3)_2$	H	OAc	OAc	OH
Calonectrin <u>10</u>	H	H	H	OAc	H	OAc
Trichodermol <u>11</u>	H	H	H	H	OH	H
Trichodermin <u>12</u>	H	H	H	H	OAc	H
Deoxynivalenol <u>13</u> (vomitoxin)	0	0	OH	OH	H	OH

with greatly diminished activity.[5]

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

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

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

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

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

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

Table II[1e]

Modes of Inhabition of Selected Trichothecenes

Compound	Type of Inhibition	LD_{50} values (mg/kg) (mouse i.p.)
Roridin A 16	Initiation	0.5
Verrucarin A 25	Initiation	0.5
Verrucarin J 27	Initiation	0.5
T-2 Toxin 9	Initiation	5.2
Trichodermin 12	Elongation	>500
Trichothecin 5	Elongation	<250
Trichodermol 11	Termination	500-1000

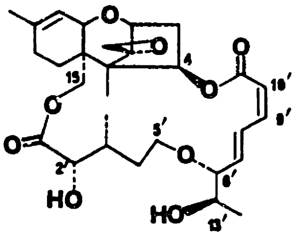
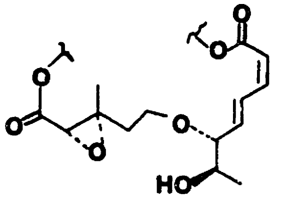
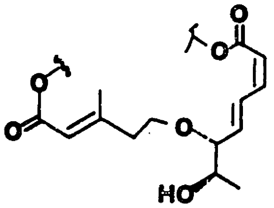
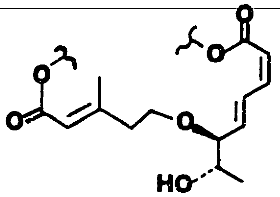
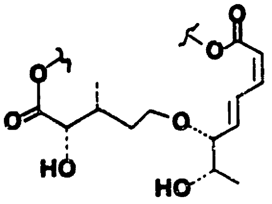
the problem is dramatically illustrated by the finding of the Canadian government that 100% of the samples collected from Quebec's 1980 crop of red spring wheat were contaminated with varying levels of vomitoxin (deoxynivalenol).[13] Similarly, 99% of the samples of Ontario's 1980 crop of white winter wheat were also contaminated with this toxin.[14] Little difference was noted in the levels of vomitoxin in grain samples taken from fields designated for human consumption (0.09 to 1.1 μg) and those designated for animal consumption (0.06 to 7.0 μg).[14]

Trichothecenes, like other mycotoxins, have been shown to induce feed refusal in swine and other farm animals, wherein the animal will not eat the contaminated food source.[15a,b] It has been shown that 40 μg of vomitoxin/g of feed corn will induce this response. The resulting loss of weight will generally make the animal unmarketable and in prolonged cases the animal will die.[15a] A financially disasterous episode of feed refusal by swine occurred in northwestern Ohio in 1975.[2] In the aftermath of this outbreak, it was shown that the feed corn was in fact contaminated with vomitoxin (13).[2] Incidents such as this have served to heighten the awareness of farmers to the potential problems associated with feedstock contaminated with various trichothecene-producing fungi. Many farmers now visually inspect their feed for the presence of toxin-producing fungi in order to avoid such problems.[2]

In retrospect, outbreaks of various human toxicosis have been attributed to the consumption of grains contaminated with trichothecene-producing molds.[13,16] Perhaps the most tragic

Structures of Selected Roridins

Table III

Entry	Structure	Reference
1. Roridin A 16		18
2. Roridin D 17		18, 21
3. Roridin E 18		19, 21, 22
4. Isororidin E 19		18
5. Isororidin A 20		18

incident occurred during the winter of 1943-4 in the Orenberg region of the Soviet Union.[16] The lack of available food forced both men and animals to forage the fields for unpicked wheat and millet. Unfortunately, the over-wintered grain had acquired substantial amounts of trichothecene-producing Fusarium fungi. The ingestion of the moldy grain was believed to be the cause of an epidemic of alimentary toxic aleukia (ATA), the symptoms of which include internal hemorrhaging, loss of muscle coordination, vomiting, and depletion of bone marrow.[16] Joffe reported that more than 10% of the population of this region contracted this disease, which has a mortality rate of 60%.[16] Thirty years after the epidemic, a sample of the wheat, supplied by the Soviet Union, was shown by Mirocha and coworkers to contain high levels of T-2 toxin (9).[17]

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

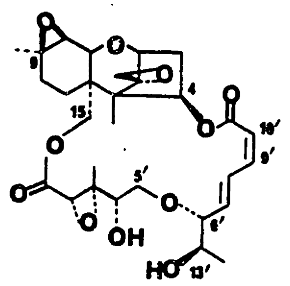
The baccharins and baccharinols (Table IV) are structurally similar to the roridins; like the roridins, the baccharinoids exist naturally as epimers at C(13').[23] They differ from the roridins, however, in that the nucleus contains a β-epoxide at the 9,10 positions in the case of the baccharins, and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

The bacchinoids are generally more phytotoxic than the precursor roridins. However, the interesting question of how *B. megapotamica* remains immune to the effects of these compounds remains unanswered. Jarvis has suggested that *B. megapotamica*'s insensitivity to the trichothecenes may derive from the inability of baccharinoids to bind to the plant's 60S ribosomal subunit.[24]

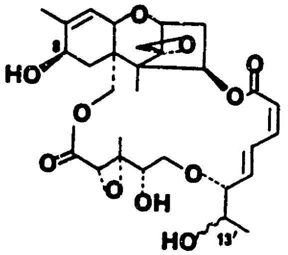
That is, this shrub may have a mutant form of the appropriate ribosomal protein. This phenomenon has been observed in the case of the fungus *M. verrucaria*[26] and probably explains why these fungi are resistant to the toxins they produce.

Table IV[18,23,24]

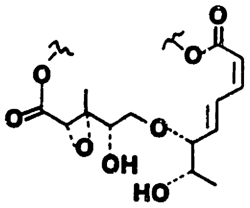
The Baccharinoids



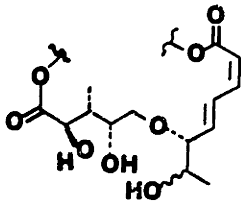
Baccharin B5 21



Baccharinols B4 and B6 23



Baccharin B8 22

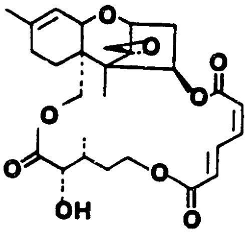
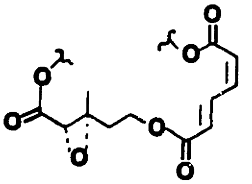
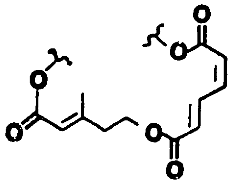


Baccharinols B3 and B7 24

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

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

Table V[1h]

Compound	Structure
Verrucarin A 25	
Verrucarin B 26	
Verrucarin J 27	

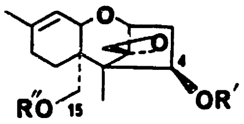
The Verrucarins

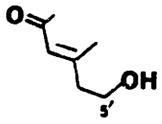
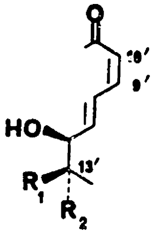
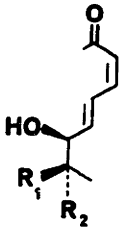
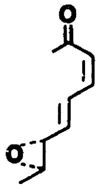
verrucarins. Thus, whereas trichoverrin A (28) shows no activity at dose levels below 32 mg/kg, isororidin E (19) is active at ca. 5 mg/kg.[1h,20,27] This diminished activity may reflect the difficulty which these relatively polar compounds experience in crossing cell membranes.

Jarvis and coworkers have conducted a series of experiments which suggest that the trichoverrins are biogenetic precursors

Table VI [20,27,28]

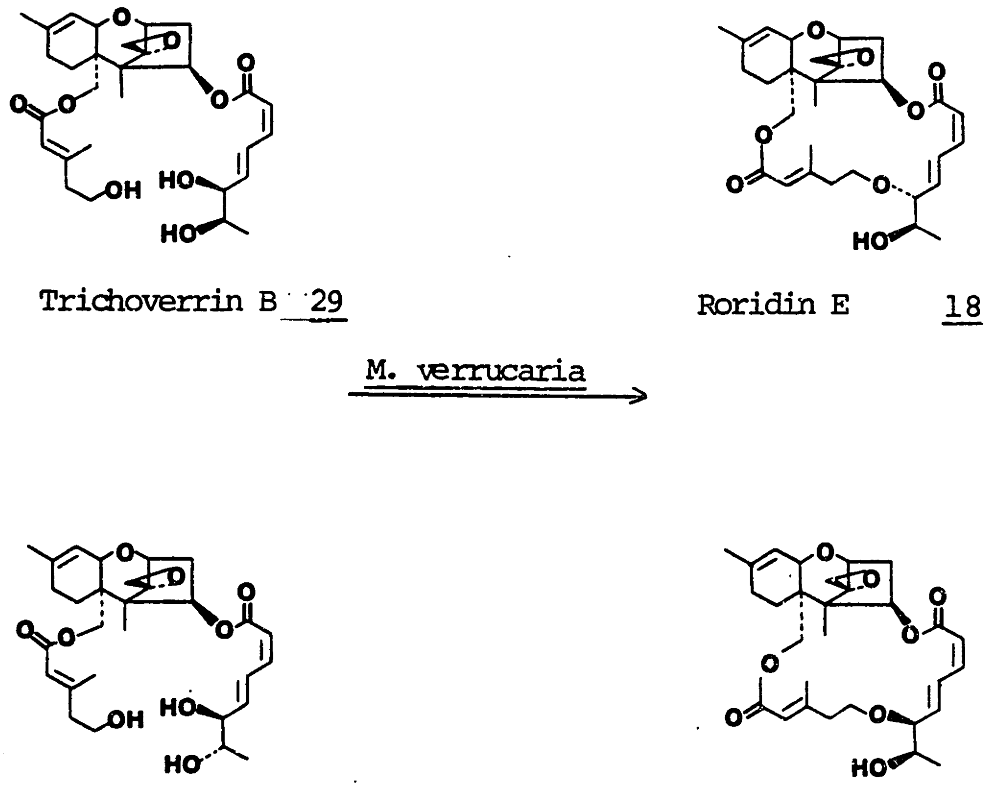
The Trichoverroids



	R″	R′
Trichoverrins	 28 A: R_1 = H ; R_2 = OH 29 B: R_1 = OH ; R_2 = H	
Trichoverrols	H 30 A: R_1 = H ; R_2 = OH 31 B: R_1 = OH ; R_2 = H	
Trichodermadiene	32 H	

to the macrocyclic trichothecenes (Scheme II).^{20,27}

Scheme II



Trichoverrin B 29

Roridin E 18

+ Roridin A 16

and Verrucarins

A(25), B(26), and J(27

Trichoverrin A 28

Isororidin E 20

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

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

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

Table VII

Activity of Selected Trichothecenes for P388 Carcinoma

Entry	Compound	dose (mg/kg)	T/C[a]	Ref.
1.	Baccharin	7.5	246	1a
2.	Baccharinol	2.5	185	1a
3.	9,10-Epoxyverrucarin A	8.0	210	1a
4.	Verrucarin A <u>25</u>	2.0	127	1a
5.	8-β-Hydroxyroridin A	3.75	205	1a
6.	Roridin A <u>16</u>	.08	128	1a
7.	Roridin D <u>17</u>	Inactive		1a
8.	Trichoverrin A <u>28</u>	Inactive		27
9.	Trichoverrin B <u>29</u>	Inactive		27
10.	Roridin E <u>18</u>	ca. 5	~160	1h
11.	Iso Roridin E <u>19</u>	ca. 5	~160	1h

a) The activity is expressed as T/C values, which is defined as the number of days the test animals live, divided by the number of days the control animal lives, multiplied by 100. Compounds with T/C values ≥ 120 are considered active; those with T/C > 180 are considered very active.

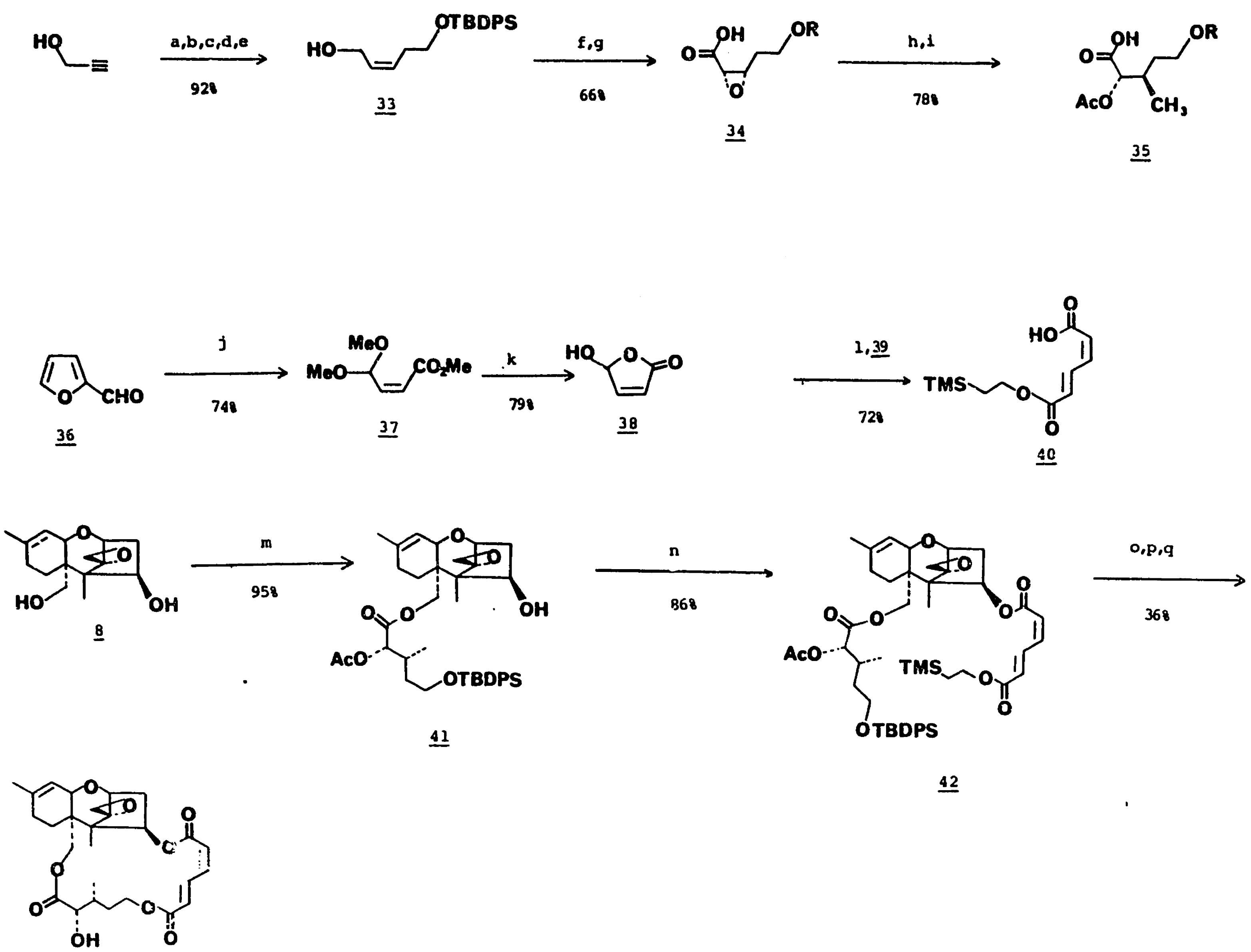
structure-function relationships of the trichothecenes will lead to a series of effective chemotherapeutic agents. In addition, it is probable that such studies will afford new insights into the mechanism of action of the epoxytrichothecenes at the molecular level.

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

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

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

Scheme III[35]



Key to Scheme III:

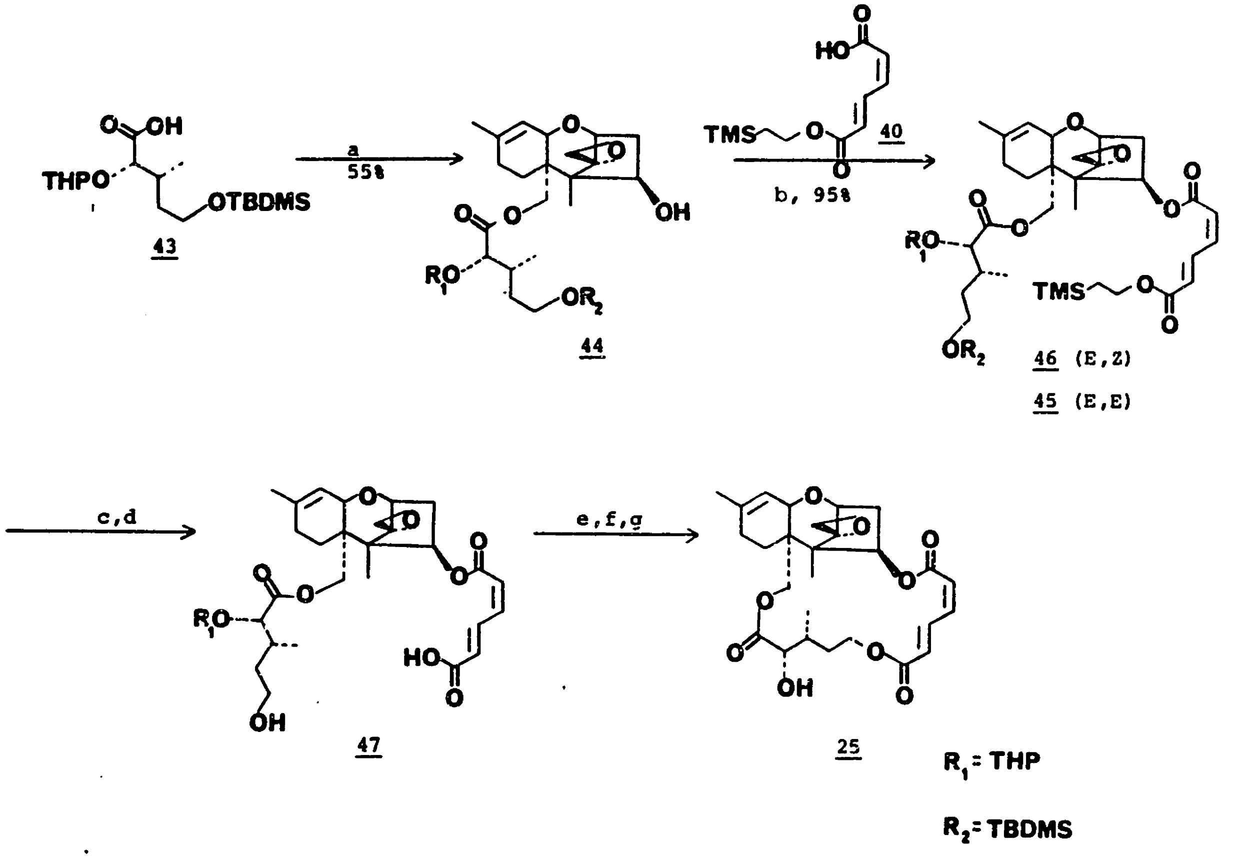
a) $EtOCH=CH_2$, p-TsOH; b) iPrMgBr, THF, ethylene oxide; c) TBDPS-Cl, imidazole, DMF; d) AcOH, H_2O; e) H_2, Lindlar catalyst, MeOH; f) t-BuOOH, $(iPrO)_4Ti$, CH_2Cl_2, -20°C; g) 2% $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O; h) $Al(Me)_3$, petroleum ether, 25°C, 40h; i) Ac_2O, pyridine; j) Pt electrodes, MeOH, Et_4NClO_4, 1.5 amps, 18h; k) 1 N H_2SO_4, 25°C, 18h; l) $(Ph)_3P=CHCO_2CH_2CH_2SiMe_3$, 39; m) 38, DCC, 4-pyrrolidinopyridine, CH_2Cl_2, 25°C, 5h; n) 40, DCC, 4-pyrrolidinopyridine, CH_2Cl_2, 25°C, 5h; o) $(nBu)_4NF$, THF, 25°C, 3h; p) $(Ph)_3P$, $EtO_2CN=NCO_2Et$, 25°C, 20h, 52%; q) NaOMe, MeOH, 0°C, 2h, 70%.

Carboxylic acid 35 was prepared in 28% overall yield from 4-butyn-1-ol. Key steps of this sequence included the enantioselective epoxidation of (Z)-allylic alcohol 33 followed by $RuCl_3$ catalyzed oxidation, which afforded epoxy acid 34. Introduction of the β-methyl group at C(3') was accomplished with trimethylaluminum. Subsequent acylation afforded the C(15) acyl synthon 35. Mono-protected (Z,E) muconic acid 40 was prepared from furfural in three steps in 42% overall yield. Interestingly, the Wittig olefination of pseudoacid 38 with ylid 39 afforded only the desired (E,Z) muconate derivative.

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

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

Scheme IV[39]

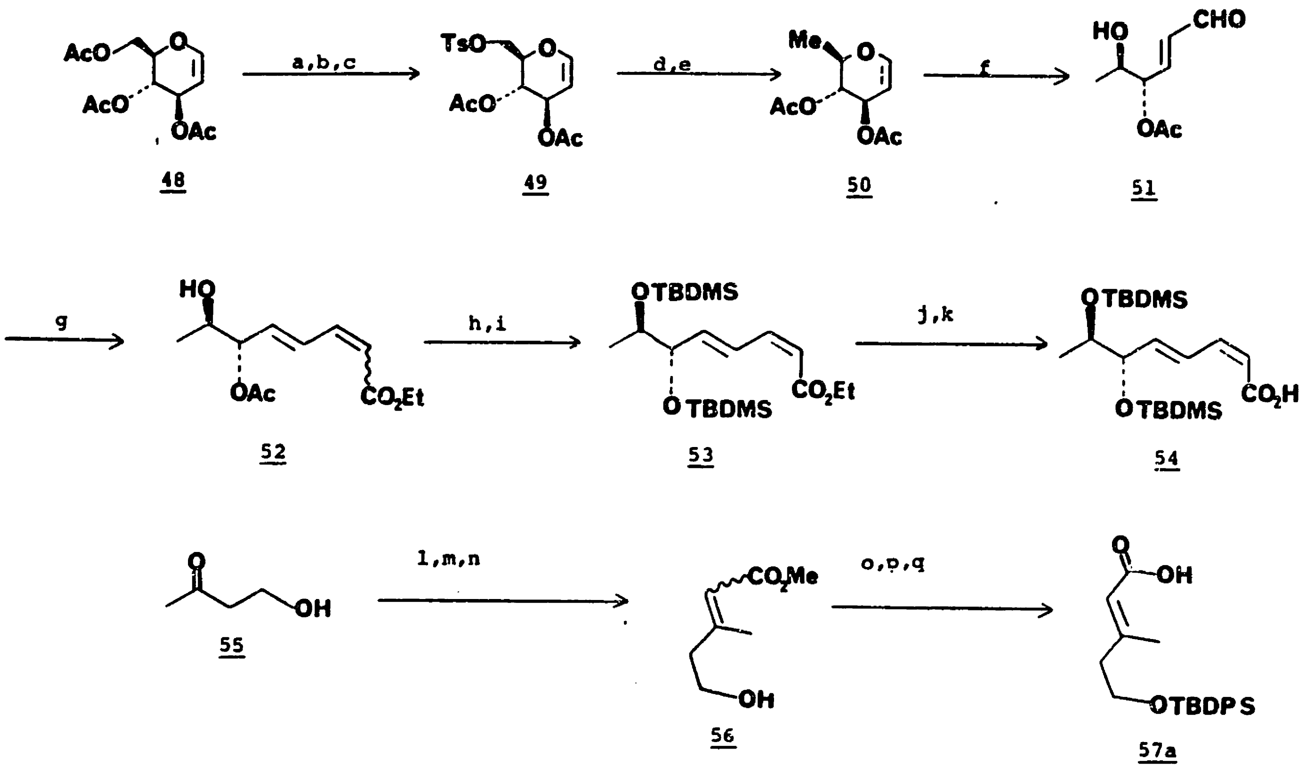


a) 8, DCC, 4-pyrrolidinopyridine; b) 40, DCC, 4-pyrrolidinopyridine; c) separation; d) $(nBu)_4NF$, THF; e) 2,4,6-trichlorobenzoylchloride; f) 4-dimethylaminopyridine, toluene, 110°; g) pyridinium p-toluenesulfonate, MeOH, 50°C.

acylation of the C(15) position of verrucarol 8 with acid 43 in the presence of DCC and 4-PP afforded monoester 44 in 55% yield. Acylation of C(4) with the monoprotected muconic acid 40 under similar conditions afforded diester 46 in 95% yield as a 3:1 mixture of (Z,E) and (E,E)-products. These isomers were separated by silica gel chromatography at this stage. Removal of the silyl groups followed by macrolactonization and THP ether hydrolysis proceeded in 50% overall yield to provide verrucarin A (25). Two additional verrucarins have been synthesized: verrucarin J (27) by both Fraser-Reid[40] and Roush,[41b,c] and verrucarin B (26) by Roush.[42] The synthesis of verrucarins J and B by Roush and Blizzard will not be described here as they are the subject of a recent Ph.D. thesis[41a] from these laboratories. The synthesis of verrucarin J by Fraser-Reid was accomplished in connection with work on the synthesis of trichoverrin B which is outlined below.

Fraser-Reid and coworkers in 1982 published the synthesis of trichoverrin B (29) and its conversion to verrucarin J (27) (see Scheme V).[40] The synthesis of the octadienoate fragment was first developed in order to determine the absolute stereochemistry of C(6') and C(13') of the trichoverrins.[28,43] This synthesis starts from commercially available triacetyl glucal 48. Reduction of the C(6) to a methyl group was accomplished in five steps in 51% overall yield. Compound 50 was then transformed to the α,β-unsaturated aldehyde 51 using the method reported by Perlin (H_2SO_4, H_2O, dioxane) in 95% yield. Final

Scheme V[40]



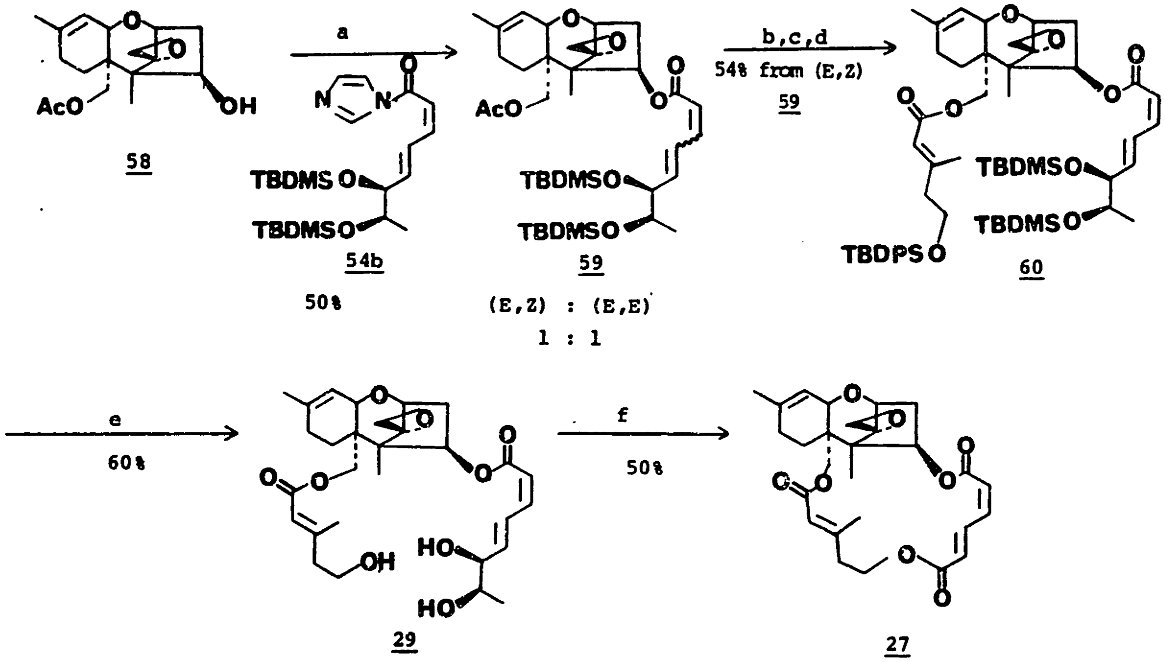
a) NaOMe, MeOH; b) TsCl, pyridine, 0°, 48h; c) Ac_2O, pyridine; NaI; e) $n(Bu)_3SnH$; f) $HgSO_4$, H_3^+O, dioxane; g) LDA, $Me_3SiCH_2CO_2Et$, THF, -78°; h) NaOMe, MeOH; i) TBMDS-Cl, DMF, imidazole; j) chromatography; k) LiOH, DME, H_2O; l) 2-methoxypropene, TsOH; m) methyl trimethylphosphono acetate, NaH, DME; n) H_3O^+; o) NaOH, followed by H_3O^+; p) TBDPS-Cl, imidazole, DMF; q) LiOH, DME, H_2O.

elaboration to diene acid 54 was accomplished in four steps. First aldehyde 51 was homologated to diene esters 52 as a (2:1) mixture of (Z,E) and (E,E)-isomers via a Peterson olefination with ethyl trimethylsilylacetate. These isomers were separated and the major compound was elaborated to 54 by a straightforward sequence.

The synthesis of the acrylic acid side chain was accomplished in five steps from β-hydroxyketone 55 (Scheme V). Protection of the free hydroxyl group of the 55 as a mixed ketal followed by olefination with trimethyl phosphonoacetate (NaH, DME) and hydrolysis of the protecting group gave hydroxy ester 56 as a 5:1 mixture of E:Z olefin isomers in 65% overall yield. Saponification of the methyl ester (NaOH, H_2O) gave the corresponding hydroxy acid in 75% yield. Treatment of this material with tert-butyldiphenylsilyl chloride followed by hydrolysis of the silyl ester (LiOH, DME:H_2O) gave, after chromatographic separation of the isomeric acids, pure E-acid 57 in 81% yield.

Coupling of these two fragments to the trichothecene nucleus is outlined in Scheme VI. Selective acetylation of of verrucarol 8 (Ac_2O, py, CH_2Cl_2) gave the C(15) monoacetate 58. Acylation of 58 with diene acid 54 proved to be somewhat problematic. However, treatment of the C(4) sodium alcoholate (THF, 1% HMPT, -10°C) with the acylimidazolide 54b afforded diester 59 in 50% yield as a 1:1 mixture of (E,E) and (Z,E) isomers, which were separated by HPLC. Selective hydrolysis (LiOH, DME, H_2O) of the C(15) acetate of 59 afforded the

Scheme VI



a) NaH, THF, 1% HMPT, -10°; b) LiOH, DME, H_2O; c) NaH, THF 1% HMPT, -10°; d) $(nBu)_4NF$, THF; f) PDC, DMF.

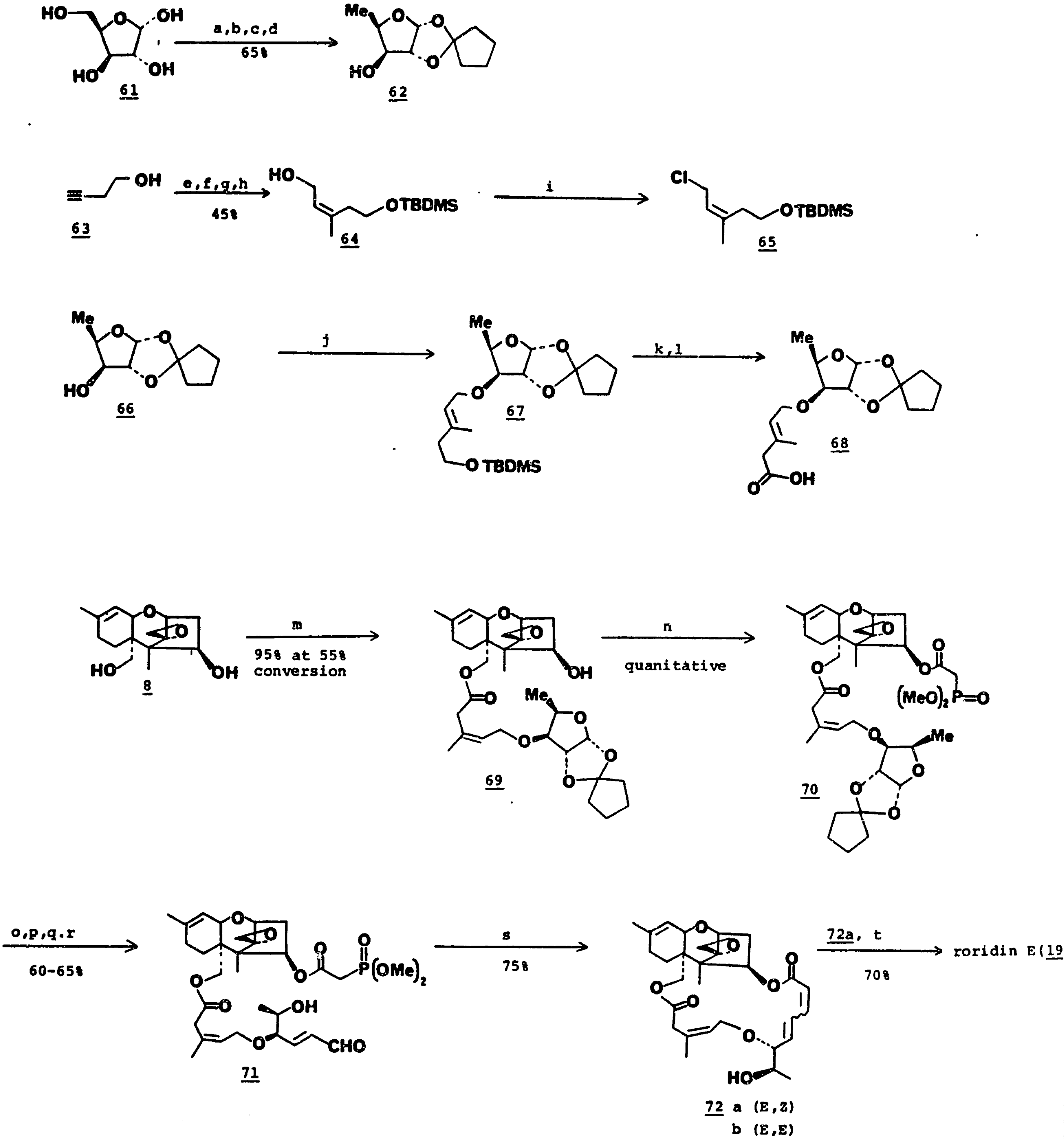
corresponding C(4) monoester in 91% yield.

Acylation of the C(15) portion with acrylic acid 57 required somewhat different conditions than those used for the acylation of C(4)-OH. Thus, treatment of the C(15) sodium alcoholate in THF with the acylimidazolide 54b and tetra n-butylammonium iodide with 57b gave diester 60 in 60% yield. Desilylation with $(nBu)_4NF$ in THF then afforded trichoverrin B (29) in 60% yield. Exposure of trichoverrin B to pyridinium dichromate in DMF for 13 days effected oxidative ring closure and gave verrucarin J (27) in 50% yield.

Still and coworkers have recently completed syntheses of roridin E (19) and baccharin B5 (21). These represent the first syntheses of members of the roridin/baccharinoid classes of trichothecenes (see Scheme VII).[19] The side chain synthon 68 was prepared in a straightforward manner from D-xylose (61) and 3-butyne-1-ol (63). Acylation of verrucarol with 68 proceeded in high yield at moderate conversion to afford monoester 69 which was subsequently acylated with dimethylphosphonoacetic acid to afford diester 70. Through a series of standard transformations the furanose moiety was converted to the desired unsaturated aldehyde 71, which served as the precursor for the macrocyclization step. Still had hoped that the intramolecular Horner-Emmons olefination reaction would afford only the desired (Z,E) diene 72a.[19] The cyclization of 71, however, afforded both possible isomers 72a and 72b in a ratio of 1.5:1.[44] Macrocycle 72a was obtained in 45% yield from 71 after chromatographic removal of 72b. Treatment of 72a with potassium tert-butoxide effected stereoselective olefin conjugation and completed the synthesis of roridin E. This synthesis is also important in that it established the (R)-stereochemistry at C(6') and C(13'), which had not been known with certainty prior to this work.

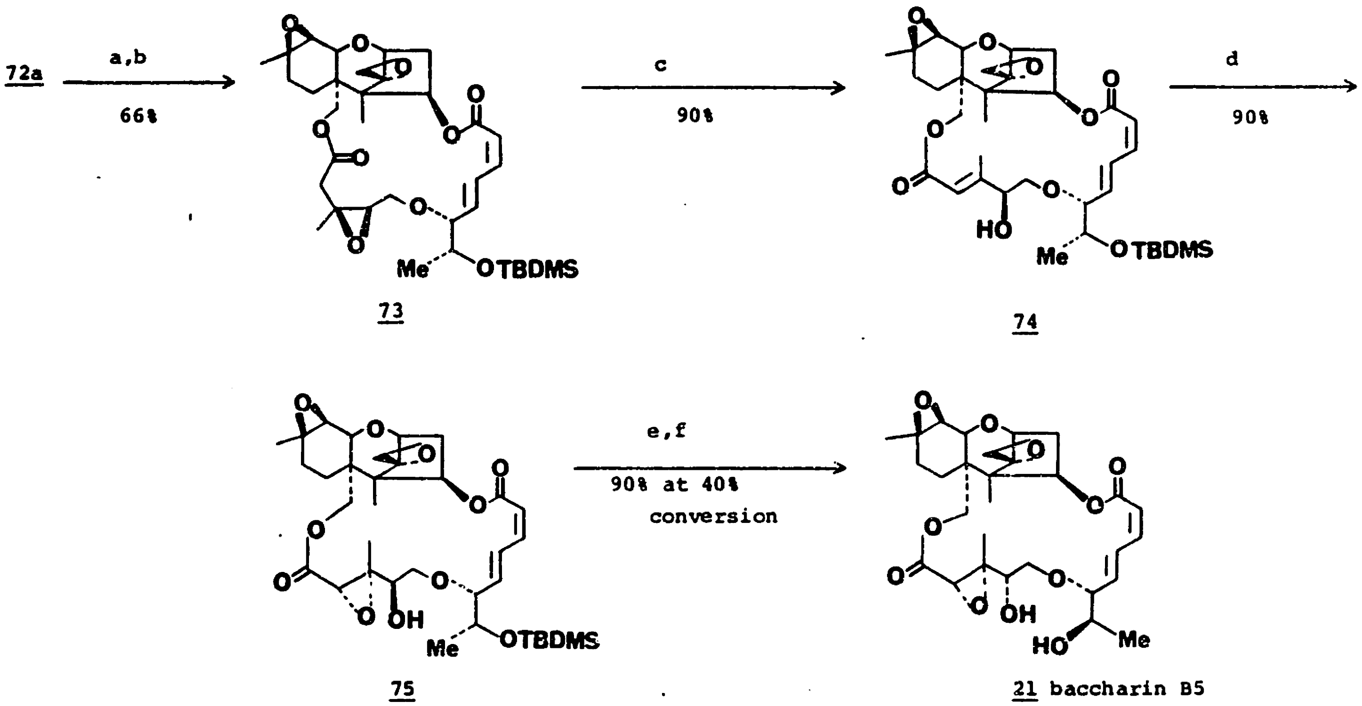
Macrocycle 72a also served as an intermediate in the synthesis of baccharin B5 (see Scheme VIII). Thus, protection of the C(13') hydroxyl group as a tert-butyldimethylsilyl ether, followed by epoxidation of the C(9,10) and C(3',4') double bonds afforded bis epoxide 73. The stereoselectivity for this

Scheme VII[19]



a) cyclopentanone, $CuSO_4$, cat. H_2SO_4; b) 0.2% HCl, THF, H_2O; c) p-TsCl, pyridine; d) $LiAlH_4$; e) TBDMS-Cl, imidazole, DMF; f) i. n-BuLi, ii. $ClCO_2Et$; g) $(Me)_2CuLi$, Et_2O; h) $LiAlH_4$; i) NCS, Me_2S; j) 65, NaH, THF, HMPT, cat. n-Bu_4NI; k) $(nBu)_4F$ THF; l) Jones oxidation; m) 8, 68, DCC, 4-pyrrolidinopyridine; n) $(MeO)_2POCH_2CO_2H$, DCC, 4-pyrrolidinopyridine; o) 0.1 M p-TsOH, 1:3 H_2O:AcOH; p) $NaIO_4$, THF, H_2O; q) Et_3N, MeOH; r) $(Ph)_3P{=}CHCHO$, toluene, 25°, 40h; s) K_2CO_3, 18-crown-6, toluene, -20° to 0°C; t) K^tOBu, isopropanol

Scheme VIII



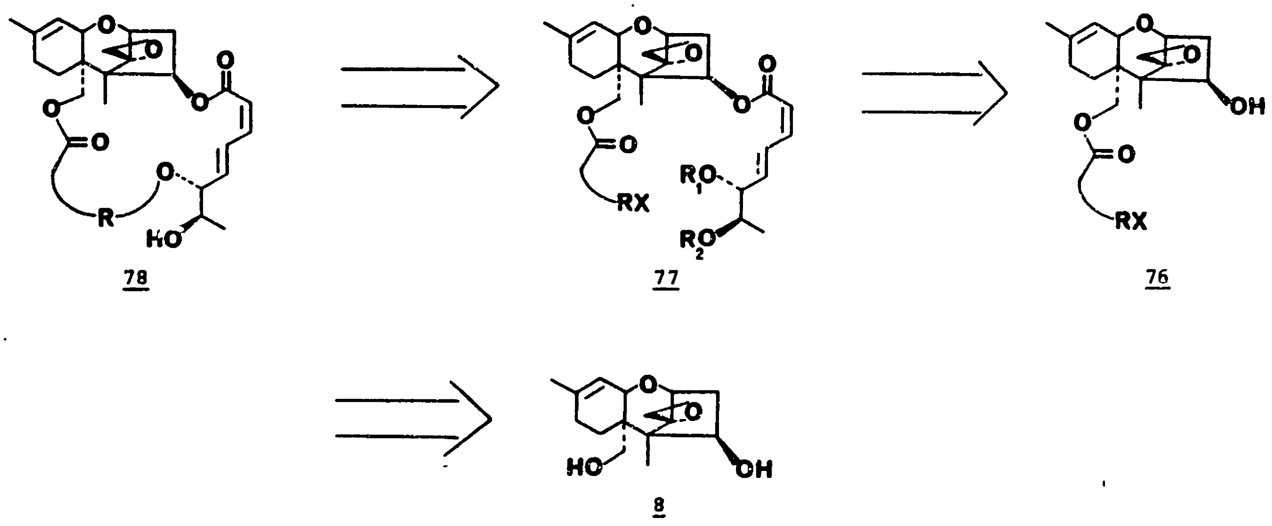
a) TBDMSOTf, lutidine; b) mCPBA benzene, 25°C, 4h; c) K^tOBu, isopropanol, -25°C, 2h; d) tBuOOH,VO(acac)$_2$, CH_2Cl_2, 25°; e) Ph_3P, $EtO_2CN{=}NCO_2Et$, formic acid, benzene; f) $(nBu)_4NF$, THF.

epoxidation was greater than 15:1 at both positions. Treatment of 73 with potassium tert-butoxide afforded (E)-unsaturated ester 74 as the sole product. Transition metal-mediated epoxidation of the C(2',3') olefin afforded a single epoxide 75. This product proved to have the natural stereochemistry at

C(2') and C(3'), but incorrect stereochemistry at C(4'). Mitsunobu inversion of the C(4') hydroxyl group followed by fluoride ion promoted cleavage of the tert-butyldimethylsilyl group completed the synthesis of baccharin B5 (21). The absolute stereochemistry of baccharin B5 had previously been established by single crystal X-ray analysis, carried out by Kupchan and coworkers.[23b] All of the work described above concerning synthetic efforts toward the macrocyclic trichothecenes, had not yet been published when we began our research program in 1980. Thus, the retrosynthetic analysis presented below represents our initial dissection of this synthetic problem.

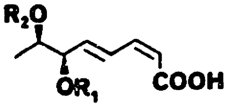
One characteristic feature of the roridins, as discussed earlier in this chapter, is the presence of the octadieneoate fragment attached to the C(4) position of the trichothecene nucleus. This observation suggested to us a simple retrosynthetic plan (Scheme IX) which would be applicable to the synthesis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

Scheme IX



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

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

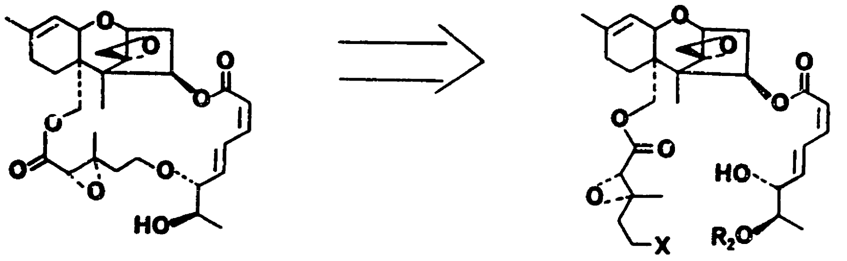


79

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

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

Scheme X



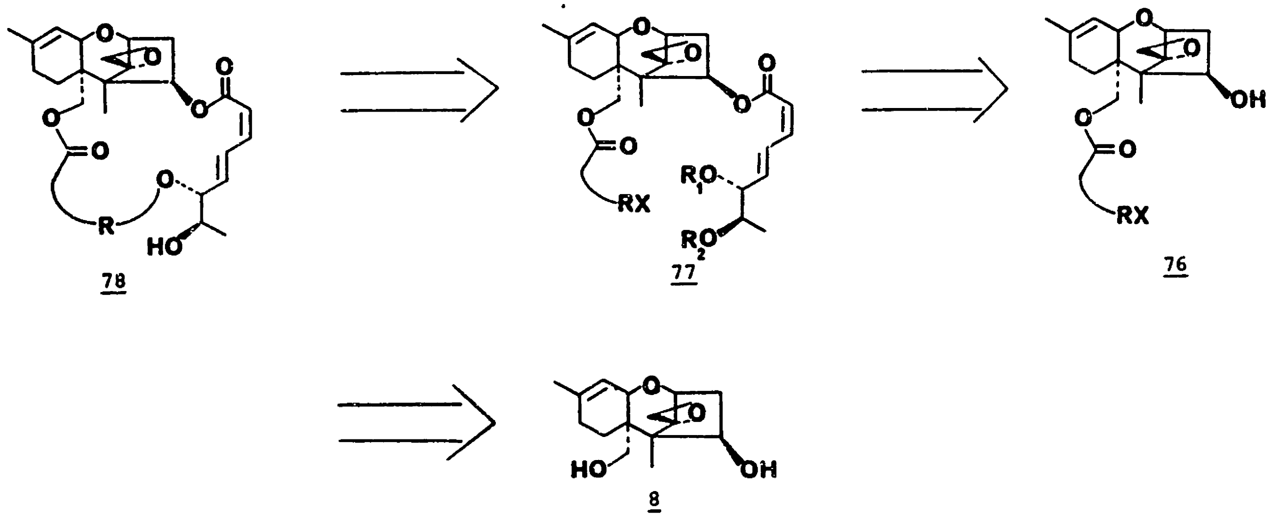
the synthesis of roridin D are discussed in Chapter 4.

CHAPTER II

SYNTHESIS OF THE OCTADIENOATE FRAGMENT OF THE RORIDINS AND TRICHOVERRINS

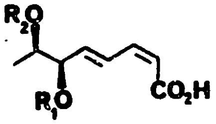
Our objective was to develop a general synthetic strategy for the synthesis of the roridin and baccharin classes of macrocyclic epoxy trichothecenes. One potentially versatile method would involve diesters of the general structure 77, which would be cyclized to yield roridins of the general structure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

Scheme XI



An appealing aspect of this strategy is that 77 would be constructed by the sequential coupling of verrucarol (8) and the C(4)- and C(15)-ester units. Preparation of 77 would take advantage of the greater reactivity of the C(15)-hydroxyl group under a range of acylation conditions.[35,36,40] Thus, we envisaged that the requisite C(15)-acyl fragment could be coupled to verrucarol to give monoester 76 which would then be converted to 77 by coupling with the necessary dihydroxy-octadienoic acid unit. Access to any roridin, in principle, would be possible by selecting the appropriate C(15)-acyl fragment (see Table III, Chapter I).

We envisaged that these relatively simple C(15) acyl units could be constructed with little difficulty. On the other hand, the octadienoic acid fragment (e.g. 79) necessary for esterification to the C(4) hydroxyl is a much more challenging target. Clearly, a satisfactory synthesis of 79 must achieve high optical and diastereomeric purity of the threo dialkoxy unit as well as permit the introduction of the (E,Z)-diene in a highly stereocontrolled manner. Our research thus began with an examination of strategies for the preparation of the differentially protected dihydroxy octadienoic acid 79.



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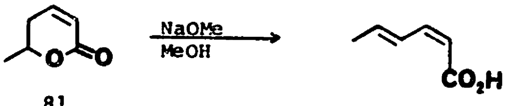
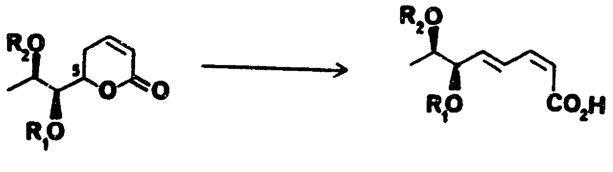
Base-promoted rearrangements of α,β-unsaturated δ-lactones have long been known to afford (Z,E)-diene acids stereospecifically. Eisner, for example, reported in 1953 that unsaturated lactone 81 gave diene acid 82.[47] More recently, Corey et al



81

82

have used this rearrangement to prepare the dienoic acid portion of the ansa bridge of rifamycin S.[48] An example of this rearrangement also appears as the last step of their bongkrekic acid synthesis.[49] On the basis of this precedent we believe that 83 would serve as a suitable precursor to 79. Although the stereocenter at C(5) in 83 would appear to be inconsequential, the selection of 83 as a key intermediate required that we design a synthesis which would control three contiguous stereocenters so as to avoid diastereomeric mixtures at earlier stages in the synthesis.



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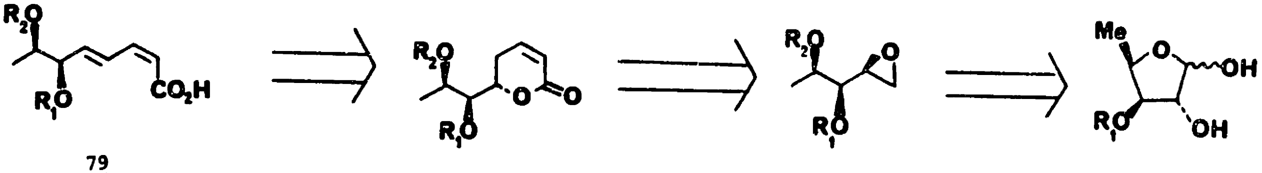
79

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

Scheme XII



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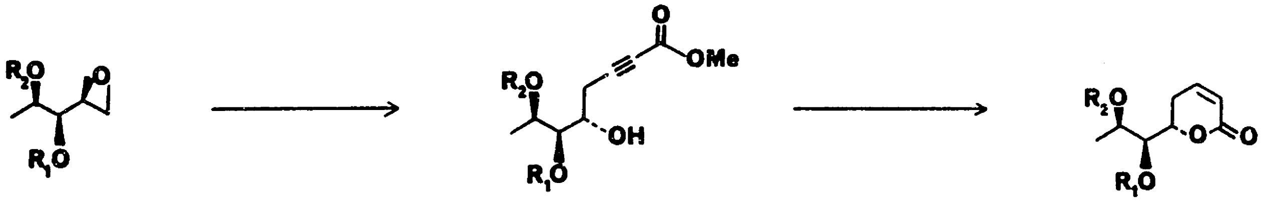
83

84

85

epoxide 84 could be converted to lactone 83 by a three-step sequence. For example, alkylation of 84 with $LiC\equiv C-CO_2Me$ would afford acetylenic hydroxy ester 86, catalytic hydrogenation, and lactonization of which could lead to unsaturated lactone 83, (Scheme XIII).

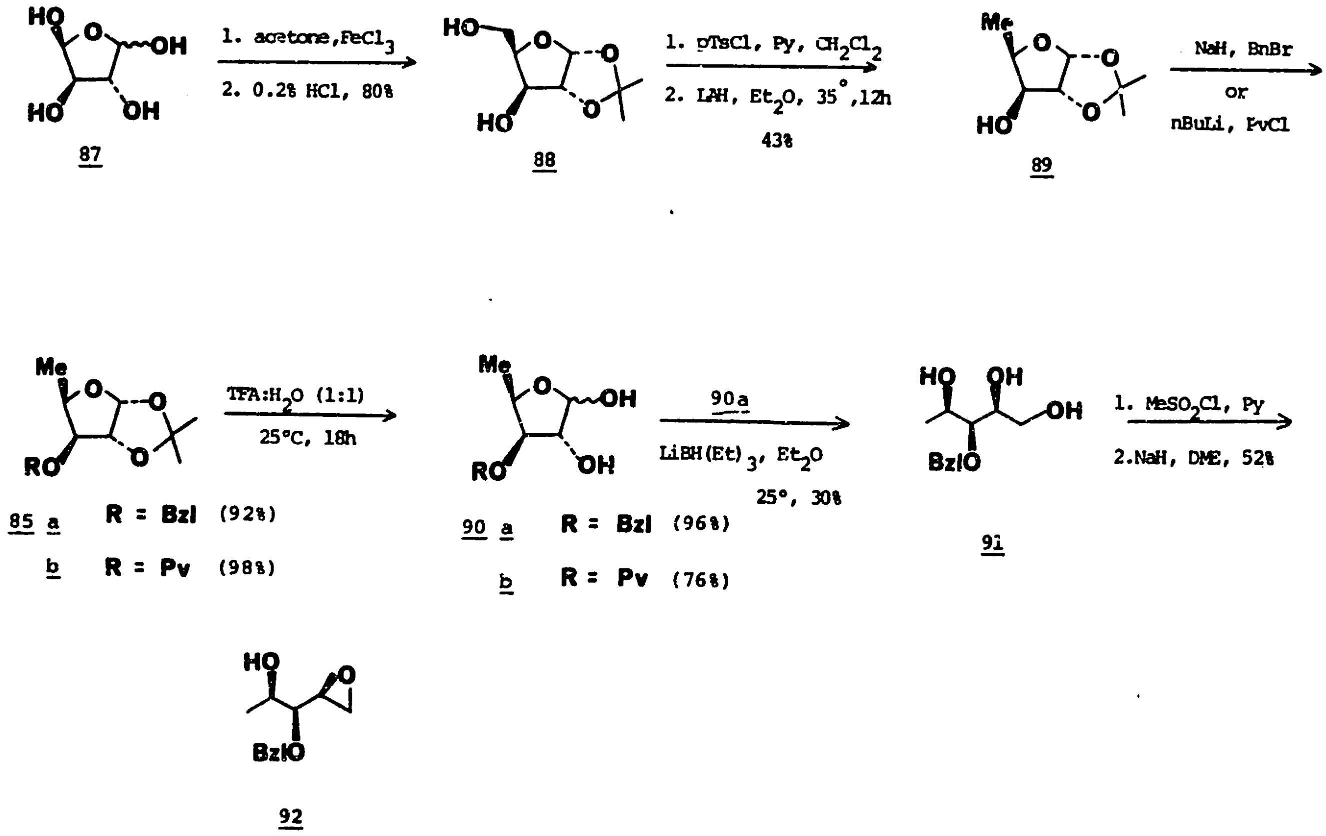
Scheme XIII



84 86 83

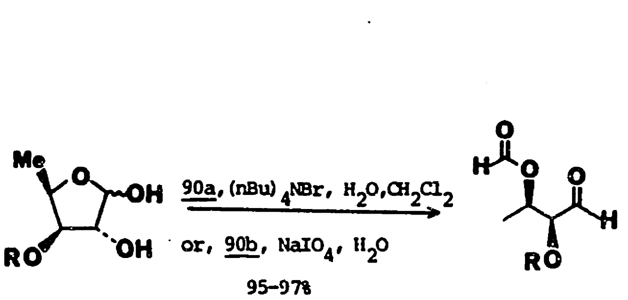
Preparation of the first key intermediate, epoxide 84, is outlined in Scheme XIV. D-xylose was treated with catalytic $FeCl_3$ in acetone at reflux (30 min) to afford the 1,2,-3,5-bisacetonide derivative in 96% yield.[50] Selective hydrolysis of the 3,5-acetonide[51] (0.2% HCl, H_2O) gave 1,2-isopropylidine D-xylose (88,82%) which was selectively tosylated (pTsCl, pyridine, CH_2Cl_2)[51] and subsequently reduced with lithium aluminum hydride to afford the 5-deoxy sugar 89 in 43% yield from 88. Protection of the free hydroxyl group as either a benzyl ether (85a) (benzyl bromide, NaH, DME) or a pivaloyl ester (85b), (n-BuLi, pivaloyl chloride, THF) followed by hydrolysis of the 1,2 acetonide (50% aqueous trifluoroacetic acid)[52] cleanly afforded hemiacetals 90a,b. Unfortunately, repeated attempts to reduce hemiacetal 90a to triol 91 met with only limited success. Seven different reducing agents were tried under a variety of conditions to affect this transformation.[53] The best result was obtained with lithium triethylborohydride in diethylether at

Scheme XIV



25°C which afforded triol 91 in a maximum yield of 30%. Although 91 could be converted to 92 in 52% yield ($MeSO_2Cl$, pyridine, followed by NaH) the problems associated with the reduction of hemiacetal 90 precluded our further investigation of this sequence.

It was clear that modifications of the synthetic plan were called for at this stage. We found, in contrast to the difficulties encountered with the reduction of 90, that oxidative cleavage ($NaIO_4$, water; or $NaIO_4$, 3 mol% $(n\text{-}Bu)_4NBr$, CH_2Cl_2-H_2O) proceeded smoothly to afford aldehydes 93a,b in high yields. We were



90 a, b

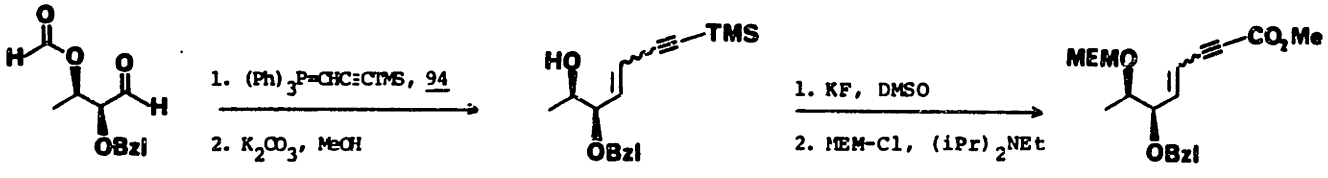
93a R = Bzl

b R = Pv

encouraged by this result since we imagined that aldehyde 93 would condense with appropriately functionalized intermediates suitable for elaboration to the required diene acid.

Initial experiments focused on attempts to convert 93 b acetylenic ester 86. Unfortunately, treatment of 93 b with allenyl magnesium bromide,[54] $BrZnCH_2C{\equiv}CCO_2Me$ or $BrMg(CH_2)_3CH(OEt)_2$ afforded complex mixtures of uncharacterized materials. In contrast, condensation of 93a with trimethylsilylethynylmethylenetriphenylphosphorane 94[55] afforded ene-yne 95 as a 4:1 mixture (E:Z) of double bond isomers in 55% yield (Scheme XV).

Scheme XV



93a

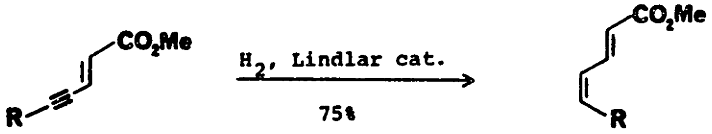
95

96 a (E)

b (Z)

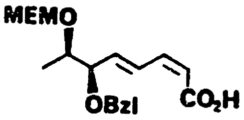
Removal of the trimethylsilyl group (KF, DMSO, 66%) followed by protection of the free hydroxyl group as a methoxyethoxymethyl ether (MEMCl, $(iPr)_2NEt$, CH_2Cl_2, 86%)[56] and carbomethoxylation of the lithium acetylide (nBuLi, Et_2O, -78°C; $ClCO_2Me$, 0°C) afforded ester <u>96</u> in 61% yield (along with 30% of recovered starting material). Unfortunately, at no point during this sequence were the olefin isomers separable by thin layer chromatography. Separation of the olefin isomers was finally accomplished by semi-preparative reverse-phase HPLC of <u>96</u>.

We were optimistic that <u>96a</u> would serve as a suitable precursor to <u>79</u> since Crombie had reported the selective catalytic hydrogenation of several α,β-unsaturated acetylenic esters to afford exclusively the corresponding (E,Z)-dienes.[57] This methodology seemed ideally suited for our purposes.



<u>97</u> <u>98</u>

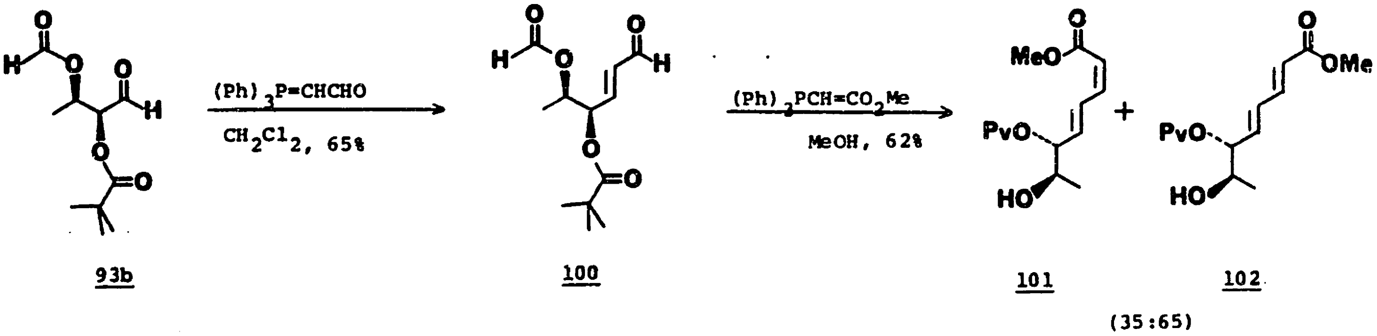
Unfortunately, several attempts to reduce <u>96a</u> selectively with hydrogen and Lindlar catalyst were unsuccessful. After the consumption of one equivalent of hydrogen the reaction mixture contained some desired product <u>99</u> along with unreacted starting material and products of over reduction. This situation was further complicated since the components of this mixture



99

coeluted in several solvent systems. Since it was apparent that this approach to the synthesis of diene acid 99 was flawed, this sequence was also abandoned.

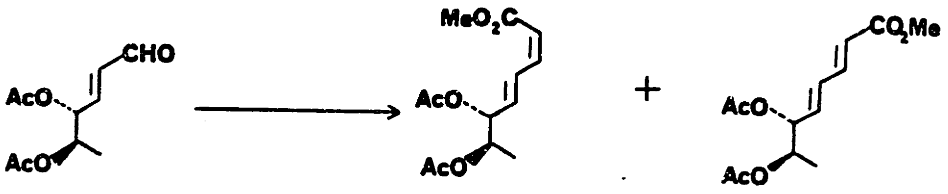
A synthesis of an octadieneoate ester (e.g. 101) was finally developed from aldehyde 93b via two successive Wittig olefinations (Scheme XVI). Thus, treatment of 93b with formylmethylenetriphenylphosphorane in dichloromethane afforded (E)-unsaturated aldehyde 100 in 65% yield as a 10:1 mixture of (E):(Z) isomers. Unfortunately, the subsequent olefination of aldehyde 100 with carbomethoxymethylenetriphenylphosphorane in methanol did not proceed with comparable stereoselectivity. This



reaction afforded a mixture of esters 101 and 102 in a ratio of 35:65 (62%), respectively, as determined by 250 MHz ^1H NMR analysis.

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

Table VIII



103 104 105

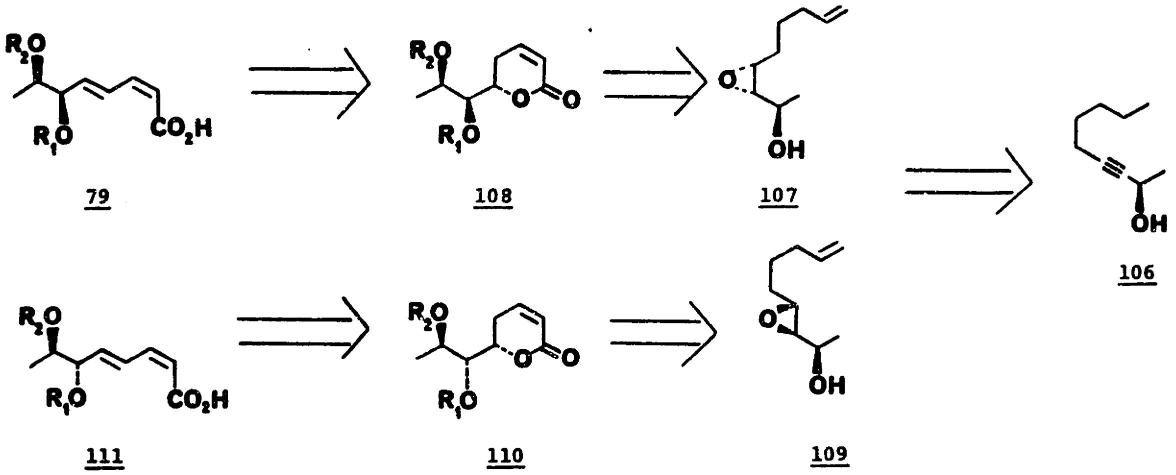
Reagents	Ratio (104:105)
$(EtO)_2PCH_2CO_2Me$,NaH,Et_2O,-78	0 : 100
$Ph_3P{=}CHCO_2Me$, CH_3CN	20 : 80
$Ph_3P{=}CHCO_2Me$, MeOH, 25°	35 : 65
$Me_3SiCH_2CO_2Me$, n-BuLi, -78°	50 : 50
$Me_3SiCH_2CO_2Et$, n-BuLi, -78°	67 : 33[40]

of selectivity fell far short of our expectations. We decided, therefore, to completely redesign our approach to diene acid 79 to ensure that the (Z,E)-diene unit would be constructed in a highly selective manner (c.f. 83 → 79).[58]

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

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

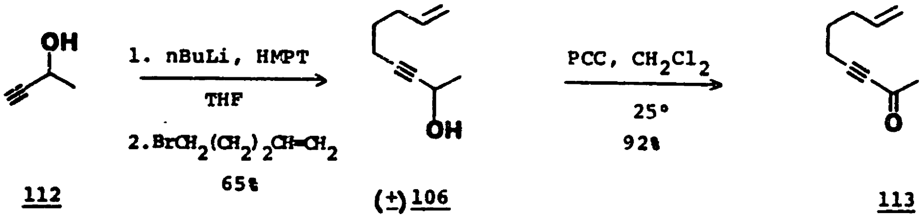
Scheme XVII



Thus, reduction of 106 to either the (E)- or (Z)-allylic alcohol followed by stereoselective epoxidation would yield 107 and 109.[59] Oxidative cleavage of the vinyl group to the carboxylic acid followed by lactonization and subsequent enolate oxidation would afford the required unsaturated lactones 108 and 110. Finally, base-promoted rearrangement of these lactones would afford the desired acids 79 and 111.

Our initial plan called for optically active 106 to be synthesized by an enantioselective reduction[60] of the corresponding propargyl ketone 113, which was synthesized as outlined in Scheme XVIII. Thus, alkylation of the dianion of 3-butyne-2-ol

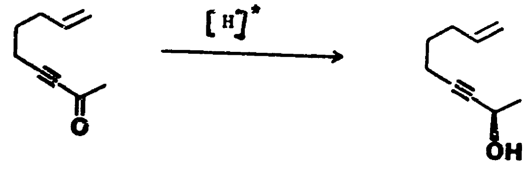
Scheme XVIII



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

The results of reduction of 113 with two chiral hydride reagents reagents are summarized in Table IX.[60]

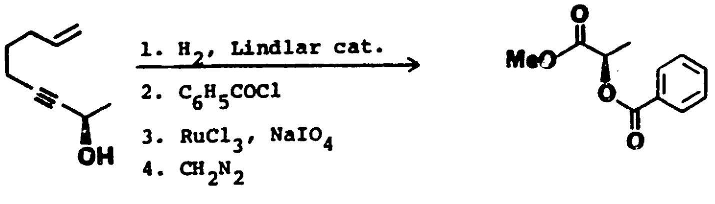
Table IX


113
(R)-106

Reagent	Chemical Yield	Optical Purity[a]
$LiAlH_4$, Chirald® Et_2O	70-76%	64-72% ee
$LiAlH_4$, (R)-2,2'-binapthol, EtOH, THF	50%	76% ee

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

The absolute configuration of 106 was determined to be (R) by

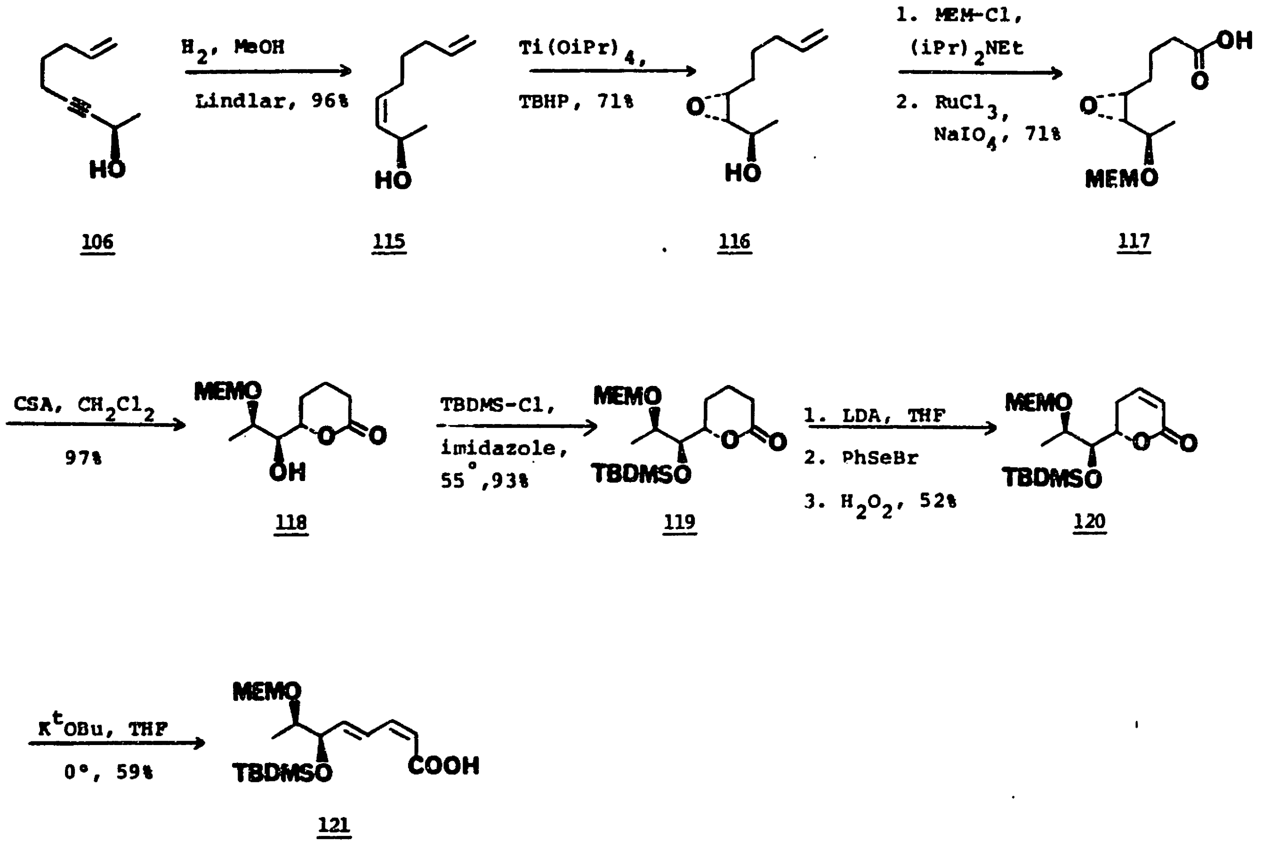


106
114

degradation to the lactic acid derivative (-)-114. The absolute configuration of the (S)-(+)-enantiomer of 114 is known.[62] Unfortunately, however, the enantioselective reduction of 113 with either of these reagents afforded alcohol (R)-106 in only moderate chemical and optical yields. Of the reagents currently available for enantioselective reduction of methyl propargyl ketones, Noyori's BINAL-H reagent is reported to give superior results.[60,63] Since our results with this reagent were modest at best we did not pursue a lengthy investigation of other optically active hydride reagents.

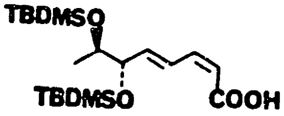
Although the optical purity of 106 was lower than we had hoped for originally, we decided to demonstrate the feasibility of our proposed sequence to diene acid 121 before exploring alternative methods for the synthesis of optically pure 106 (see Scheme XIX).[64] A satisfactory solution to this problem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

Scheme XIX



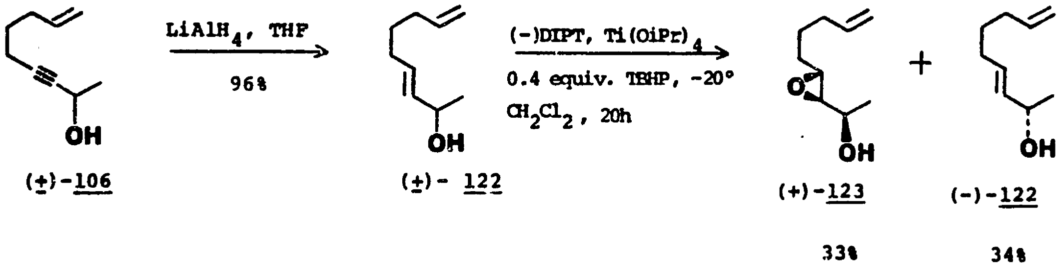
Lindlar hydrogenation of 106 afforded (Z)-allylic alcohol 115 in 96% yield. Epoxidation of 115 was accomplished by using *tert*-butylhydroperoxide (TBHP), and titanium tetraisopropoxide in dichloromethane to give epoxy alcohol 116 in 81% yield with 95% *threo* selectivity.[59b] The free hydroxyl group of 116 was protected as a methoxyethoxymethyl ether[56] (MEM-Cl, $(iPr)_2NEt$, CH_2Cl_2, 82%) and the vinyl group was cleaved oxidatively (catalytic $RuCl_3$,$NaIO_4$, $CH_3CN-CCl_4-H_2O$, 0°C)[65] to give crude 117 in 87% yield which contained approximately 10% of hydroxylactone 118. Cyclization of the remaining acid by treatment with catalytic camphorsulfonic acid gave hydroxy lactone 118 in 69% yield from 116. Protection of the free hydroxyl group of 118 as a *tert*-butyldimethylsilyl ether (TBDMS) required forcing conditions (TBDMS-Cl, DMF, 50°C, 5-7 days) but nonetheless proceeded in high yield (93%). Oxidation of the lithium enolate of 119 was accomplished by using the procedure of Reich and Renga[66] ((i) LDA, THF, -78°; (ii) PhSeBr, -78°; (iii) H_2O_2, CH_2Cl_2, 25°) to afford enone 120 in 50-60% overall yield. Unfortunately, however, this procedure was not entirely reproducible. The crucial rearrangement of 120, however, proceeded smoothly to afford isomerically pure diene acid 121 in 59% yield after silica gel chromatography.

The development of an efficient synthesis of an optically pure *erythro*-dihydroxy (E,Z) octadienoic acid derivative (c.f. 54) suitable for use in a synthesis of the trichoverrins (B series,



54

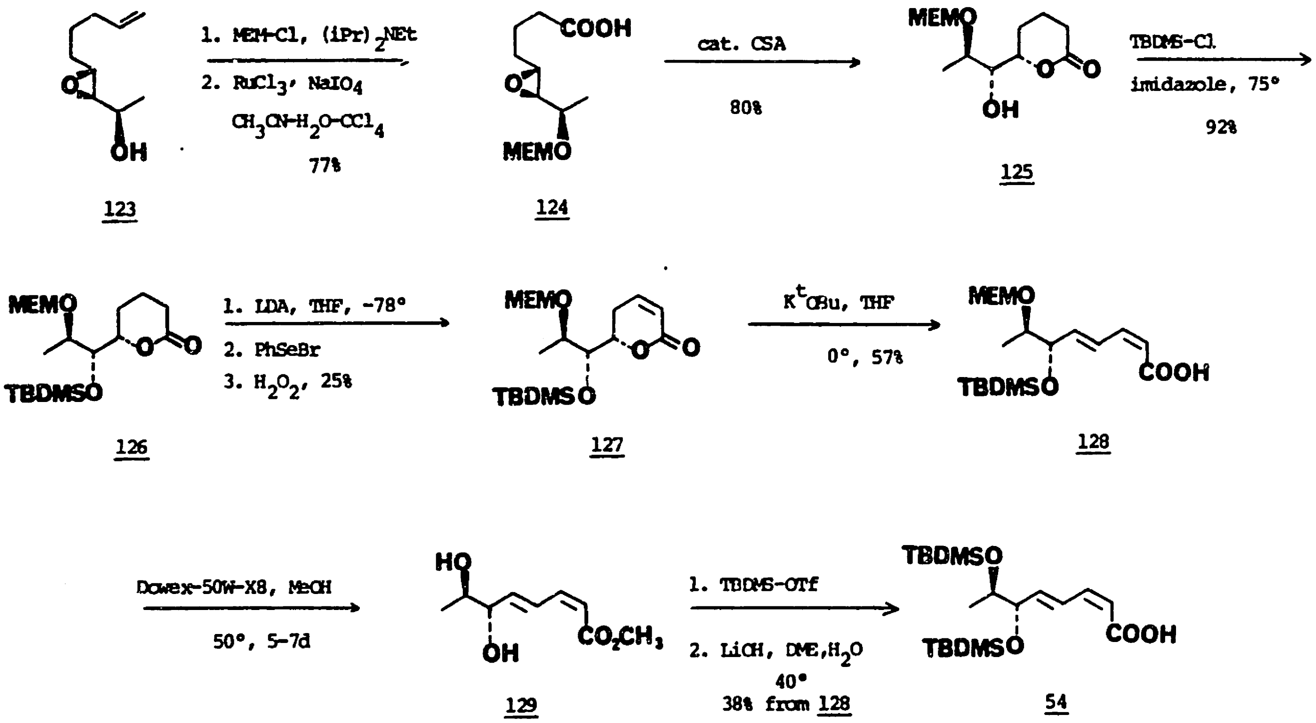
Table VI) centered around erythro epoxyalcohol 123 as a key intermediate. This substance was prepared from racemic 106 which was reduced to (E)-allylic alcohol 122 by use of $LiAlH_4$ in THF (96%). Epoxidation of 122 by the kinetic resolution protocol developed by Sharpless and co-workers[59b] ((-)diisopropyltartrate (DIPT), titanium tetraisopropoxide, 0.4 equiv. of tert-butylhydroxperoxide (TBHP), -20°C, CH_2Cl_2, 20h) afforded erythro-epoxyalcohol 123 in 33% yield along with 34% of kinetically resolved (-)-122. The optical purity of 123 and (-)-122 was



determined to be 95% and 90%, respectively by the Mosher ester technique.[61] It should be noted parenthetically that an analogous kinetic resolution in the roridin series (c.f., kinetic resolution-enantioselective epoxidation of 115) was not pursued since (Z)-allylic alcohols are not satisfactory substrates for this procedure.[67,59b]

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

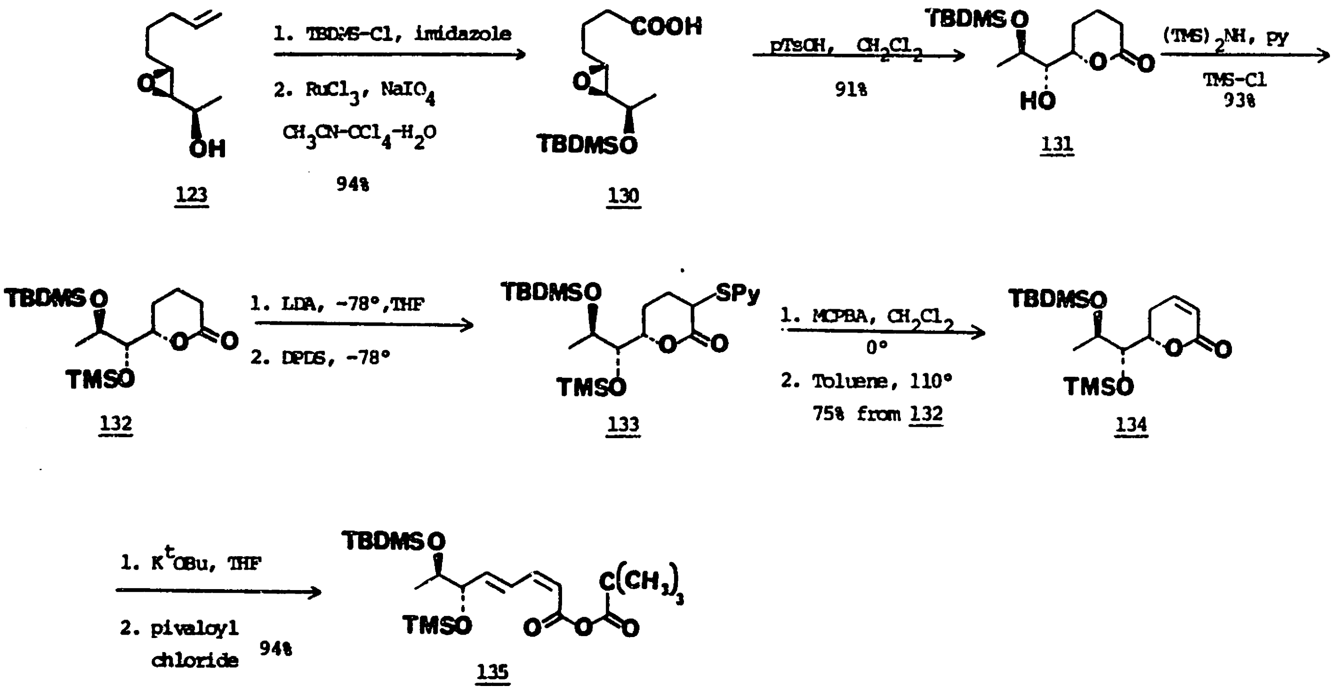
Scheme XX



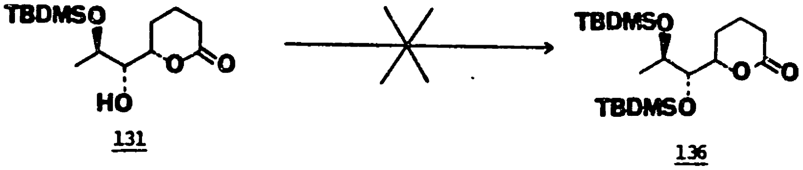
A more direct and highly efficient synthesis of the trichoverrin diene system 135 is outlined in Scheme XXI. This sequence is discussed in detail since 135 ultimately proved to be a useful acylating agent in our synthesis of trichoverrol B (31) discussed in Chapter 3.

Treatment of 95% optically pure epoxyalcohol 123 with tert-butyldimethylsilyl chloride and imidazole in DMF followed by oxidative cleavage of the vinyl group (cat. $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O) afforded epoxyacid 130 in 94% yield. Lactonization of 130 was then accomplished in 91% yield by treatment with catalytic p-toluenesulfonic acid in CH_2Cl_2. We had hoped

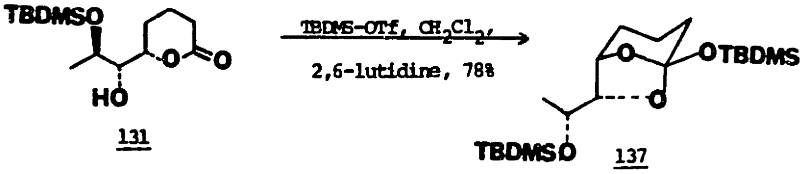
Scheme XXI



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

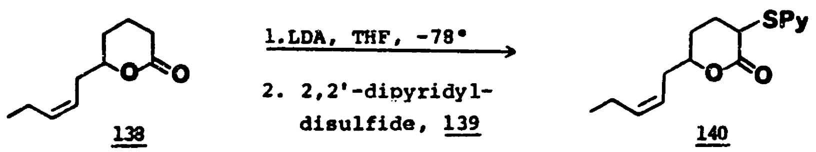


group of 131 is much more hindered than that in 125 (Scheme XVI). Interestingly, treatment of 131 with tert-butyldimethylsilyl triflate[68] rapidly afforded ortho ester 137 in good yield.

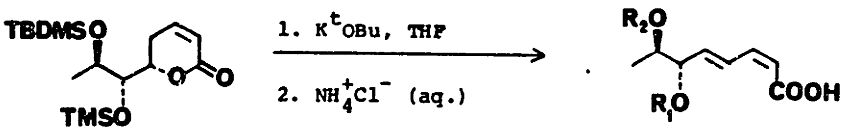


In contrast, 131 underwent rapid trimethylsilylation with bis-hexamethyldisilizane and trimethylsilyl chloride in pyridine to give lactone 132 (93%), which was successfully elaborated to 135 as discussed below.

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



Treatment of unsaturated lactone 134 with potassium *tert*-butoxide in THF followed by a mild acidic workup afforded a mixture of monosilylacids 141a and 141b. Thus, the trimethylsilyl group which had easily survived the three preceding transformations was extremely sensitive to acidic conditions after rearrangement of 134. This problem was circumvented by quenching the intermediate potassium carboxylate with pivaloyl



134

		R_1	R_2
141	a	H	TBDMS
	b	TBDMS	H

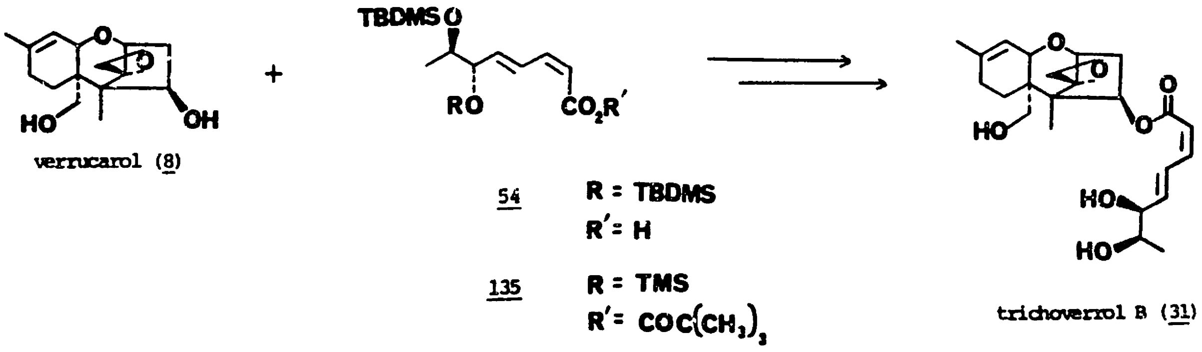
chloride to afford the isolable mixed anhydride 135 in 94% overall yield. It is critical to note that the latter two step sequence never becomes acidic which ensures the stability of the trimethylsilyl ether. The overall yield of 135 from 123 was 56% (see Scheme XXI).

The stage was now set for initiating studies on the acylation of the trichothecene nucleus with diene systems such as 54 and 135. As will be discussed in the next chapter, mixed anhydride 135 proved to be a key intermediate in our synthesis of trichoverrol B.

CHAPTER III

SYNTHESIS OF TRICHOVERROL B

Having successfully developed methodology for the synthesis of the dihydroxyoctadienoate fragment of the trichoverrins and roridins, we turned our attention to the esterification of these acids to C(4)-OH of the trichothecene nucleus. We decided to concentrate initially on the synthesis of trichoverrol B since the requisite acid derivatives 54 and 135 were in hand in optically pure form. Moreover, we imagined that the methodology developed in connection with this synthesis would be applicable to our projected approach to the roridins and baccharinoids.



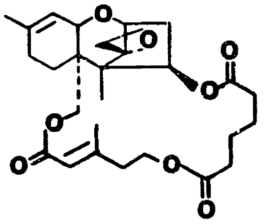
verrucarol (8)

54 R = TBDMS
R' = H

135 R = TMS
R' = $COC(CH_3)_3$

trichoverrol B (31)

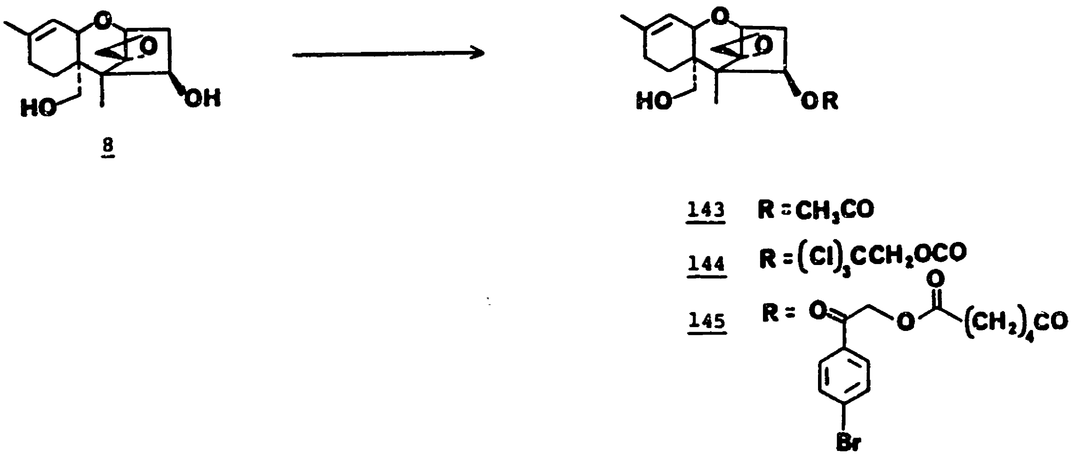
When we began our synthetic studies in 1980 none of the natural verrucarin or roridins had been synthesized. Indeed, very few acylations of the C(4)-hydroxyl group of verrucarol derivatives had been reported. Several cases, however, had been published by Tamm and coworkers in 1978 in connection with their synthesis of tetrahydroverrucarin J (142).[37] For example, acetylation of verrucarol (8) with acetyl chloride



142

and pyridine afforded C(4)-monoacetate 143 in 38% yield (Scheme XXII). Similarly, acylation of verrucarol with 2,2,2-trichloroethyl chloroformate in the presence of pyridine afforded carbonate 144 in excellent yield (95%). Finally, acylation of 8 with the acylimidazolide 146 in the presence of DBU provided C(4) monoester 145 in 35% yield.

Scheme XXII

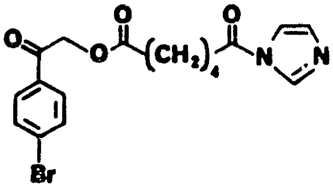


8

143 R = CH_3CO

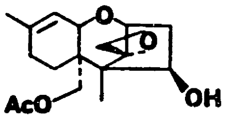
144 R = $(Cl)_3CCH_2OCO$

145 R =



146

These results implied that it should be possible to selectively esterify C(4)-OH of verrucarol with 54 or 135 under appropriate conditions. Data published after 1980, however, indicated that C(15)-OH is actually the more reactive of the two hydroxyl groups under a range of acylation conditions.[35,36] For example, Fraser-Reid observed that verrucarol could be acylated with acetic anhydride and pyridine to afford the C(15) monoacetate 58 in 70% yield.[36] Similarly, Still and coworkers noted in connection with their synthesis of verrucarin A that DCC mediated esterification reactions were highly selective for C(15)-OH.[36] This method was used by Still to acylate verrucarol 8 with 35 to afford C(15) monoester 41 in 95% yield. Analogous DCC-mediated coupling reactions were subsequently



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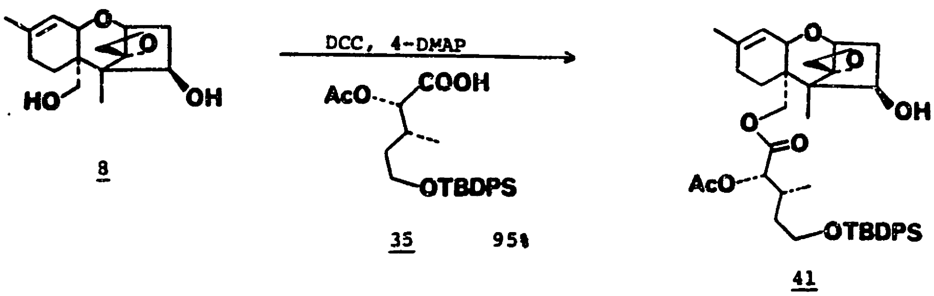
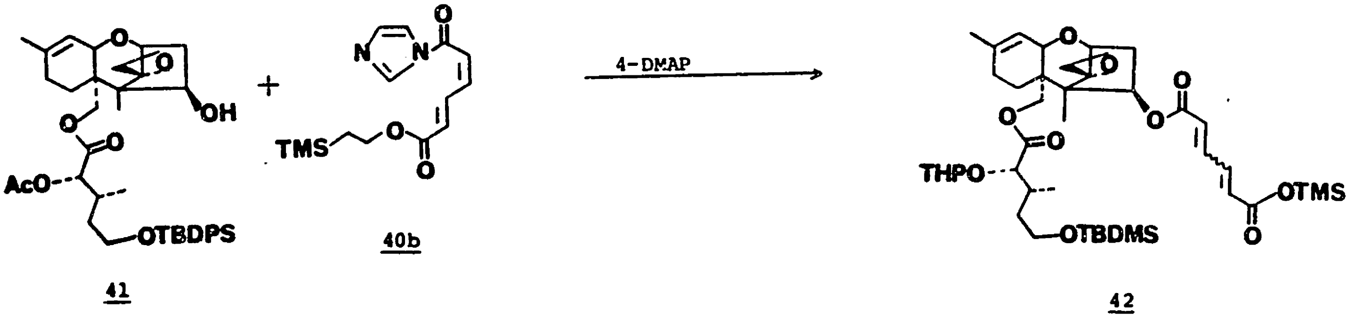
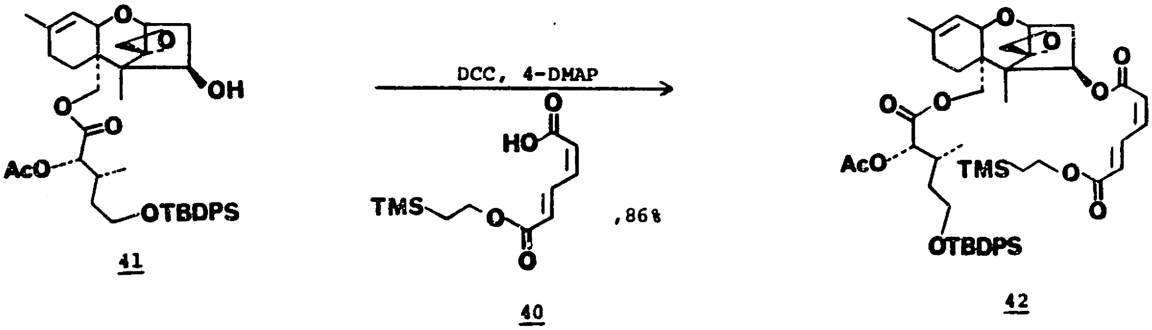
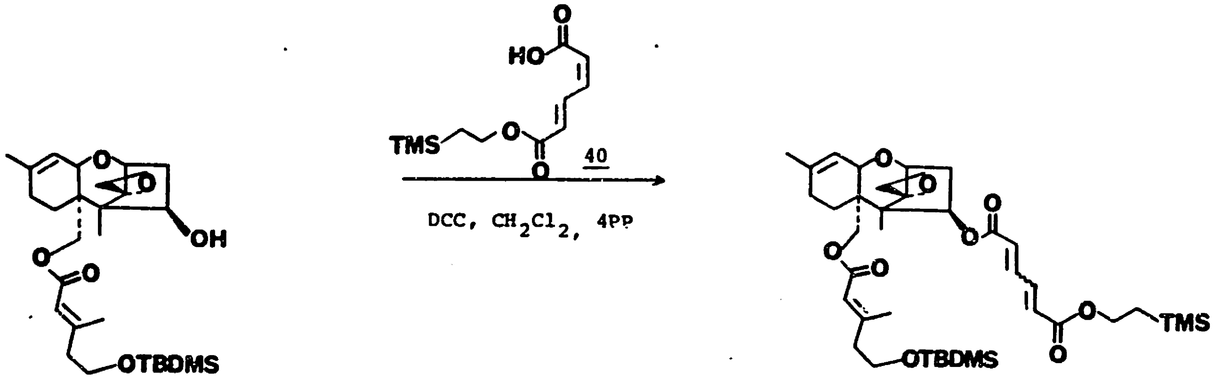


used by Tamm[39] and Roush and Blizzard[41b] in their synthesis of verrucarins A and J, respectively.

A problem which has plagued all syntheses of the verrucarins is olefin isomerization during the coupling of α,β-unsaturated acids to the trichothecene nucleus. Still, for example, observed significant isomerization to (E,E)-muconate derivatives during their coupling of 40b to 41. This isomerization was avoided, however, by coupling 41 and 40 with DCC in the presence of 4-DMAP.[36] In contrast, however, Tamm[39] and Roush[41] observed substantial isomerization in analogous experiments. For example, when 147 was treated with 40, DCC, and 4-pyrrolidinopyridine, Roush and Blizzard observed mostly (E,E)-diester 148.[41c] Roush and Blizzard attempted to overcome this problem by performing the muconate esterification





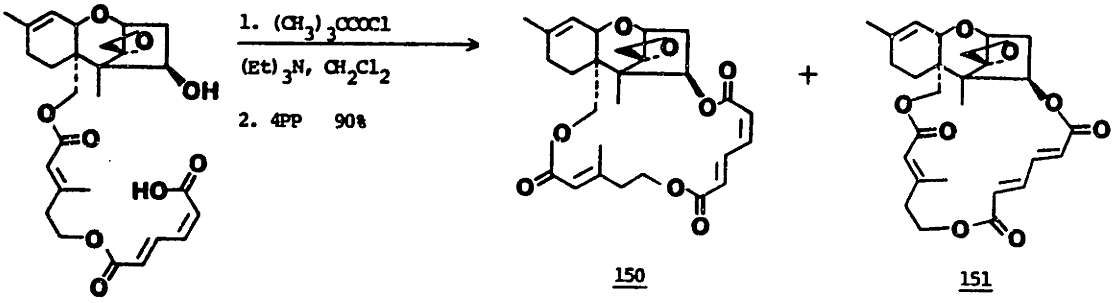


147

mostly (E,E)

148

intramolecularly, on the assumption that olefin isomers of the natural product would be too strained to be easily produced.[41c] Unfortunately, cyclization of the (E,Z)- and (E,E)-seco acids 149 and 152 occurs readily to give a mixture of macrocycles.



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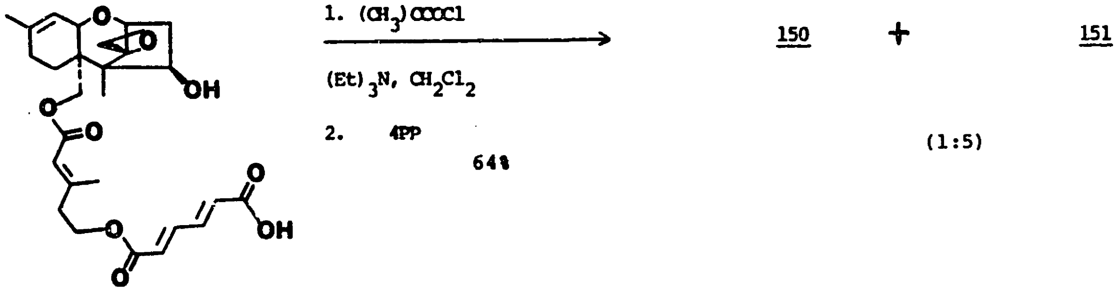
150

151

(2:1)



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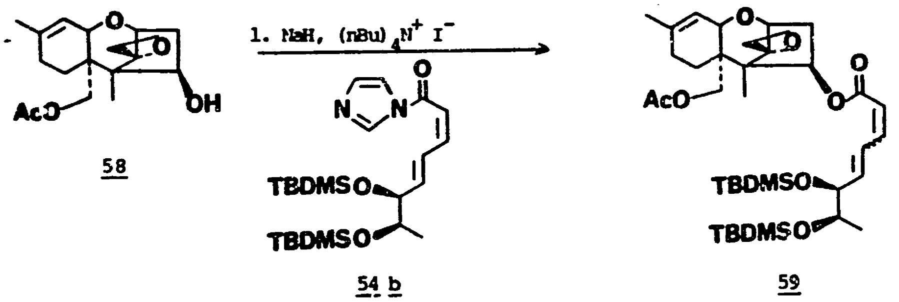
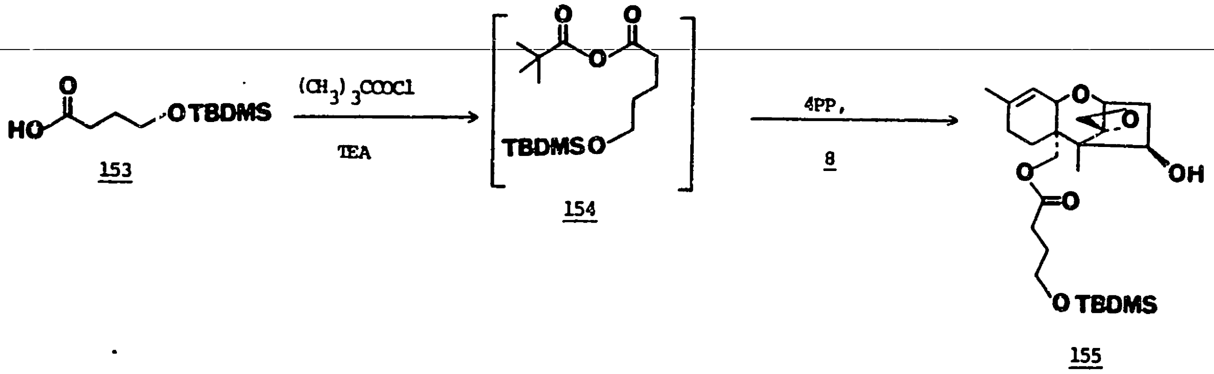
152

A final result which had direct bearing on our work was published by Fraser-Reid and Jarvis shortly before our investigations of esterification methodology was initiated.[40] These



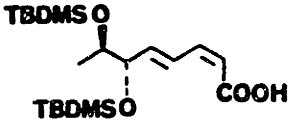
workers reported that acylation of the sodium alkoxide of 58 with acylimidazolide 54b afforded a 1:1 mixture of (Z,E)- and (E,E)-diene ester products. The (Z,E)-isomer served as a key intermediate in the synthesis of trichoverrin B and verrucarin J.[40]

It was clear from this analysis of the literature that the development of efficient syntheses of the macrocyclic epoxytrichothecenes must focus on this olefin isomerization problem. Our work therefore began with the preparation of C(15)-monoester 155 which would serve as the starting material for our trichoverrol B synthesis. The γ-[(tert-butyldimethylsilyl)oxy]-butyryl residue is a convenient protecting group for the C(15)-OH of the trichothecene nucleus and is easily removed by treatment with (nBu)$_4$F in THF. This protecting group was developed as an alternative to the levulinic acid protecting group by Blizzard in these laboratories.[41a,b] We prepared 155 in 55% yield by acylation of verrucarol with mixed anhydride 154, which was generated in situ from acid 153 and pivaloyl chloride.



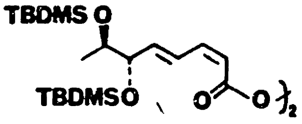
Alternatively, Blizzard prepared 155 in 70% yield by acylation of verrucarol with 154, DCC and catalytic 4-DMAP in CH_2Cl_2.[41a,b]

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



54

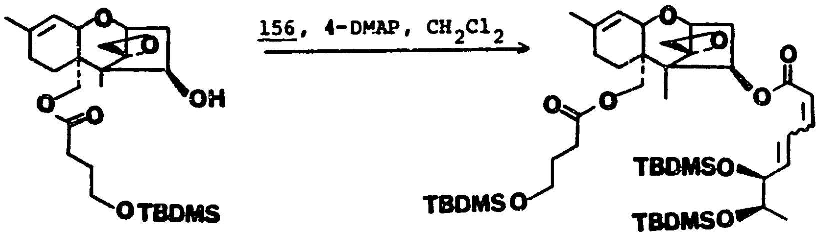
treatment of C(15) monoprotected trichothecene 155, or other hindered alcohols, with acid 54 in the presence of a variety of dehydrating agents (N,N-bis(2-oxo-2-oxazolidinyl)phosphorodiamidic chloride, (BOP-Cl), Et_3N, menthol; N-methyl-2-chloropyridinium iodide, CsF, 155;[71] DCC,4PP, isopropanol; trifluoroacetic anhydride, 155; mesitylenesulfonyl chloride, pyridine, 155) afforded none of the desired product. It was noteworthy, however, that symmetrical anhydride 156 could be isolated in 70-80% yield from the Mukaiyama salt[71] and BOP-Cl[72] experiments. This result was encouraging since it established that 54 could



156

be activated without olefin isomerization.

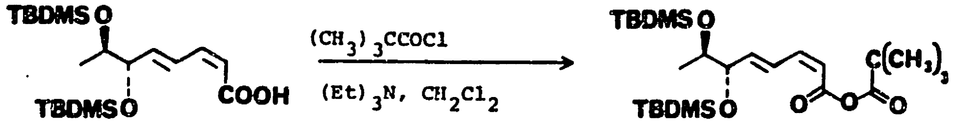
Treatment of trichothecene 155 with anhydride 156 and 4-DMAP as an acylation catalyst afforded diester 157 as a 2:1 mixture of (Z,E)- and (E,E)-diene isomers in 25% yield. We were encouraged by this result and therefore sought to prepare mixed anhydrides for the obvious practical consideration of conserving the precious chiral diene acid 54. We found mixed anhydride 158 was easily prepared from 54, pivaloyl chloride and Et_3N.



155

157

25% (2:1 mixture)



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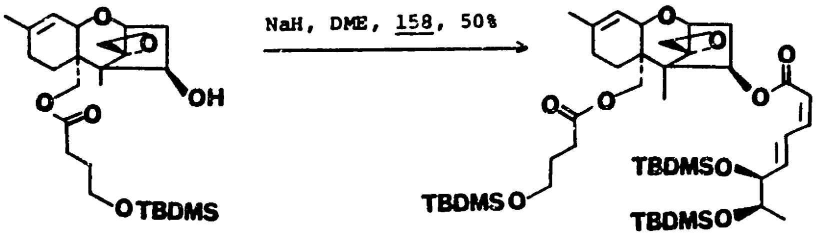
158

Acylation of 155 with either 156 or 158 in the presence of 4-DMAP as an acylation catalyst afforded diester product (25-32 %) containing anywhere from a 1:1 mixture of (Z,E)- and (E,E)-diene isomers to one case in which the (E,E)-isomer was obtained exclusively. It is important to note that these preliminary experiments were carried out with an undetermined amount of acylation catalyst. Later experiments, summarized in Chapter 4, in which the amount of acylation catalyst was controlled gave reproducible results.[73]

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

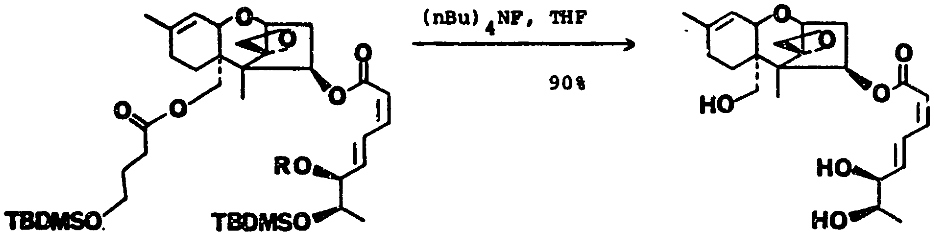


155

157 a

anhydride 135 affored comparable results (50-55% yield of 157b).

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



31

157 **a: R = TBDMS**
b: R = TMS

in THF, 20°C). This reaction afforded synthetic trichoverrol B identical in all respects to a sample of natural trichoverrol B supplied by Professor Bruce B. Jarvis.[74,75] The 250 MHz ^{1}H NMR spectra of synthetic and natural trichoverrol B are reproduced in Figures 2-5.

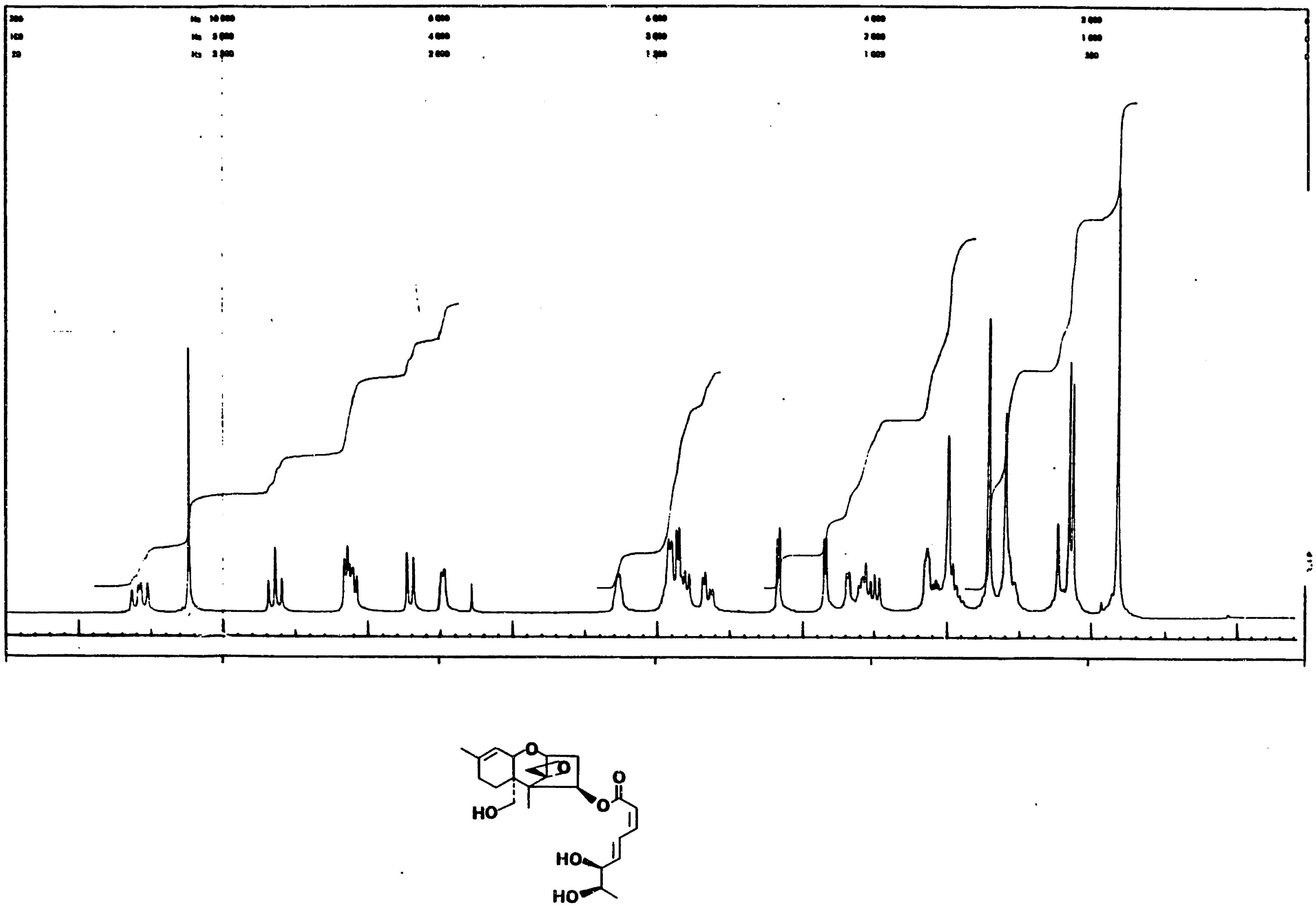


Figure 2. 250 MHz ^{1}H NMR spectrum of synthetic trichoverrol B (31)

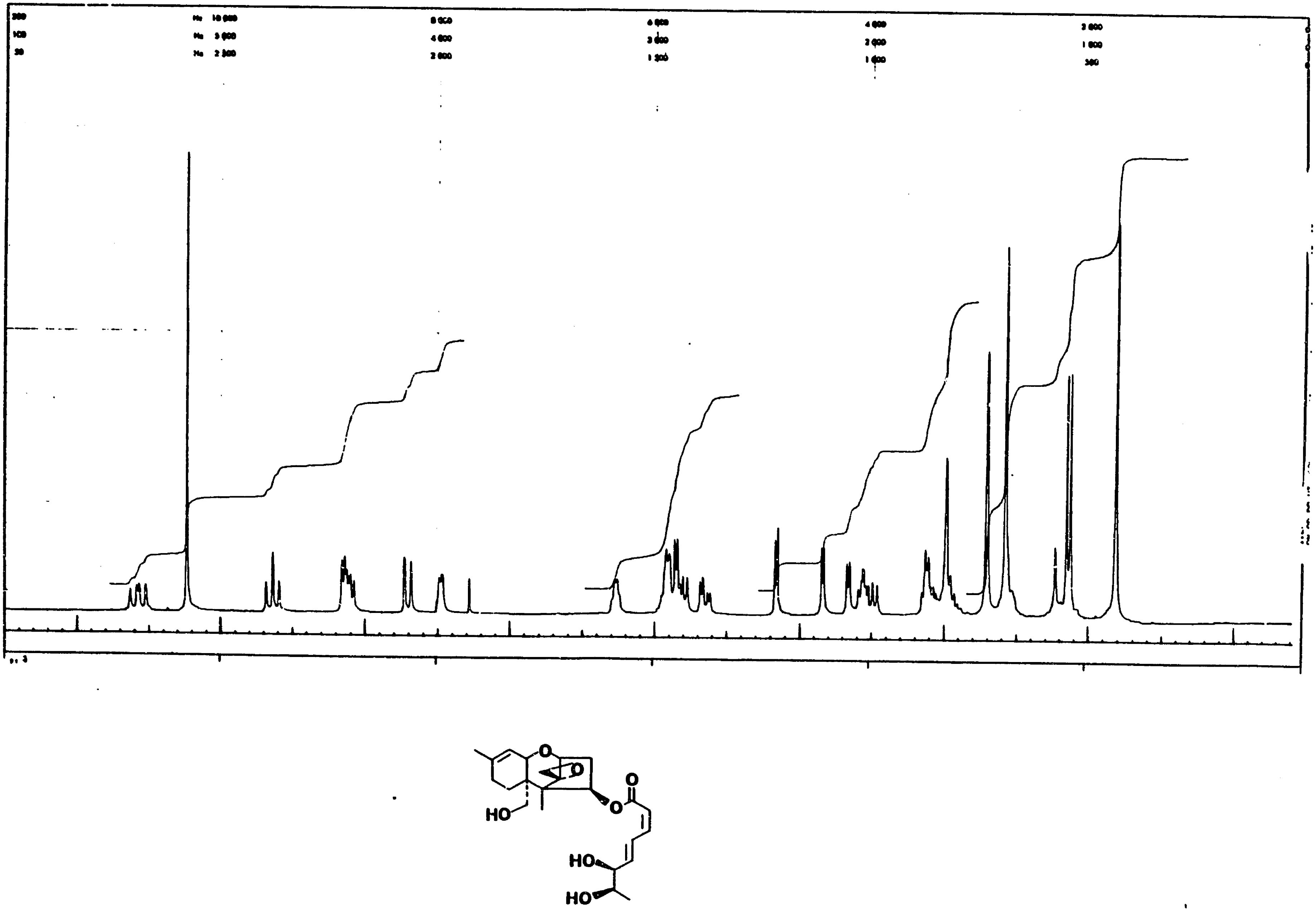


Figure 3. 250 MHz ^{1}H NMR spectrum of natural trichoverrol B (31)

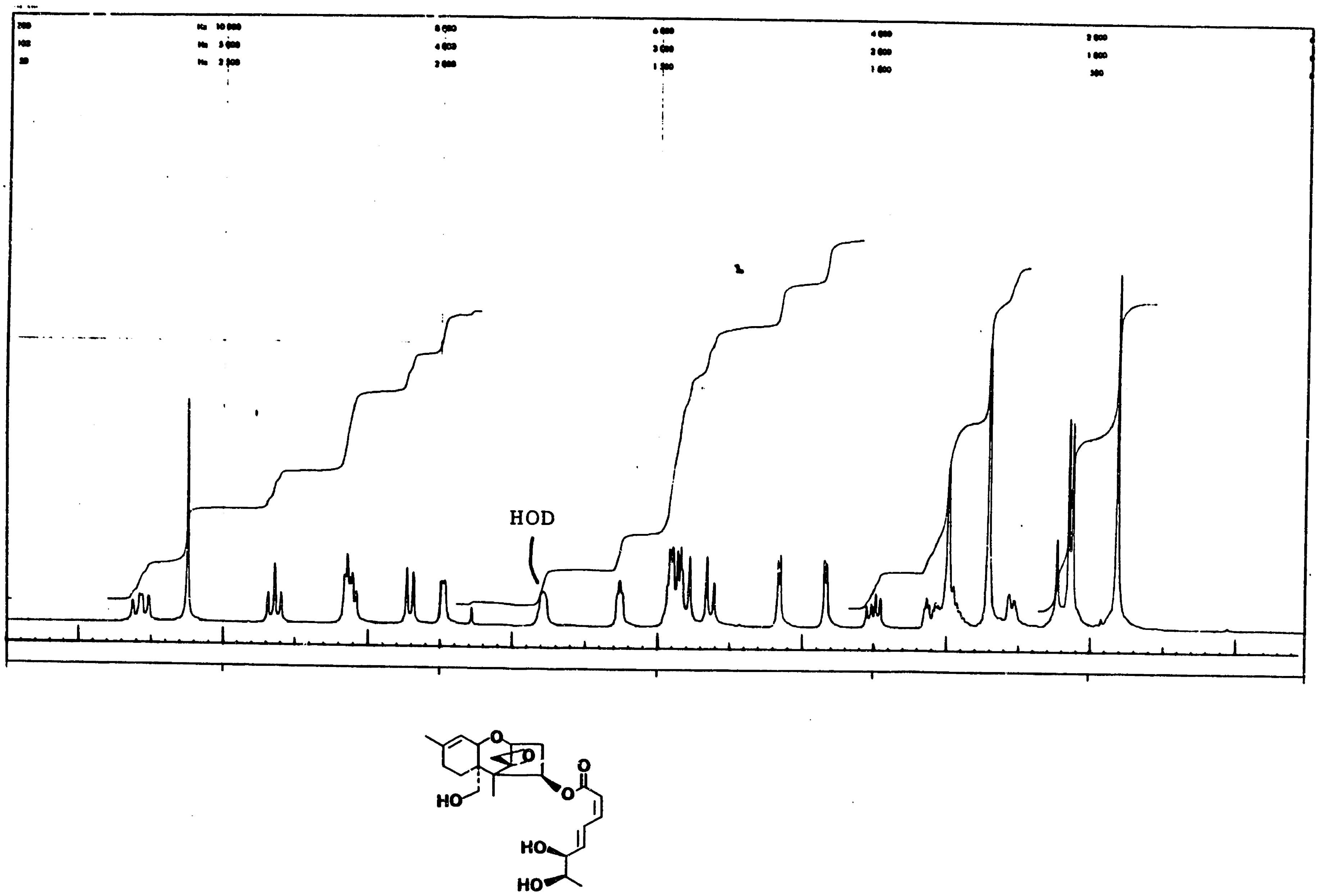


Figure 4. 250 MHz ^{1}H NMR spectrum of synthetic trichoverrol B (31) after D_2O exchange

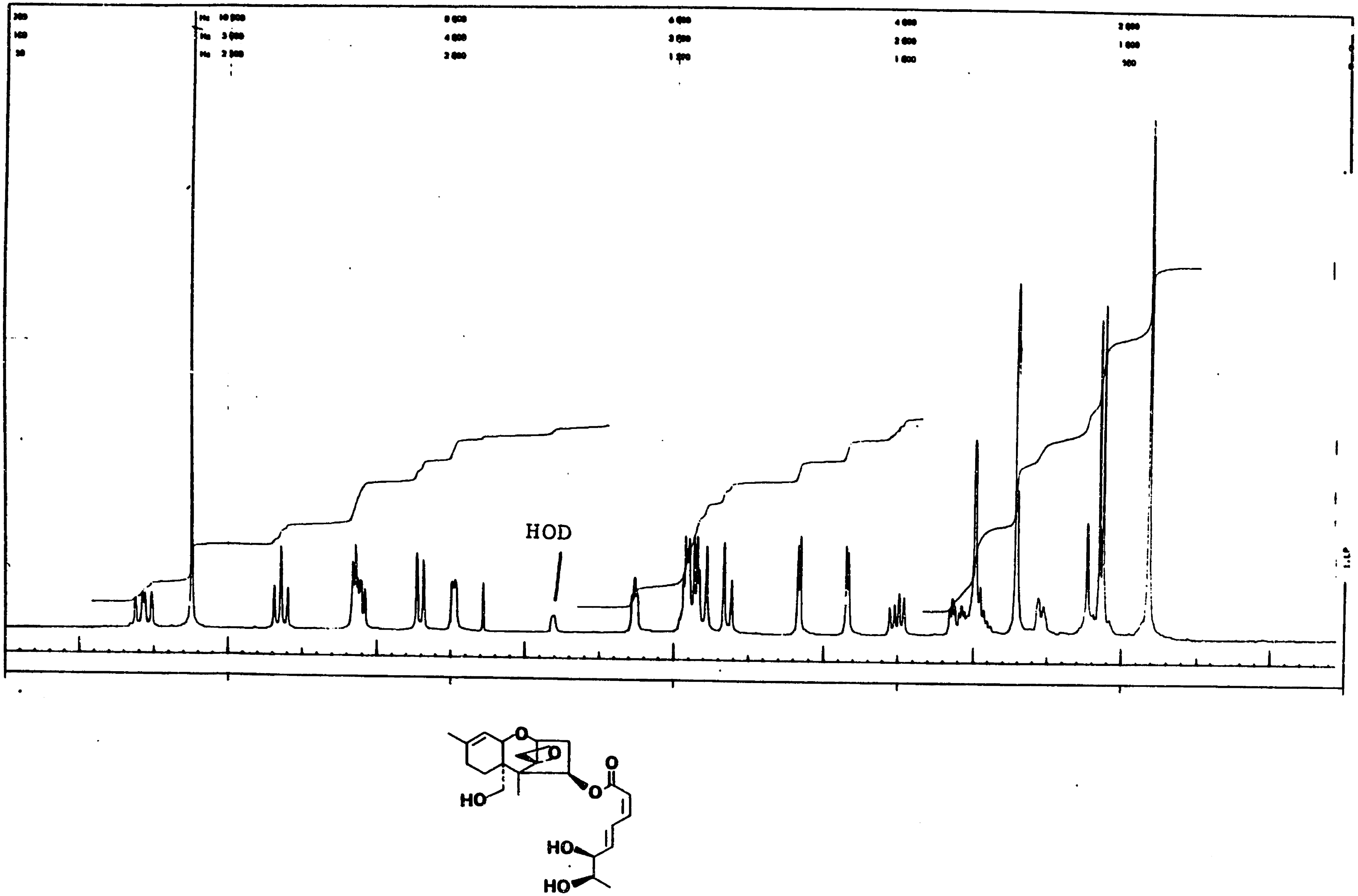
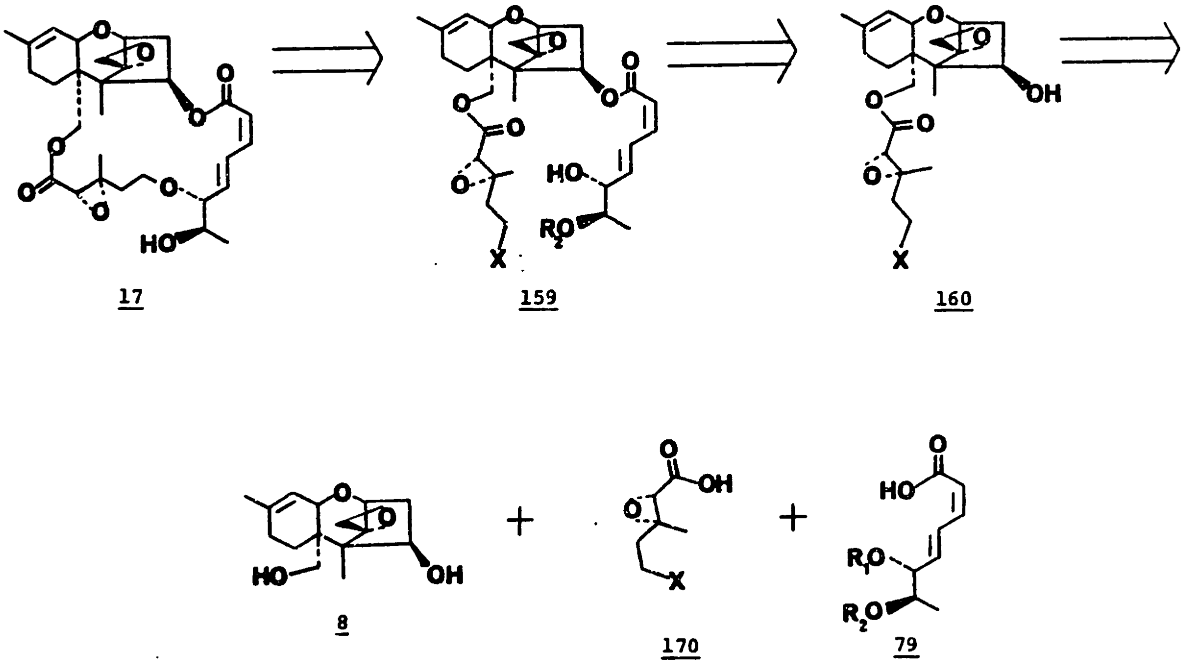


Figure 5. 250 MHz ^{1}H NMR spectrum of natural trichoverrol B (<u>31</u>) after D_2O exchange

CHAPTER IV

STUDIES TOWARD THE SYNTHESIS OF RORIDIN D

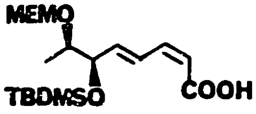
With the completion of the synthesis of trichoverrol B described in the preceding chapter, we were ready to begin our investigations into the synthesis of the roridins. We selected roridin D (17) as the target of our initial studies since this compound possesses many of the same structural features as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



17 159 160

8 170 79

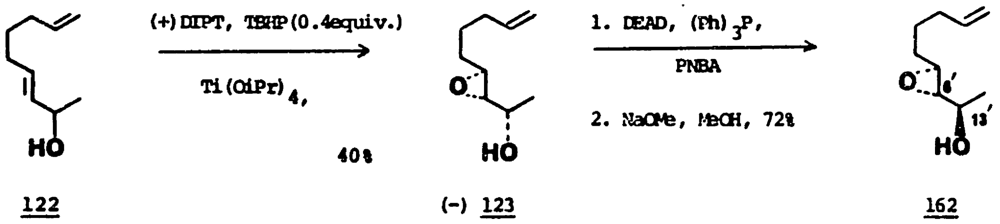
Our original synthesis of threo-diene acid 121, (Scheme XIX, Chapter 2) suffered from the fact that 121 was produced in only 65-74% optical purity, which we regarded as being too low



121

to be of use on the synthesis of roridin D (17). Two solutions to this problem were investigated. The first sequence originated from *erythro*-epoxyalcohol 123 (>95% ee), the enantiomer of which was an intermediate in our synthesis of trichoverrol B. Subjection of 123 to a Mitsunobu inversion sequence cleanly afforded epoxyalcohol 162 with the desired *threo* relationship between C(6') and C(13'). (Scheme XXIV)

Scheme XXIV

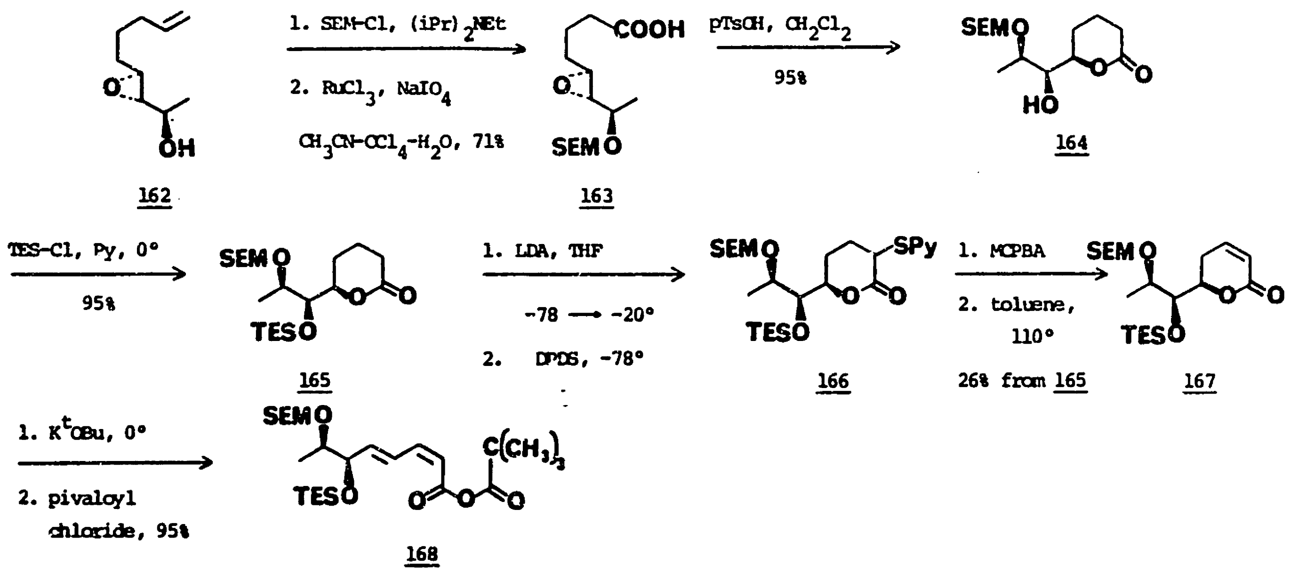


Before we could continue with our synthesis of 161, however, one additional modification had to be made. We felt that conditions required for eventual removal of the MEM ether used as a protecting group for C(13')-OH of 121 would be too vigorous for the trichothecene nucleus to survive.[76] One protecting group which seemed to fit our requirements was the

2-(trimethylsilyl)ethoxymethyl (SEM) ether.[77]

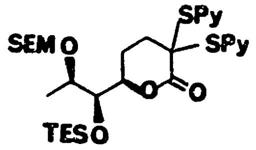
Scheme XXV outlines our initial synthesis of mixed anhydride 168, an activated form of diene acid 161. Thus,

Scheme XXV



epoxyalcohol 162 was protected as the corresponding SEM ether (SEM-Cl, (iPr)$_2$NEt, CH$_2$Cl$_2$, 95%) and the vinyl group oxidatively cleaved (cat. RuCl$_3$, NaIO$_4$, CCl$_4$-CH$_3$CN-H$_2$O, 75%)[65] to give carboxylic acid 163. Lactonization of this intermediate was effected by treatment with catalytic p-toluenesulfonic acid (95%). Masking of the free hydroxyl group of 164 as a triethylsilyl ether proceeded smoothly to afford differentially protected lactone 165 in 95% yield.[78] At this point we began to encounter considerable difficulty in accomplishing the α-sulfenylation of lactone 165. This was completely unexpected since we had successfully employed an analogous procedure in the oxidation of 132 to 134 in our work on the synthesis of trichoverrol B (c.f. Scheme XXI). Thus, treatment of lactone 165 with 2 equiv. of LDA in THF at -78°C for 1h followed by addition of 2,2'-dipyridyldisulfide (DPDS) afforded 20-30% of the desired α-sulfenyl lactone 166 along with 70-89% of recovered 165. Addition of 4 equiv. of LDA and 4 equiv. of DPDS gave similar results.

A closer investigation of this reaction sequence revealed that the enolate of 165 was not forming completely under these conditions. Thus, treatment of lactone 165 with 2 equiv. of LDA at -78°C for 1h followed by quenching with 2 equiv. of D_2O afforded 165 with only ca. 20% deuterium incorporation. This result was surprising since the lithium enolate of lactone 132 is generated in high yield under these conditions. On the other hand, if the mixture of 165 and LDA was allowed to warm to -20°C for 1h before being recooled to -78°C still afforded only ca. 30% of 166 along with 70% of unreacted 165, as determined by ^1H NMR analysis of the crude reaction mixture. It is interesting to note that the sulfenylation step appeared to be complete within 20 min. at -78°C, since longer reaction times at this temperature did not significantly increase the amount of monosulfenylated product. Moreover, addition of fresh base (up to 6 equiv. of LDA) or additional DPDS did not increase the percentage of 166 produced, since the LDA appeared to react instead with the DPDS. Other side reactions intervened if the reaction mixture was warmed to -20°C. Thus, under these conditions bissulfenylated 169 was observed at the expense of 164 and 165.



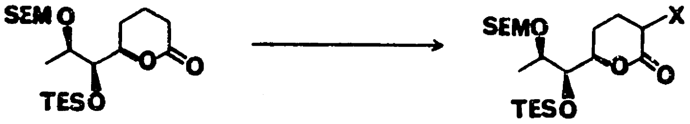
169

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

In spite of these results, we were able to produce small amounts of unsaturated lactone 167 from 166 as outlined in Scheme XXV. In practice, 165 was treated with 2 equiv. of LDA at -78°C and warmed to -20°C for 1h before being recooled to -78°C and quenched with 2.2 equiv. of 2,2'-dipyridyldisulfide, (DPDS). This crude reaction mixture was oxidized (mCPBA, CH_2Cl_2, 0°) and the intermediate sulfoxide (32% yield)

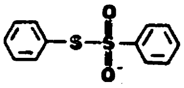
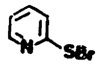
Table X

α-Functionalization Attempts



165

166 a

Base	Electrophile	Conditions[a]	Products[b] %			
			165	166	166a	169
LDA (2 equiv.)	DPDS (2 equiv.)	-78°,2h	60	30	-	-
LDA (2 equiv.) HMPT (2 equiv.)	DPDS (2 equiv.)	-78°,2h	60	30	-	-
LDA (2 equiv.)	DPDS (2 equiv.)	-20°,0.5h	50	-	-	50
LDA (1.1 equiv.)	 (1.2 equiv.)	-78°,1h	66	33	-	-
LDA (1.1 equiv.)	 (1.1 equiv.)	-78°,2h	>90	trace[c]	-	-
KDA (1.3 equiv.)[80]	DPDS (1.3 equiv.)	-78°,1h -20°,40min	30	-	-	70
KH (1.2 equiv.)	DPDS (1.2 equiv.)	-78°,1h	50	-	-	50
NaN(TMS)$_2$ (1.5 equiv.)[81]	DPDS (1.5 equiv.)	-78°,20min	mostly 169			
LDA (1.2 equiv.)	I$_2$ (1.2 equiv.)	-78°,1h	mixture of mono and diiodolactones			

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

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

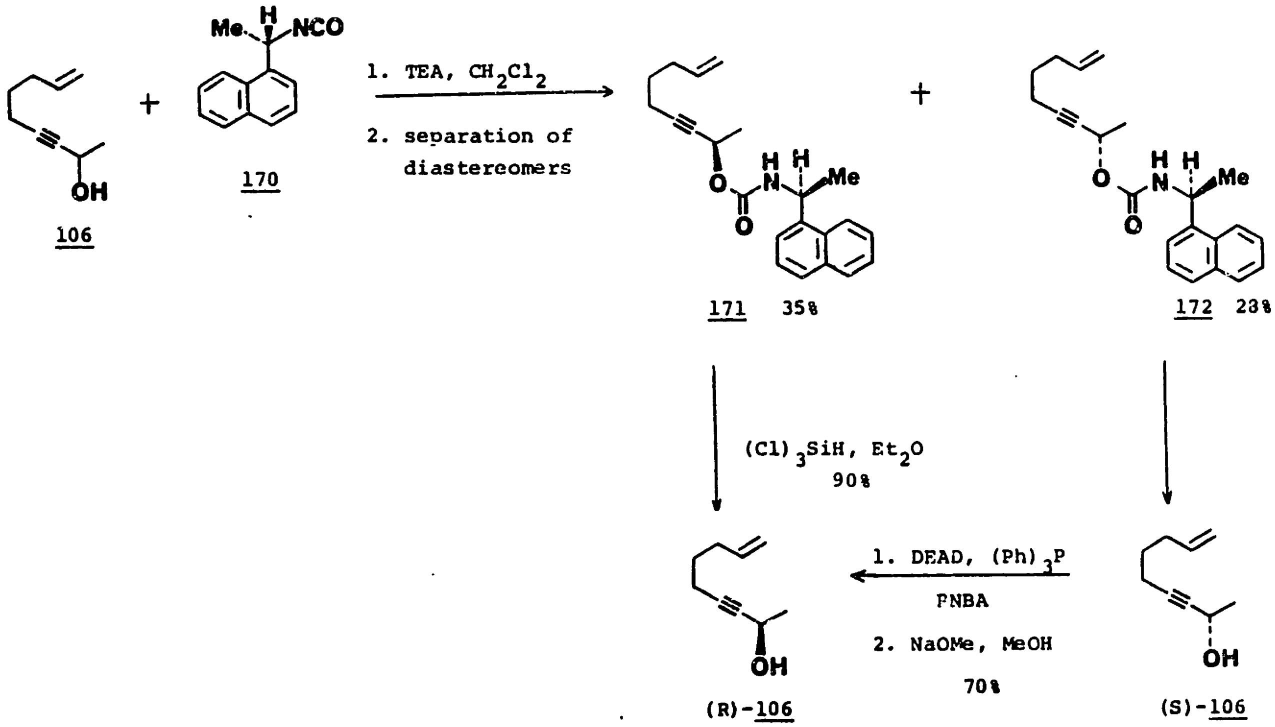
(c) Product ratio determined after oxidation of the crude reaction mixture.

was separated by chromatography from unreacted 165 (47% yield) which could be recycled. Thermal sulfoxide elimination (toluene, 110°C) proceeded smoothly to afford 167 in 26% yield from 165 (48% if corrected for recovered 165). Exposure of 167 to KO^tBu in THF at 0°C followed by quenching with pivaloyl chloride afforded mixed anhydride 168 in high yield (>95%).

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

Treatment of 106 with (R)-(-)-α-napthylethyl isocyanate (98% ee)[82b] 170 afforded a mixture of diastereomeric carbamates 171 and 172 in 76% yield[82c] (Scheme XXVI). These carbamates were separable by repeated flash column chromatography[83] to afford 171 and 172 in 35% and 28% yields (based on racemic 106), respectively. The urethane functions of both diastereomers were removed by treatment with trichlorosilane (Et_2O, 25°, 12h) afforded propargyl alcohols (S)-106 and (R)-106 in high optical purity (95%, Mosher ester analysis).[61] Inversion of (S)-106 *via* the Mitsunobu protocol (diethyl azodicarboxylate (DEAD), Ph_3P, *p*-nitrobenzoic acid (PNBA))[38] followed by ester hydrolysis afforded additional (R)-106(>95% ee) in 70% yield from (S)-106.

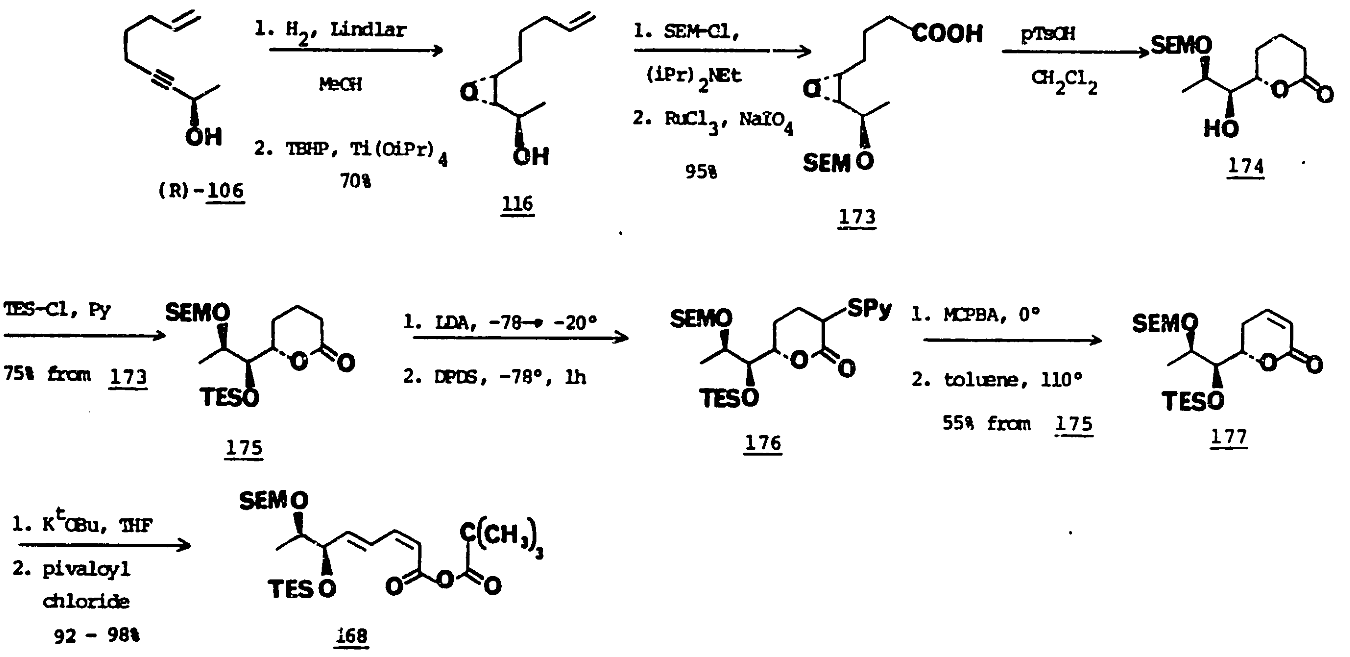
Scheme XXVI



The overall yield of (R)-106 from racemic 106 was 49%.

With optically pure (R)-106 in hand we were in a position to proceed with the synthesis of 168 (Scheme XXVII). Thus, selective catalytic semihydrogenation of 106 followed by *threo*-selective epoxidation of the resulting (Z)-allylic alcohol afforded epoxyalcohol 116 in 70% overall yield from 106.[59b] The free hydroxyl group was protected as a 2-(trimethylsilylethoxy)methyl ether (SEM-Cl, $(iPr)_2NEt$, CH_2Cl_2, 5h)[77] and the vinyl group cleaved oxidatively (cat. $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O)[65] to give epoxyacid 173 (contaminated with approximately 5% of the hydroxy lactone 174) in 95% yield

Scheme XXVII

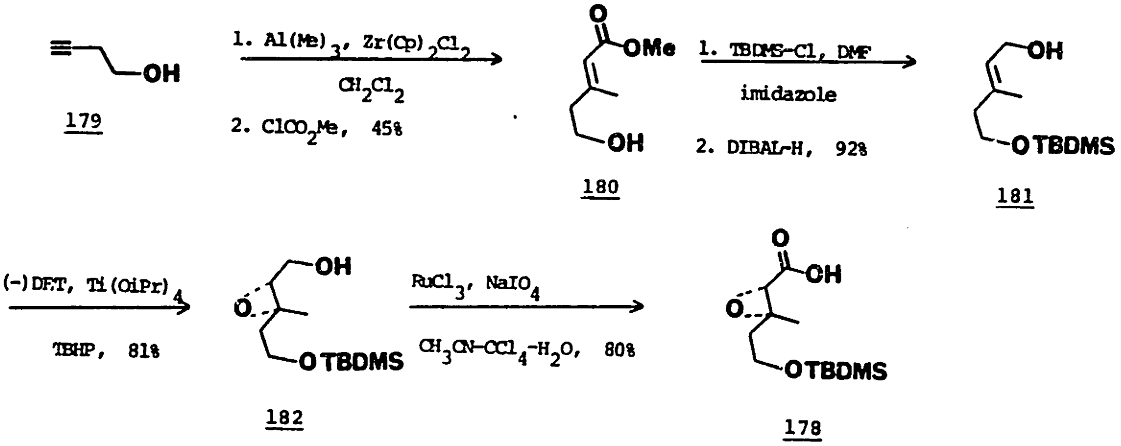


from 116. Lactonization of the remaining epoxy acid (0.03 equiv. p-TsOH, CH_2Cl_2, 25°, 2h) followed by masking of the free hydroxyl group as a triethylsilyl ether afforded the differentially protected lactone 175 in 75% yield from carboxylic acid 173. Treatment of 175 with 2 equiv. of LDA at -78° and warming to -20°C for 1h followed by quenching at -78° with 2 equiv. of DPDS afforded a mixture containing approximately 80% of the desired monosulfide 176 and 20% of unreacted 175. This result, in contrast to our work with epimeric lactone 165 (vide supra) proved to be very reproducible. *It is not obvious to us why 175 is well-behaved under these co[illegible]ions whereas 165 is not.* Oxidation of 176 with MCPBA (CH_2Cl_2, °, 1h)

followed by silica gel chromatography afforded 10% of recovered 175 and 68% of the desired sulfoxide as a diastereomeric mixture. Thermolysis (toluene, 110°C, 2h) of the diastereomeric sulfoxides afforded unsaturated lactone 177 in 80% yield (55% from 175, not corrected for recovered 175). Treatment of 177 with potassium *tert*-butoxide and quenching the intermediate carboxylate salt with pivaloyl chloride then gave mixed anhydride 168 in 92-98% yield.

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

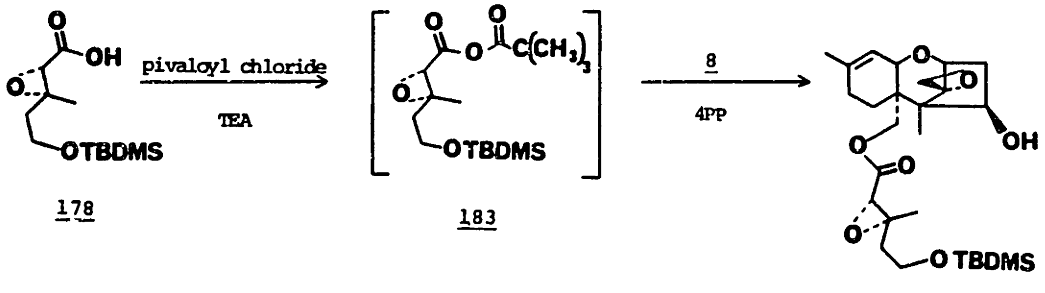
Scheme XXVIII



The synthesis of 178 was straightforward and was first accomplished in these laboratories by Blizzard[41a] (Scheme XXVIII). Thus, ester 180 was prepared from 179 in 45% yield by using Negishi's procedure ((i) $Al(Me)_3$, (3 equiv.); Zr $(Cp)_2Cl_2$, (0.1 equiv.); CH_2CH_2, 25°, 15h; ii) $ClCO_2Me$, (1.1 equiv.); 25°, 2h)).[84] Protection of the primary hydroxyl group as a *tert*-butyldimethylsilyl ether (TBDMS-Cl, imidazole, DMF, 25°, 5h) followed by reduction of the methyl ester with diisobutylaluminum hydride (DIBAL-H, Et_2O) afforded 181 in 92% yield. Enantioselective epoxidation of 181 ((-)-diethyltartrate, (DET);

<u>tert</u>-butylhydroperoxide, (TBHP); Ti(iPrO)$_4$, CH_2Cl_2, -20°C, 18h) smoothly afforded epoxyalcohol <u>185</u> in 81% yield (95% ee; Mosher ester analysis).[59b] Finally, oxidation of epoxyalcohol <u>182</u> to epoxyacid <u>178</u> was accomplished by using the Sharpless catalytic ruthenium tetroxide procedure (cat. $RuCl_3$, $NaIO_4$, CCl_4-CH_3CN-H_2O).[65] Acid <u>178</u>, obtained in 80-90% yield directly from this reaction,was used without further purification since glycidic acid <u>178</u> was not stable to silica gel chromatography.[85]

With subunits <u>168</u> and <u>178</u> in hand, we were now ready to proceed with our plan for the synthesis of roridin D (c.f., Scheme XXIII). Selective acylation of the C(15)-hydroxyl group with <u>178</u> of verrucarol was accomplished by using a mixed anhydride procedure. Thus, treatment of <u>178</u> with pivaloyl chloride and Et_3N in CH_2Cl_2 smoothly afforded <u>183</u>. Unlike the mixed anhydrides previously prepared from α,β-unsaturated acids and pivaloyl chloride, <u>183</u> proved to be too reactive to be isolated. Therefore <u>183</u> was prepared <u>in situ</u> and treated immediately with verrucarol[36] and 4-pyrrolidinopyridine (4-PP) as an acylation catalyst, which afforded C(15)-mono

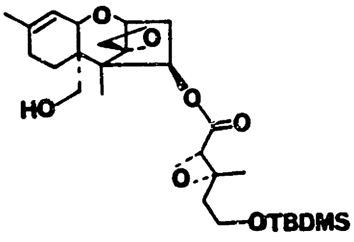


<u>178</u>

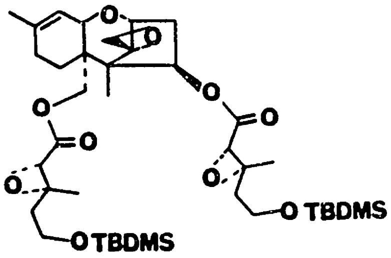
<u>183</u>

<u>184</u>

ester 184 in 59% yield after silica gel chromatography.[86] In addition, verrucarol (20%), C(4)-monoester 185 (6%) and diester 186 (7%) were also obtained. It is interesting to note that the 5:1 selectivity for C(15)-OH under these conditions

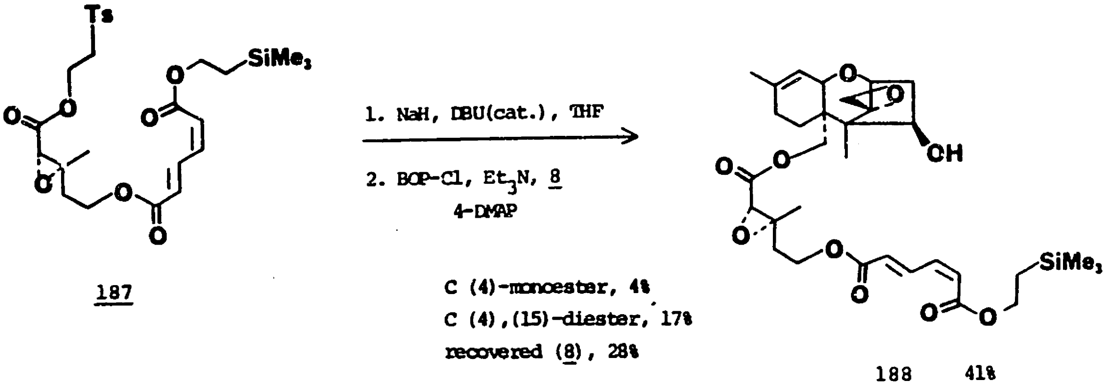


185



186

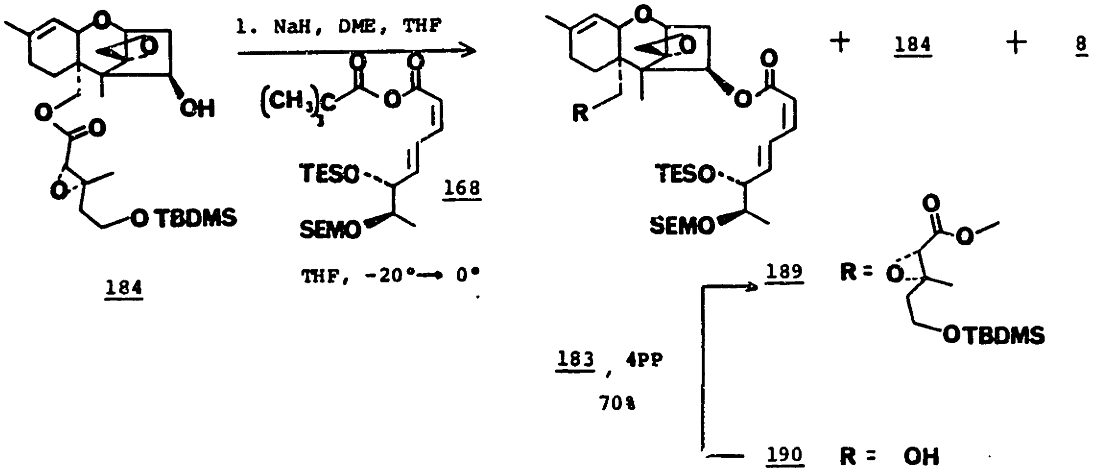
is somewhat better than the 3:1 selectivity realized by Blizzard in a closely related case:[41a]



187

188

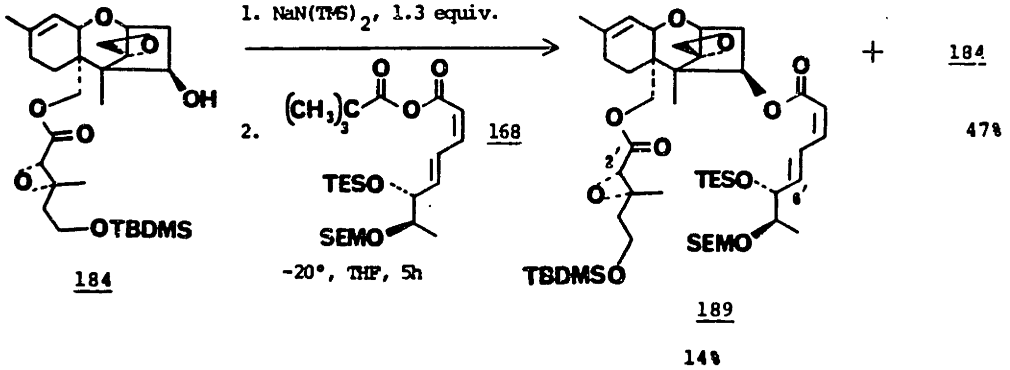
Attempts to esterify 184 with mixed anhydride 168 by using the methodology developed in our synthesis of trichoverrol B proved to be more complicated than originally anticipated owing to the sensitivity of the glycidic ester unit of 184 toward nucleophilic attack.[87] Thus, treatment of the sodium alkoxide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



Reacylation of <u>190</u> with <u>183</u> and 4-PP afforded <u>189</u> in good yield (70%).

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

In order to circumvent this problem we investigated the use of other bases which could be purified, or ones which we were confident would have little hydroxide present.[108] One base which appeared particularly attractive was sodium bis(trimethylsilyl)amide,[81] which was purified by sublimation immediately prior to use. Thus, treatment of <u>184</u> with this crystalline amide base (1.3 equiv.) in THF at -20°C followed by addition



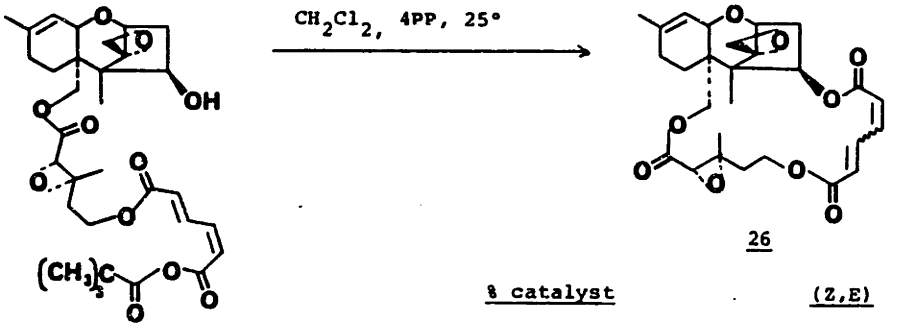
of 1.8 equiv. of mixed anhydride 168 afforded diester 189 (14%), 47% of recovered 184, 34% of recovered mixed anhydride 168 as well as some diene acid resulting from hydrolysis of 168. No C(15)-deacylation product 190 was observed. It is important to note, however, that if NaN(TMS)$_2$ was not sublimed prior to use, substantial deacylation of C(15) was realized.

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

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

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

The results of several attempts to prepare 189 from 184 and 168 by use of acylation catalyst are summarized in Table XI. As can be seen, the selectivity and rate of reaction is very much dependent on the catalyst and its concentration. The conditions which gave the least olefin isomerization were 30 mol % N-methylimidazole in CH_2Cl_2 at 25°C. This reaction afforded 189 as an 8:1 mixture of (Z,E)- and (E,E)-isomers in 17% yield



191

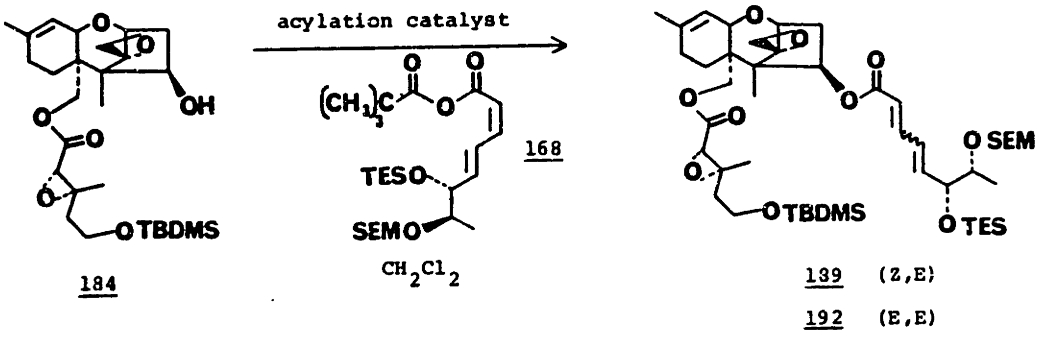
26

% catalyst	(Z,E)	:	(E,E)
1 equiv.	55		34
0.1 equiv.	54		10
0.05 equiv.	40		6

after 15 days; 43% of 184 was recovered. Clearly, this reaction is much too slow to be practical for preparative scale experiments. The use of 4-PP as an acylation catalyst led to faster rates of reaction but also greater amounts of olefin isomerization.

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

Table XI

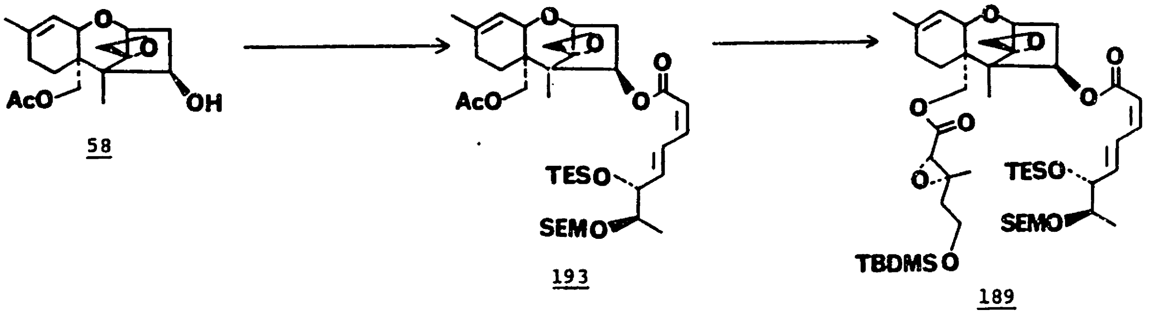


			Products[a]	
Catalyst	Conditions	187	(190	: 192)
1% 4PP	25°, 70h	100%	0	0
5% 4PP[b]	25°, 7d	50%	17%	(3 : 1)
10% 4PP	25°, 14h	16%	45%	(3 : 2)
30% N-methylimidazole	25°, 15d	43%	17%	(8 : 1)

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

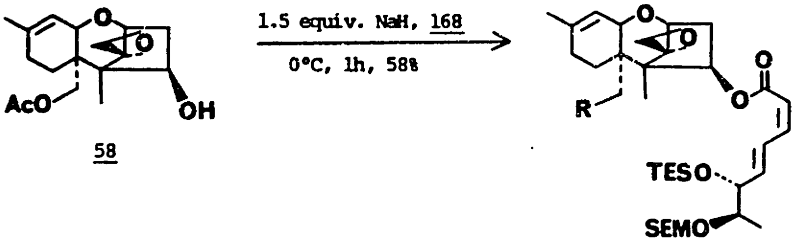
(b) It was necessary to add an additional 5% 4-PP after 2d since reaction had appeared to stop.

protecting groups and other reactive functionality present in the trichothecene monoester 190, we selected the C(15) monoacetate 58 for this work.[36] We thought that the acetate group of 193 could be selectively hydrolyzed since Fraser-Reid had accomplished this conversion on a very similar trichothecene diester.[40] Acylation of 190 with mixed anhydride 183 by using



58 193 189

the conditions we had previously described would then afford diester 189. Thus, treatment of a mixture of 58 and 168 in DME and THF (1:1) at 0°C for 1h with 1.5 equiv. of NaH



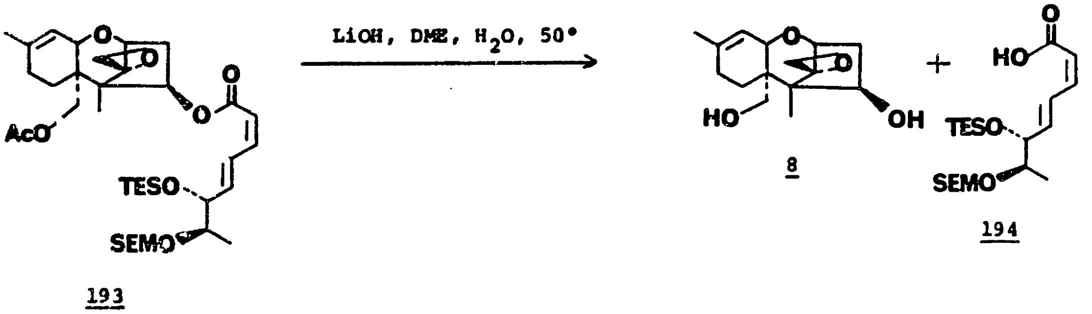
58

193 R = OAc

190 R = OH

afforded diester 193 along with a small amount of 190 in 58% yield. The yield in this case was comparable to that obtained in our work on trichoverrol B. It is important to note, however, that if this reaction was performed at room temperature for 5h, substantial deacylation was observed. Under these conditions C(4) monoester <u>190</u> and verrucarol (<u>8</u>) were obtained in 10% and 83% yield, respectively.

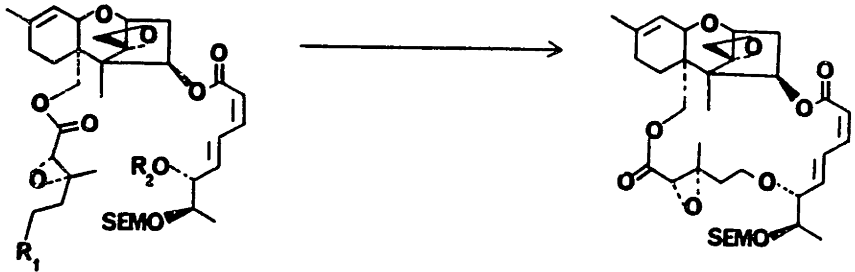
We were now ready to unmask the C(15)-OH group. Initially we intended to use the conditions published by Fraser-Reid for the selective hydrolysis of the C(15) acetate of <u>59</u> (c.f. Scheme VI). Unfortunately, initial attempts to accomplish this conversion revealed that no deacylation occurred in a 3:1 DME-H_2O solvent mixture (50°C, 15h) when the pH was 12 or lower. At pH 13, at which point the reaction mixture contained 10 equiv. of LiOH, deacylation occurred but with no selectivity, giving <u>8</u> and diene acid <u>194</u>.



It was clear from these preliminary studies that the C(15)-acetate is not an acceptable protecting group for our purposes. Reduction of this plan to practice will require that an alternative protective group scheme be developed for C(15)-OH of the trichothecene skeleton as well as for C(6') and C(13') of the C(4)-diene acid fragment (<u>vide</u> <u>infra</u>). This problem will be addressed in future studies by other members of our research group.

With limited quantities of pure diester 189 in hand (a total of 20 mg was prepared during the course of these studies), we began an examination of methods for the macrocyclization reaction which would be required to complete the construction of the roridin ring system.[91] As a necessary first step, diol 195 was prepared by acid catalyzed hydrolysis.

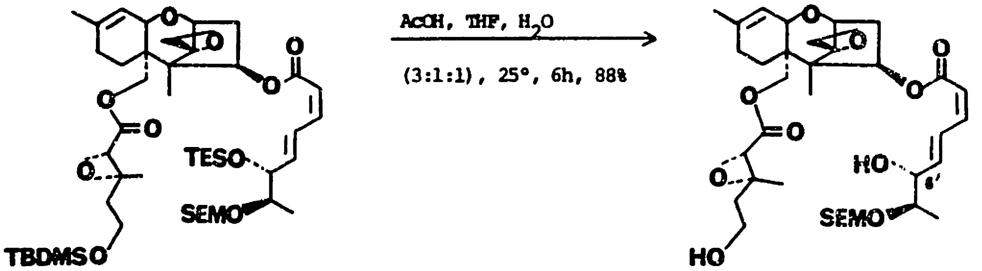
Scheme XXIX



197

	R$_1$	R$_2$
195	OH	H
196	I	H

(HOAc, H_2O, THF (3:1:1), 25°C, 6h) of 189 in 88% yield.



189

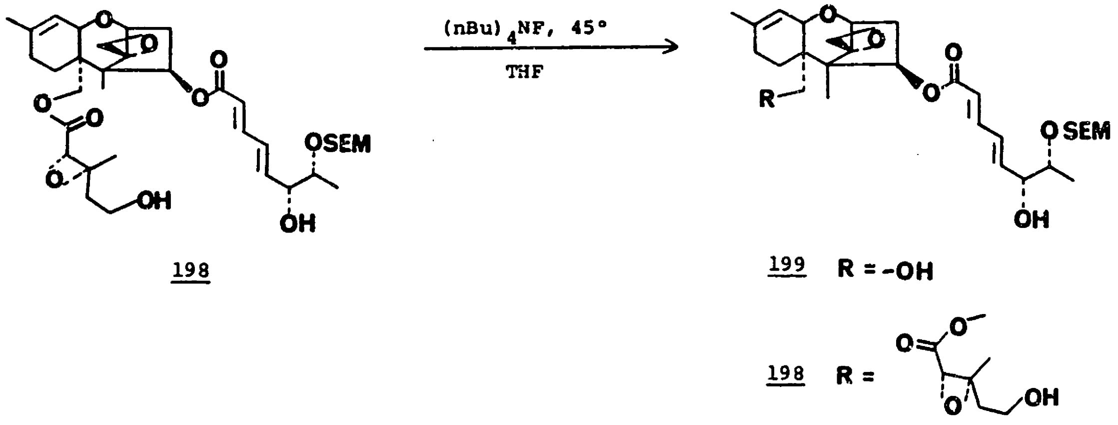
195

We imagined that cyclodehydration of 195 could be accomplished by using the Mitsunobu reaction. This method has been used for the synthesis of cyclic ethers from diols.[92] Moreover, we imagined that cyclization of 195 would occur with retention of configuration at C(6') since C(5')-OH, the least hindered hydroxyl group in this system, would probably be activated towards substitution.

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

Having failed to effect any cyclization under the Mitsunobu reaction conditions we attempted to prepare primary iodide 196 with the intent of accomplishing the macroetherification by using one of the variants of the Williamson ether synthesis.[91] Attempts to prepare iodide 196 for this purpose, however, by using methyltriphenoxyphosphonium iodide afforded none of the desired product. Rather, a mixture of several uncharacterized trichothecenes, all much more polar than the starting diol, were isolated. Of course many other means for selective activation of the C(5')-OH could also be envisaged.[92]

The final step in our currently proposed synthesis of roridin D would be the cleavage of the SEM ether protecting group. Although we had not prepared macrocycle 197, we decided to test our original assumption that the SEM ether could be removed at the end of the synthesis. (E,E)-Diene diester 198, prepared by hydrolysis of trichothecene 192, was used to examine conditions necessary for this deprotection. Treatment



of 198 with $(nBu)_4NF$ in wet THF at 45° as recommended by Lipshutz[75,93] afforded recovered 198 and C(15) deacylated product 199. The SEM ether was intact in both reaction products. Several other reagents and reaction conditions were examined in attempts to remove the SEM ethers of 198 and epoxy-ether 200, all to little avail (see Table XII). In contrast, however, treatment of 200 with 1.1 equiv. of trityl tetrafluoroborate at -78° with slow warming to 25°C over a 2h period gave epoxyalcohol 116 in 62% yield after chromatography.[94]

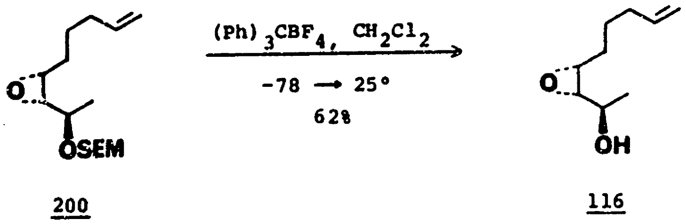
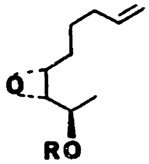


Table XII

Deprotection Attempts



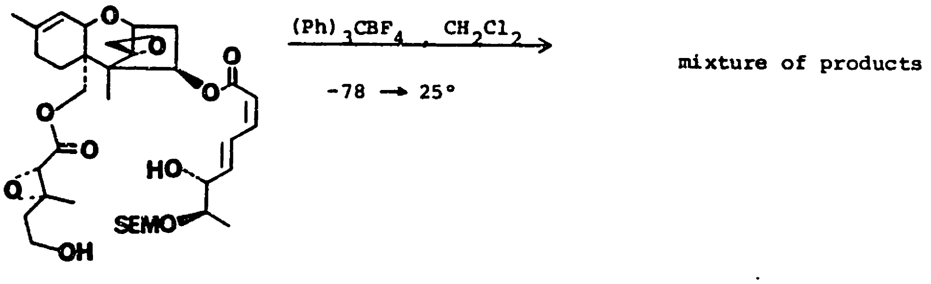
200 R = SEM

116 R = OH

Reagents	Conditions	Products 198	 199	 200	 116
198, $(nBu)_4NF$, THF	45°, 46h	50%	50%	-	-
198, $KF \cdot H_2O$, DMSO	45°, 48h	100%	-	-	-
198, $KF \cdot H_2O$, DMSO, 18-crown-6	25°, 36h	100%	-	-	-
200, KF (10 equiv.), AcOH, THF, H_2O (3:1:1)	25°, 36h	-	-	100%	-
200, $[(Me)_2N]_3S^{\oplus}F_2Si^{\ominus}(Me)_3$ (4 equiv.) in CH_3CN	55°, 48h	-	-	60%	40%
198 $[(Me)_2N]_3S^{\oplus}F_2Si^{\ominus}(Me)_3$ (4 equiv.) in CH_3CN	55°, 12h	complete deacylation[a]			

(a) Determined by TLC analysis.

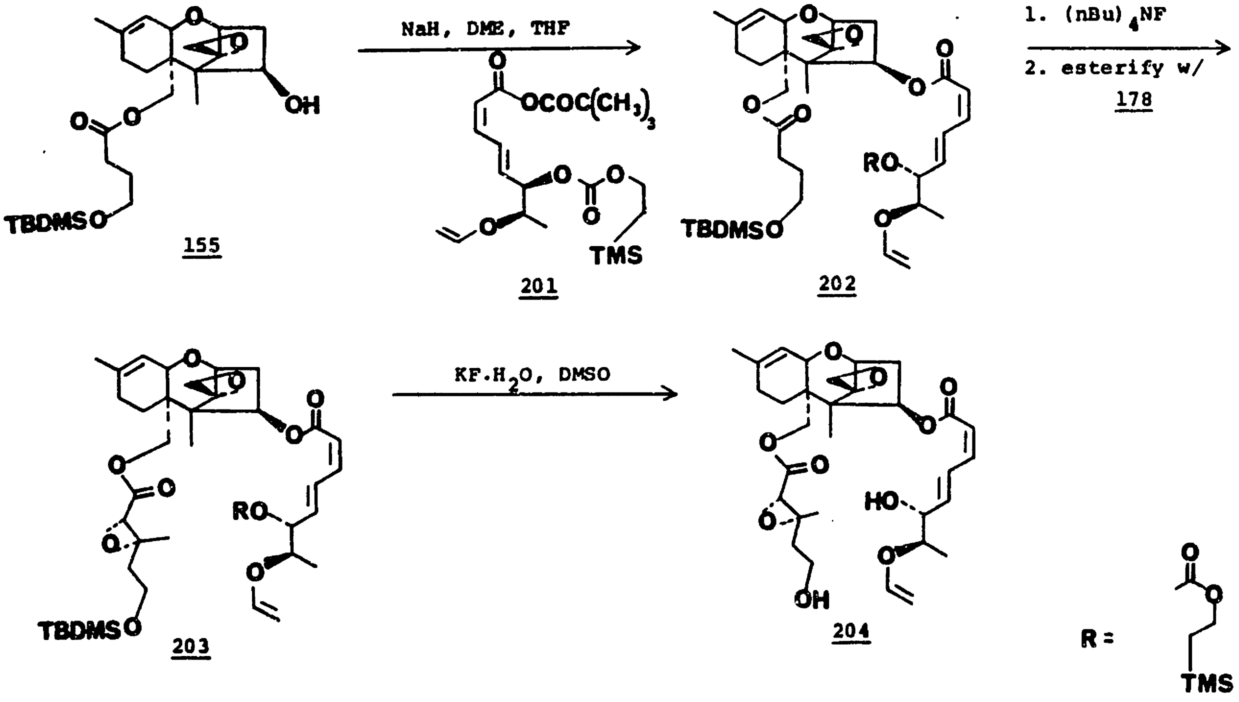
Unfortunately, treatment of trichothecene 195 under these conditions afforded a complex mixture of products.



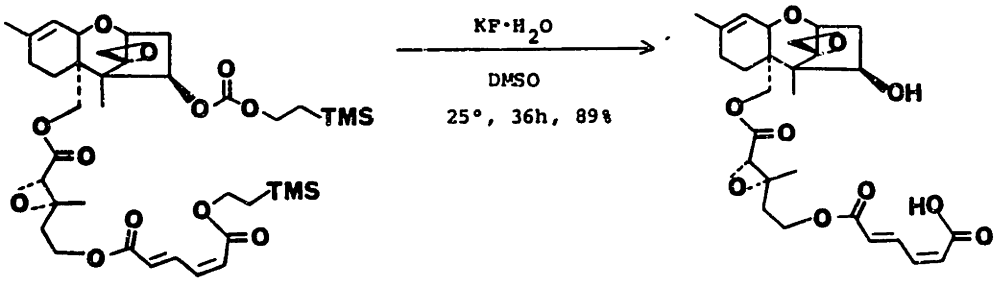
195

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

Scheme XXX



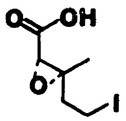
modified to yield mixed anhydride 201. The 2-(trimethylsilyl)-ethyl carbonate as a protecting group for C(6')-OH has been selected on the basis of Blizzard's favorable results in his verrucarin B synthesis (e.g., 205 → 188).[41a]



205

188

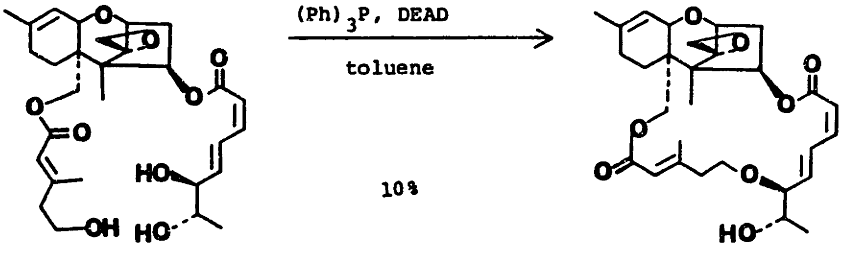
Coupling of 201 (diene system) with trichothecene monoester 155 according to the methodology developed in our synthesis of trichoverrol B would afford diester 202. Treatment of 202 with one equivalent of (n-Bu)$_4$NF would remove the C(15)-acyl group and set the stage for introduction of glycidic acid 178. Finally, treatment of 203 with KF in wet DMSO would afford diol 204, a substrate for additional, more extensive macrocyclization studies. Of course, it should also be possible to esterify 155 with acids such as 206 which would



206

directly introduce functionality pertinent to the macrocyclization studies.

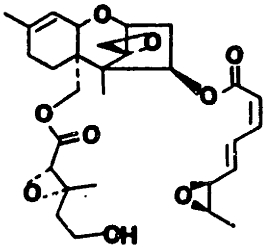
We must also develop contingency plans for future studies in the event that the cyclization of 204 can not be readily accomplished. Indeed, our results with 195 are not particularly encouraging. On the other hand, we remain optimistic that this key ring closure reaction can be effected owing to a report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



28

207

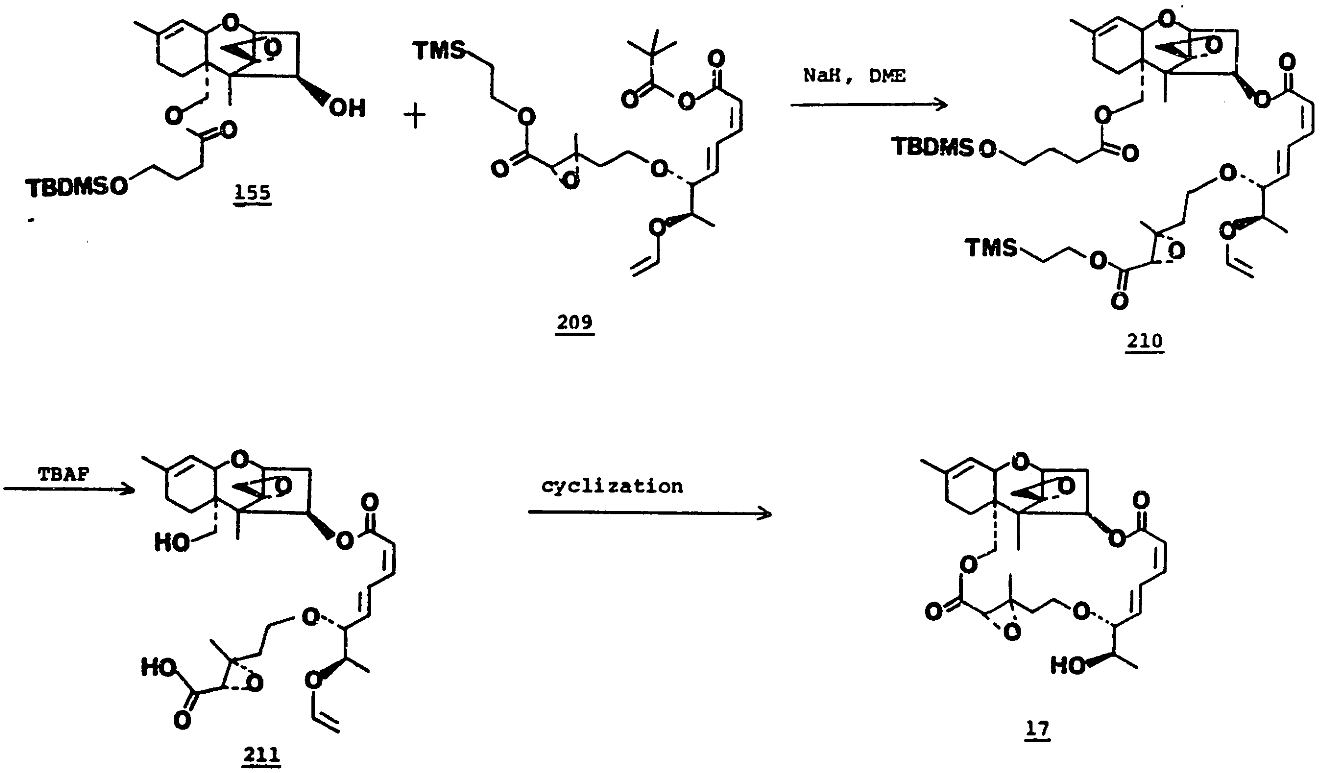
An alternative approach, which may also have biomimetic implications, would involve the acid or base catalyzed cyclizations of a trisepoxide substrate such as 208. It is interesting to speculate that an epoxide intermediate may be involved in the cyclization of 28 to 207, given the fact that the Mitsunobu reaction readily converts vicinal diols to epoxides.[90] Finally, one could investigate an approach



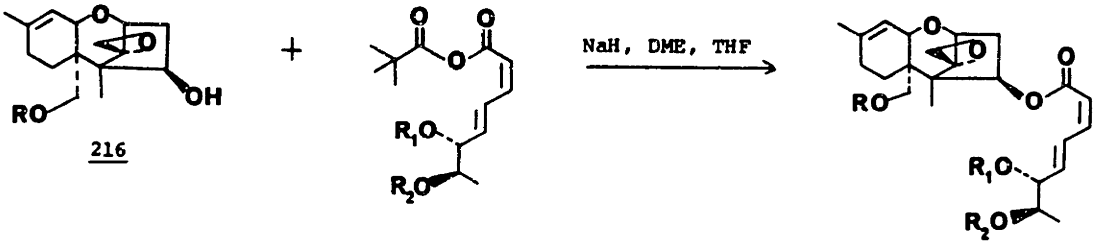
208

wherein the intact macrocyclic side chain is attached to the trichothecene nucleus and the macrocyclization completed by a lactonization process (see Scheme XXXI). In fact, this approach is under current investigation by another member of the Roush research group.

Scheme XXXI



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



216 217 218

CHAPTER V

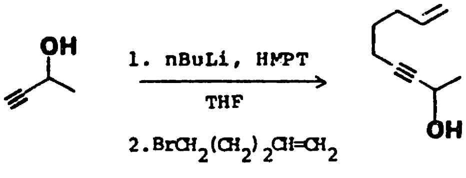
EXPERIMENTAL PROCEDURES

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

All reactions were conducted in oven dried (170°C) glassware with magnetic stirring under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and DME were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2), acetonitrile, t-butanol, diisopropylamine, were distilled from CaH_2. Benzene and toluene were distilled from sodium metal. DMF was dried over molecular sieves then distilled (reduced pressure). Triethylamine was predried over $CaSO_4$ then distilled from P_2O_5. Pyridine was distilled from sodium hydroxide. Diisopropylethyl amine and diisopropylamine were distilled from KOH and stored over activated 4Å molecular sieves. 4-Pyrrolidinopyridine (4-PP) was recrystallized from hexane. 2,2' Dipyridyldisulfide (DPDS) was recrystallized (2X) from ether, hexane (1:1) and dried by concentration from toluene before use. Potassium tert-butoxide was purified by sublimation. The weighing of all moisture sensitive materials was done under an atmosphere of dry nitrogen. Pivaloyl chloride was distilled from K_2CO_3 at atmosphere pressure under nitrogen. Diisopropyl tartrate, diethyl tartrate and titanium tetra-iso-propoxide were distilled.

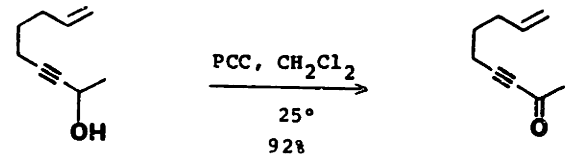
Lithium diisopropylamide was generated at -78°C as a stock solution in THF and titrated immediately prior to use. All enolates were generated from lactones which had been azotropically dried from either dry toluene or benzene before use.

Analytically thin layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.25-, 0.5-, and 1.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized with shortwave UV light, or by staining with either phosphomodybdic acid (PMA) or by charring with ethanolic H_2SO_4. 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.[83] All chromatography solvents were distilled prior to use.



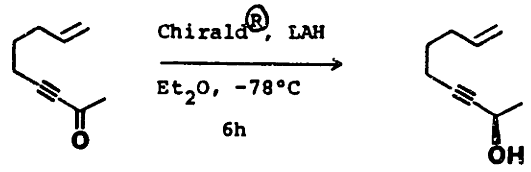
112 ± 106

n-Butyllithium (32.0 mL of a 2.5 M hexane solution, 80.0 mmol) was added dropwise under nitrogen purge to a solution of 1-butyne-3-ol (2.8 g, 40.0 mmol) in 20 mL of tetrahydrofuran and 20 mL (120 mmol) of hexamethylphosphoramide (HMPT) at 0°C. The resulting reddish-brown solution was stirred for 30 min at 0°C. 1-Bromo-4-pentene (5.9 g, 40.0 mmol) was added dropwise over a period of 5 min. The resulting pale yellow solution was warmed to room temperature over a period of 30 min. This mixture was maintained at room temperature for 3 hrs. Tetrahydrofuran and hexane were remained *in vacuo*. The resulting yellow oil was partitioned between 150 mL of a saturated aqueous solution of LiCl and 100 mL of pentane. The layers were separated and the aqueous layer was extracted with pentane (3x20 mL). The combined extracts were dried (Mg_2SO_4), filtered and evaporated to give 5.46 g of crude product. The crude product was purified by flash chromatography (SiO_2, 45x210 mm, Et_2O, hexane, 1:1 R_f 0.65) to give 3.73 g (67%) of pure 106: NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.69 (m, 1 H, H_8), 5.05-4.94 (m, 2 H, H_9), 4.46-4.51 (m, 1 H, H_2), 2.19 (td, J=7.3 Hz, 1.9 Hz, 2 H, H_5), 2.11 (t, J=7.3 Hz, 2 H, H_7), 1.63 (d, J=4.9 Hz, 1 H, -OH), 1.57 (quintet, J=6.8 Hz, 2 H, H_6), 1.41 (d, J=6.8 Hz, 3 H, H_1); IR (CH_2Cl_2), 3600, 3490, 3080, 2980, 2930, 2240, 1635 cm^{-1}; mass spectrum m/e 138 M^+; Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.90; H, 10.49.



± 106 113

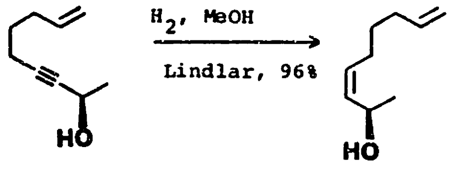
To a solution of 106 (2.05 g, 14.9 mmol) in CH_2Cl_2 (100 mL) was added solid PCC (6.49 g, 30.1 mmol). This mixture was stirred vigorously at 25° for 4h. Addition of anhydrous Et_2O (100 mL) and trituration of the resulting solids afforded after filtration through a bed of Florisil, and concentration in vacuo, 1.92 g of a yellow oil. Distillation of this material (bulb-to-bulb, 90-100°C, 10 mm) gave 1.81 g, 90%, of pure 113: NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.65 (m, 1 H, H_8), 5.1-4.95 (m, 2 H, H_9), 2.35 (t, J=7 Hz, 2 H, H_5), 2.30 (s, 3 H, H_1), 2.21-2.11 (m, 2 H, H_7), 1.75-1.60 (m, 2 H, H_6); IR (CH_2Cl_2) 3040, 2940, 2860, 2210, 1680, 1640 cm^{-1}; mass spectrum m/e 136 M^+; Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.22; H, 9.13.



113

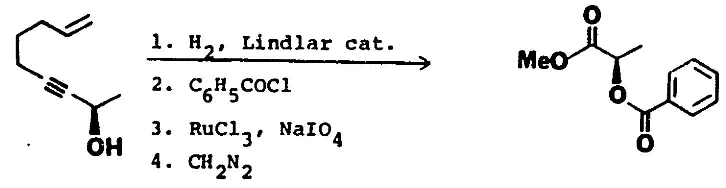
(R)-106 (64-72% ee)

To a stirred suspension of $LiAlH_4$ (578 mg, 15.2 mmol) in anhydrous Et_2O (425 mL) at 0°C was added a precooled solution (0°C) of Chirald ^{R} (9.37 g, 33.1 mmol) in Et_2O (68 mL) over a period of 2 min. The resulting suspension was stirred under N_2 at 0°C for an additional 2 min then cooled to -78°C. Once the temperature of this suspension had reached -78°C (5 min) a solution of 113 (1.66 g, 12.2 mmol) in Et_2O (70 mL) was added over a period of 5 min. The resulting suspension was maintained at -78°C under N_2 for 6h. To this mixture was added Et_2O saturated with H_2O (100 mL). This suspension was warmed to ambient temperature and extracted with 3M HCl (1x50 mL). The aqueous phase was washed with Et_2O (3x50 mL) and the resulting organic extracts washed with 2M HCl (1x30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.77 g of crude product as a brown oil. Purification of (R)-106 was accomplished by flash column chromatography (50x185 mm, Et_2O:hexane, 1:1, R_f 0.65) to afford 1.50 g of a pale yellow liquid which was further purified by distillation (bulb-to-bulb, 100-105°C, 5 mm) to yield 1.2 g (77%) of (R)-106. Mosher ester analysis indicated that this material was 64% optically pure. $[\alpha]_D^{21}$ + 14.8° (C=0.7, CH_2Cl_2).



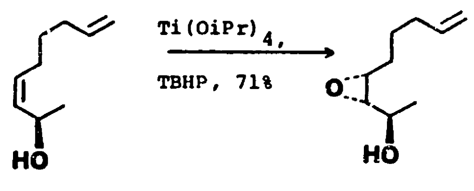
106 115

A solution of 523 mg of (R)-106 (3.8 mmol) in methanol 6 mL) containing Lindlar catalyst (52 mg, 10% by weight) was stirred vigorously under an atmosphere of hydrogen. After consuming 106 mL of H_2, 1.3 equiv.) the reaction mixture was filtered through a sintered glass frit. The resulting filter cake was washed with pentane (2x10 mL) and concentrated *in vacuo* to afford 513 mg (96%) of 115. In practice, this material was used without further purification. Analytically pure 115 could be obtained by preparative layer chromatography (SiO_2, 0.5 mm Et_2O, hexane, 1:1 R_f 0.53) for spectral data: $[\alpha]_D^{21}$ + 4.0° (C=.86 CH_2Cl_2) (95% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1 H, H_8), 5.50-5.41 (m, 2 H, H_3, H_4), 5.08-4.94 (m, 2 H, H_9), 4.70-4.60 (m, 1 H, H_2), 2.20-2.02 (m, 4 H, H_5, H_7), 1.63 (bs, 1 H, -OH), 1.48 (quintet, J=6.7 Hz, 2 H, H_6), 1.25 (d, J=6.1 Hz, 3 H, H_1); IR (CH_2Cl_2) 3600, 3070, 2980, 2920, 1640 cm^{-1}; mass spectrum m/e 122 (M^+ - H_2O); *Anal.* Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.90; H, 11.59.



106 114

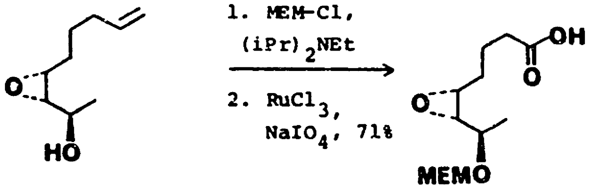
Catalytic hydrogenation of 106 was accomplished as described in the conversion of 106 to 115. Benzoylation of (Z)-allylic alcohol (27.1 mg, .19 mmol) with benzoyl chloride (40.8 mg, .29 mmol), pyridine (46 mg, .57 mmol) gave the intermediate benzoate derivative (56 mg), (R_f .70, Et$_2$O, hexane 1:1) after extractive workup. Without further purification, this material was oxidatively cleaved with RuCl$_3$, NaIO$_4$ (5 mg, 2%; 364 mg, 1.71 mmol) in CCl$_4$-CH$_3$CN-H$_2$O (.8 mL, .8 mL, 1.2 mL) at -25°C for 4h to afford, after standard workup 52 mg of the crude lactic acid derivative. Treatment of this material with CH$_2$N$_2$ in Et$_2$O gave, after chromatography (SiO$_2$, .25 mm, Et$_2$O, hexane 1:1, R_f .60) 9 mg (24% from 106) of pure 114: $[\alpha]_D^{21}$ - 8.0° (c=7.2, CHCl$_3$) (Lit for enantiomer: $[\alpha]_D^{21}$ + 13.9 (c=1.0, CHCl$_3$)).[62] NMR (^{1}H, 250 MHz, CDCl$_3$) δ 8.06 (d, J=7 Hz, 2 H), 7.61-7.40 (m, 3 H), 5.32 (q, 7 Hz, 1 H, H$_2$), 3.76 (s, 3 H, OMe), 1.62 (d, J=7 Hz, 3 H, H$_2$).



115 116

To a solution of $Ti(OiPr)_4$ (1.05 g, 3.7 mmol) in CH_2Cl_2 (40 mL) cooled to -20°C under a nitrogen atmosphere was added a solution of 115 (513 mg, 3.7 mmol) in CH_2Cl_2 (10 mL). After 5 min at -20°C TBHP (5.6 M in CH_2Cl_2, 7.3 mmol) was added and the resulting mixture maintained at -20°C for 15h. To this mixture was added Et_2O (10 mL) and saturated Na_2SO_4 (aq.) (1.1 mL) and the whole stirred vigorously at ambient temperature for 1h before being filtered through a bed of Celite. The filter cake was washed with Et_2O (5x20 mL) and the combined filtrates were concentrated *in vacuo* to afford 870 mg of crude 116 which was purified by flash column chromatography (SiO_2, 20x180 mm, Et_2O:hexane, 1:1, R_f .25) to afford 415 mg (73%) of 116 as a 19:1 mixture of *threo* and *erythro* products: $[\alpha]_D^{21}$ + 16.3° (C=1.5 CH_2Cl_2) (95% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.70 (m, 1 H, H_8), 5.05-4.90 (m, 2 H, H_9), 3.70-3.59 (m, 1 H, H_2), 4.05-3.95 (m, 1 H, H_4), 2.80-2.90 (m, 1 H, H_3), 1.35 (bd, J=3 Hz, 1 H, OH), 1.15-1.05 (m, 2 H, H_7), 1.68-1.48 (m, 4 H, H_5, H_6), 1.23 (d, J=7 Hz, 3 H, H_1); IR (CH_2Cl_2) 3600-3200, 3080, 2980, 2920, 2860, 1640 cm^{-1}; mass spectrum m/e 111 (M^+ - 45, $-CH_3CH_2O$); *Anal*. Calcd for

$C_9H_{16}O_2$: C, 68.96; H, 10.52. Found: C, 69.11; H, 10.32.

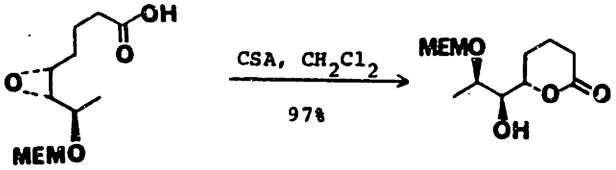


116

117

To a solution of epoxyalcohol 116 (421 mg, 2.69 mmol, 64% ee) in CH_2Cl_2 (16 mL) was added MEM-Cl (672 mg, 5.39 mmol) followed by diisopropylethyl amine, (1.04 g, 8.07 mmol). The resulting mixture was maintained under nitrogen for 24h. The orange reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with $NaHCO_3$ (aq). The aqueous phase was washed with CH_2Cl_2 (2x20 ml), filtered through a cotton plug and concentrated to give 820 mg of a dark yellow oil. Pure epoxyether was obtained by flash chromatography (SiO_2, 25x190 mm, Et_2O, hexane, 1:1, R_f .49) as a colorless liquid (538 mg, 82%): $[\alpha]^{21}_{D}$ + 22.4° (C=1.2, CH_2Cl_2) (72% ee) NMR (^1H, 250 MHz, $CDCl_3$) δ 6.85-6.65 (m, 1 H, H_8), 6.00-5.85 (m, 2 H, H_9), 5.85 (A of AB, J=3.5 Hz, 1 H, $-OCH_2O-$), 5.72 (B of AB, J=3.5 Hz, 1 H, $-OCH_2O-$), 3.72-3.48 (m, 5 H, H_2, MEM), 3.32 (S, 3 H, MEM), 2.90-2.82 (m, 2 H, H_3, H_4), 2.00-2.11 (m, 2 H, H_7), 1.30-1.81 (m, 4 H, H_5, H_6), 1.80 (d, 6.5 Hz, 3 H, H_1); IR (CCl_4) 3070, 2975, 2920, 2880, 1640, 1450 cm^{-1}; mass spectrum m/e 185 (M-59, $-MeOCHCH_2$); Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.78; H, 10.04.

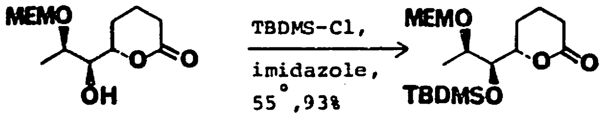
A solution of this compound (495 mg, 2.03 mmol) in CH_3CN-CCl_4-H_2O (9 mL, 9 mL, 13.5 mL) to which was added $NaIO_4$ (1.94 g, 9.13 mmol) and $RuCl_3$ (30 mg, 2%) was cooled to 0°C and stirred vigorously for 3.5 h. This mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) being careful not to mix the phases on the first wash (very bad emulsions result). The phases were separated and the aqueous phase washed with CH_2Cl_2 (3x10 mL). The combined organic extracts were filtered through cotton and concentrated in vacuo to give 464 mg (87%) of a dark green oil which also contained between 5-10% of hydroxy lactone 118. Although this mixture could be obtained as a clear, colorless oil (for spectral data) by precipitation of the ruthenium salts with anhydrous ether, in practice this was not done as these salts did not interfere with the subsequent step: $[\alpha]_D^{21}$ + 18.8° (C=0.5, CH_2Cl_2) (72% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 10-9.5 (bs, 1 H, $-CO_2H$), 4.85 (A of AB, J=6.8 Hz, 1 H, $-OCH_2O-$), 4.73 (B of AB, J=6.8 Hz, 1 H, $-OCH_2O-$), 3.75-3.50 (m, 5 H, H_2, MEM), 3.34 (s, 3 H, MEM), 2.95-2.85 (m, 2 H, H_2, H_3), 2.50-2.30 (m, 2 H, H_7), 1.90-1.35 (m, 4 H, H_5, H_6), 1.18 (d, 6.8 Hz, 3 H, H_1), IR (CH_2Cl_2), 3500-2500, 3040, 2940, 1710 cm^{-1}; mass spectrum m/e 217 (M-45).



117

118

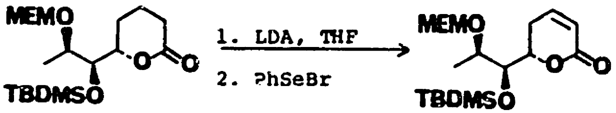
To a solution of carboxylic acid 117 (464 mg, 1.77 mmol) in CH_2Cl_2 (10 mL) was added camphorsulfonic acid (30 mg, 10 mol %). This mixture was maintained at 25°C for 3h, diluted with CH_2Cl_2 (30 mL) and extracted with $NaHCO_3$ (1/3 saturated, 10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 ml, 3x), filtered through a cotton plug and concentrated *in vacuo* to give 451 mg (97%) of hydroxy lactone 118. Although in practice 118 was used without further purification analytically pure 118 could be obtained by flash chromatography (SiO_2, CH_2Cl_2, MeOH, 9:1, R_f .58): $[\alpha]_D^{21}$ - 14.7° (c = 0.2, CH_2Cl_2) (64% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 4.80 (A of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4.70 (B of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4.42-4.35 (m, 1 H, H_5), 4.0-3.5 (m, 5 H, H_7, MEM), 3.38 (s, 3 H, MEM), 3.30-3.25 (m, 1 H, H_6), 2.65-2.35 (m, 3 H, H_2, OH), 2.05-1.50 (m, 4 H, H_3, H_4), 1.20 (d, J=7 H, 3 H, H_7); IR (CH_2Cl_2), 3660, 3560, 3420, 3020, 2920, 2880, 1730 cm^{-1}; mass spectrum m/e 262 (M^+); Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.77; H, 8.61.



118 119

To a solution of 118 (450 mg, 1.71 mmol) in DMF (12 mL) was added TBDMS-Cl (517 mg, 3.43 mmol) followed by imidazole (351 mg, 5.15 mmol). The mixture was then heated to 60°C under N_2 for 82h. The reaction mixture was cooled to ambient temperature and partitioned between Et_2O (20 mL) and H_2O (20 mL). The phases were separated and the aqueous phase was washed with Et_2O (3x50 mL). The combined organic extracts were washed with H_2O (1x30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to leave 870 mg of a pale yellow oil which was purified by flash chromatography (SiO_2, 30x210 mm, Et_2O (100%), R_f 0.60) to afford 598 mg (93%) of pure 119: $[\alpha]_D^{21}$ + 11.6° (c = 0.8, CH_2Cl_2) (72% ee); NMR (^1H,250 MHz, $CDCl_3$) δ 4.78 (A of AB, J=6.8 Hz, 1 H, $-OCH_2O-$), 4.70 (B of AB, J=6.8 Hz, 1 H, $-OCH_2O-$), 4.40 (m, 1 H, H_5), 3.82 (quintet, J=7.0 Hz, 1 H, H_7), 4.70-4.50 (m, 5 H, H_6, MEM), 3.36 (s, 3 H, MEM), 2.62-2.30 (m, 2 H, H_2), 2.0-1.60 (m, 4 H, H_3, H_4), 1.25 (d, J=7.0, 3 H, H_8), 0.87 (s, 9 H, ^tBuSi), 0.10 (s, 3 H, MeSi-), 0.06 (S, 3 H, MeSi-); IR (CH_2Cl_2), 3040, 2930, 2880, 2850, 1730 cm^{-1}; mass spectrum m/e 319 (M-57, -tBu);

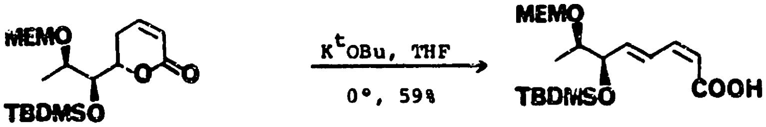
Anal. Calcd for $C_{18}H_{36}SiO_6$: C, 57.41; H, 9.63. Found: C, 57.62; H, 9.89.



119 120

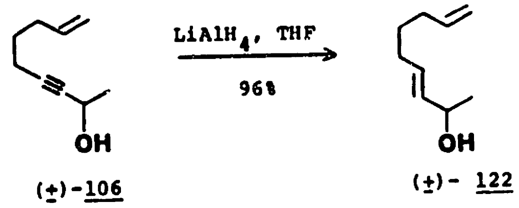
To a solution of 119 (222 mg, 0.59 mmol) in THF (5 mL) at -78°C under nitrogen was added LDA (1 M in THF, 1.0 equiv.). The resulting pale yellow solution was maintained at -78°C for 1h and quenched with PhSeBr (0.62 mmol) which was prepared in THF immediately before use according to the procedure of Reich and Regna.[66] This reaction mixture was quenched after 35 min. with sat. NH_4Cl (1 mL) at -78°C. The quenched mixture was warmed to room temperature, diluted with CH_2Cl_2 (10 mL) and the phases separated. The aqueous phase was washed with CH_2Cl_2 (2x10 mL) and the combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to give 461 mg of a thick yellow oil.

The crude α-selenolactone was dissolved in CH_2Cl_2 (8 mL) to which was added a catalytic amount of AcOH (4 mg, 1% by weight) followed by 30% H_2O_2 (361 μl, 120 mg, 3.54 mmol, 6 equiv. based on a theoretical yield of 0.59 mmol of selenolactone). This mixture was stirred vigorously at 25°C for 45 min., diluted with CH_2Cl_2 (20 mL) and extracted with 20% $NaHSO_3$ (5 mL). The aqueous extract was washed with CH_2Cl_2 (10 mL) and the combined organic extracts were washed with H_2O (30 mL), filtered through a cotton plug and concentrated in vacuo to afford 208 mg of crude 120 which was purified on two 0.5 mm SiO_2 prep plates (Et_2O, 100%) to afford 122 mg (55%) of pure 120 as a heavy oil: $[\alpha]_D^{21}$ - 26.3° (c = 4.2, CH_2Cl_2) (64% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 6.9-6.8 (m, 1 H, H_3), 5.9 (dd, J=10 Hz, 3 Hz, 1 H, H_2), 4.77 (A of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4.70 (B of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4.55-4.45 (m, 1 H, H_5), 3.9-3.5 (m, 6 H, H_6, H_7, MEM), 3.36 (s, 3 H, MEM), 2.60-2.45 (m, 2 H, H_4), 1.27 (d, J= 6 Hz, 3 H, H_8), 0.87 (s, 9 H, ^{t}BuSi-), 0.11 (s, 3 H, MeSi-), 0.08 (s, 3 H, MeSi-); IR (CH_2Cl_2), 2920, 2880, 2850, 1720 cm^{-1}; mass spectrum m/e 317 (M-57, $-^t$Bu); UV (EtOH) 212 nm (ε = 4,000); Anal. Calcd for $C_{18}H_{34}SiO_6$: C, 57.67; H, 9.15. Found: C, 57.41; H, 9.11.



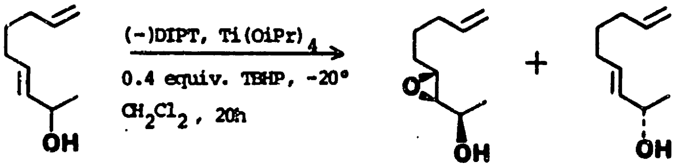
120 121

A solution of 120 (43 mg, 0.12 mmol) in THF (0.9 mL) was added to a stirred suspension of K^tOBu (20 mg, 0.18 mmol, sublimed) in THF (0.4 mL) at 0°C. This mixture was maintained at 0°C under a nitrogen atmosphere for 30 min, quenched with $NH_4^+Cl^-$ (5 mL, saturated aqueous solution) and extracted with EtOAc (3x20 mL). The organic extracts were concentrated *in vacuo* to afford 33 mg of crude acid 121 (one spot on analytical tlc) which was purified by flash chromatography (SiO_2, 10x190 mm, CH_2Cl_2, MeOH, 9:1, R_f 0.5) to yield 25 mg of pure 121: $[\alpha]_D^{21}$ + 39.7° (c = 2.5, CH_2Cl_2) (64% ee); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.58 (dd, J=15.2 Hz, 11.1 Hz, 1 H, H_4), 6.70 (t, J=11.1 Hz, 1 H, H_3), 6.16 (dd, J=15.2 Hz, 5.7 Hz, 1 H, H_5), 5.67 (d, J=11.1 Hz, 1 H, H_2), 4.80 (s, 2 H, $-OCH_2O-$), 4.35 (t, J=5.7 Hz, 1 H, H_6), 3.80-3.50 (m, 5 H, H_7, MEM), 3.40 (s, 3 H, MEM), 1.10 (d, J=6.4 Hz, 3 H, H_8), 0.91 (s, 9 H, $^tBuSi-$), 0.07 (s, 3 H, MeSi-), 0.06 (s, 3 H, MeSi-); IR (CH_2Cl_2) 3200-2500, 2920, 2880, 2860, 1725, 1690, 1635, 1600 cm^{-1}; UV (EtOH) 259 nm, (ε = 11,000); mass spectrum m/e 317 (M-57); *Anal*. Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15. Found: C, 54.29; H, 8.41.



A solution of 106 (1.30 g, 9.42 mmol) in 10 mL of tetrahydrofuran was added in one portion, via cannula, to a solution of lithium aluminum hydride (14.7 ml of a 1.6 M tetrahydrofuran solution, 23.5 mmol) at 0°C. The cooling bath was removed and the mixture was refluxed for 1h under nitrogen. The mixture was cooled to 0°C and water (890 μL) was added cautiously with vigorous stirring. To the resulting white suspension was added 15% NaOH solution (890 μL) affording a granular white precipitate. This mixture was filtered over 1 inch of Celite and the filter cake washed with ether (3x50 mL). Concentration of the filtrate *in vacuo* afforded 1.27 g of a clear, colorless oil. In practice 122 was carried on without purification. Analytically pure 122 was obtained by distillation (90°C, 2 mm): NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.86-5.69 (m, 1 H, H_8), 5.66-5.46 (m, 2 H, H_3, H_4), 5.02-4.90 (m, 2 H, H_9), 4.29-4.21 (m, 1 H, H_2), 2.07-1.97 (m, 4 H, H_5, H_7), 1.44 (quintet, J=8.0 Hz, 2 H, H_6), 1.42 (br s, 1 H, OH), 1.23 (d, J=6.4 Hz, 3 H, H_1); IR (CCl_4) 3610, 3360, 3080, 2980, 2920, 2860, 1665, 1604; mass spectrum m/e 140 M^+, 122 (M-18); Anal. Calcd for $C_9H_{16}O$:

C, 77.09; H, 11.50. Found: C, 77.33; H, 11.65.



(±)- 122 (+)-123 (-)-122

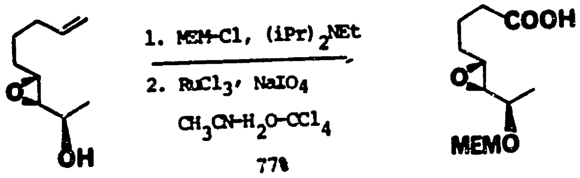
(+)-Diisopropyl tartrate (1.01 g, 4.3 mmol) was added to a flask containing dichloromethane (75 mL) at -20°C under an atmosphere of nitrogen. To this solution was added titanium tetraisopropoxide (1.03 g, 3.62 mmol) and the resulting mixture was stirred for 10 min. To this mixture was added a solution of 122 (1.27 g, 9.07 mmol) in 30 mL of dichloromethane and the resulting mixture stirred for 10 min. *tert*-Butylhydroperoxide (0.71 ml of a 5.75 *M* dichloromethane solution, 4.08 mmol) was added and the mixture was maintained at -20° for 18 h. The mixture was then diluted with ether (50 mL) and saturated aqueous Na_2SO_4 (1.1 mL). This mixture was stirred vigorously at room temperature for 1 h. The resulting white suspension was filtered through a 1 inch bed of Celite and the filter cake washed with ether (5x40 mL). Concentration of the filtrate *in vacuo* gave a colorless oil (2.5 g). The crude product mixture was dissolved in ether (20 mL) and cooled to 0°C. To this solution was added saturated aqueous NaCl (20 mL) and 15% NaOH (6.8 ml, 25.5 mmol). The biphasic mixture was stirred vigorously with a mechanical stirring apparatus. After

4h the phases were separated and the aqueous phase extracted with ether (3x20 mL). The combined extracts were dried over Na_2SO_4 powder and filtered. The filtrate was diluted with an equal volume of dichloromethane, filtered through cotton and concentrated in vacuo to afford 1.57 g of crude product. ^1H NMR analysis of this mixture indicated that some diisopropyltartrate remained. This mixture was further purified by flash column chromatography (190 x 50 mm of 70-230 mesh SiO_2, 1:1, ether: hexane) affording 503 mg (40%) of allylic alcohol 122 and 740 mg of a mixture of epoxyalcohol 123 and diisopropyltartrate. The epoxy alcohol/tartrate mixture was dissolved in ether (10 ml) and cooled to 0°C. To this solution was added saturated aqueous NaCl (10 mL) and 15% NaOH (3.4 mL, 12.75 mmol). The biphasic mixture was stirred as before. After 2 h the phases were separated and the aqueous phase was extracted with ether (2x20 mL). The combined ether extracts were washed with water (2x10 mL). The ether extracts were diluted with an equal volume of dichloromethane and filtered through cotton. Concentration, in vacuo, afforded 572 mg (40%, 90% based on oxidant) of (-)-123. The optical purity of this sample was determined by the method of Mosher et al to be greater than 95% ee.

(-)-123: $[\alpha]_D^{20}$ -8.9° (c = 1.28, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.86-5.69 (m, 1 H, H_8), 5.04-4.92 (m, 2 H, H_9), 3.00-2.95 (m, 1 H, H_4), 2.75-2.73 (m, 1 H, H_3), 2.12-2.04 (m, 2 H, H_7), 1.85 (d, J=3 Hz, -OH), 1.56-1.49 (m, 4 H, H_5, H_6), 1.23 (d, 3 H, H_1); IR (CH_2Cl_2), 3560, 3042, 2970, 2930, 2860, 1735, 1640; mass spectrum m/e 156 (M^+); Anal. Calcd for $C_9H_{16}O_2$:

C, 69.19; H, 10.32. Found: C, 68.96; H, 10.61.
(+) <u>122</u>: $[\alpha]_D^{20}$ +9.48 (C = .58, CH_2Cl_2).

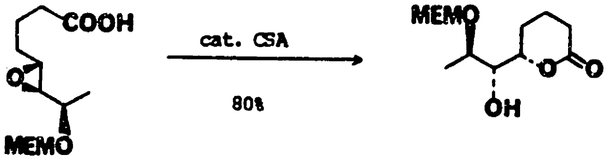
The enantiomeric <u>erythro</u>-epoxyalcohol (+)-<u>123</u> was prepared in an identical manner: $[\alpha]_D^{20}$ + 8.60 (C = 2.02, CH_2Cl_2).



123

124

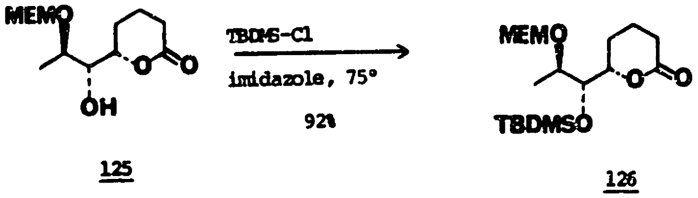
The preparation of 124 from 123 (77%) was accomplished by a procedure completely analogous to that described for the conversion of 116 to 117: R_f .5, (Et_2O, hexane 1:1); $[\alpha]_D^{21}$ + 36.2° (C = 1.58, CH_2Cl_2); NMR (^1H, 60 MHz, $CDCl_3$) δ 6.2-5.5 (m, 1 H, H_8), 5.3-4.7 (m, 2 H, H_9), 3.8-3.5 (m, 5 H, H_2, MEM), 3.4 (s, 3 H, MEM), 3.0-2.6 (m, 2 H, H_3, H_4), 2.4-1.9 (m, 2 H, H_7), 1.7-1.5 (m, 4 H, H_5, H_6), 1.21 (d, J=6 Hz, 3 H, H_1); IR (CH_2Cl_2) 3040, 2920, 2880, 1640 cm^{-1}; mass spectrum m/e 185 (M-59); 124: $[\alpha]_D^{21}$ + 28.6 (C = 1.1, CH_2Cl_2); NMR (^1H, 60 MHz, $CDCl_3$) δ 5.1-4.8 (m, 2 H, MEM), 4.5-3.6 (m, 5 H, H_2, MEM), 3.4 (s, 3 H, MEM), 3.2-2.9 (m, 2 H, H_3, H_4), 2.7-2.2 (m, 2 H, H_7), 2.1-1.8 (m, 4 H, H_5, H_6), 1.2 (d, J=7 Hz, 3 H, H_1), IR (CH_2Cl_2) 3500-2500, 2940, 2880, 1710 cm^{-1}.



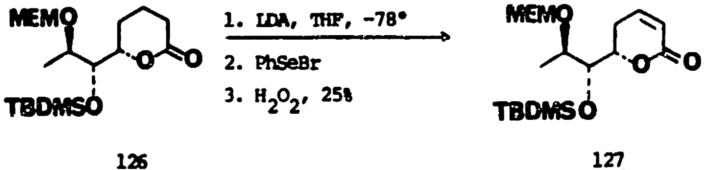
124

125

Lactone <u>125</u> was prepared from <u>124</u> using a procedure completely analogous to that used for the preparation of <u>118</u> from <u>117</u>: R_f 0.2 (Et_2O, 100%); $[\alpha]_D^{21}$ - 36.0° (C = 1.2, CH_2Cl_2); NMR (^1H, 60 MHz, $CDCl_3$) δ 5.0 (bs, 2 H, MEM), 4.7-4.5 (m, 1 H, H_5), 4.2-3.8 (m, 5 H, H_2, MEM), 3,4 (s, 3 H, MEM), 2.8-2.6 (m, 2 H, H_2), 2.3-1.9 (m, 4 H, H_3, H_4), 1.2 (d, J=7 H, 3 H, H_1); IR (CH_2Cl_2) 3580, 2940, 2920, 2880, 730 cm^{-1}; mass spectrum m/e 263 (M+1). <u>Anal</u>. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.78; H, 8.59.

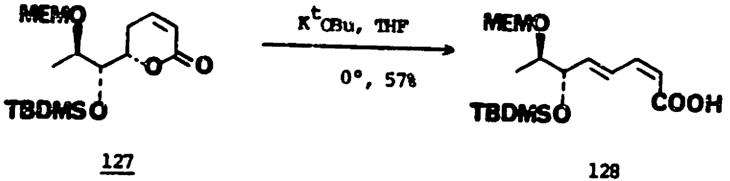


Lactone <u>126</u> was prepared (92%) by a procedure analogous to that used for the preparation of <u>119</u> from <u>118</u>: R_f 0.5 (Et_2O, 100%); $[\alpha]_D^{21}$ - 19.9° (C = 2, CH_2Cl_2); NMR (^1H, 60 MHz, $CDCl_3$) δ 4.8 (bs, 2 H, MEM), 4.6-4.4 (m, 1 H, H_5), 3.8-3.6 (m, 5 H, H_2, MEM), 2.1-1.8 (m, 4 H, H_3, H_4), 1.2 (d, J=7 Hz, 3 H, H_1), 1.0 (s, 9 H, tBu), 0.1 (s, 6 H, $Si(Me)_2$); IR (CH_2Cl_2) 2920, 2880, 2860, 1730 cm^{-1}; mass spectrum m/e 320 (M-57).



126 127

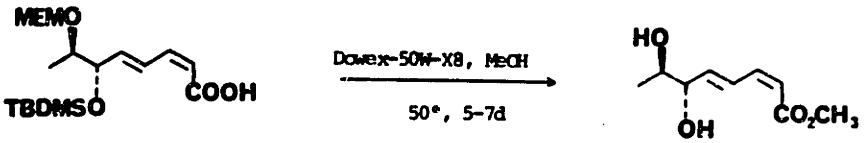
Unsaturated lactone 127 was prepared (25%) by a procedure analogous to that described for the preparation of 120 from 119: R_f .55 (Et_2O, 100%); $[\alpha]_D^{21}$ - 114.7° (C = 2.21, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 6.95-6.85 (m, 1 H, H_3), 5.98 (dd, J=10 Hz, 2 Hz, 1 H, H_2), 4.75 (A of AB, J=8 Hz, 1 H, $-OCH_2O-$), 4.65 (B of AB, J=8 Hz, 1 H, $-OCH_2O-$), 3.87-3.40 (me, 6 H, H_6, H_7, MEM), 3.36 (s, 3 H, MEM), 2.70-2.30 (m, 2 H, H_3), 1.20 (d, J=6 Hz, 3 H, H_8), 0.87 (s, 9 H, t-Bu), 0.0 (s, 6 H, $-Si(Me)_2$); IR (CH_2Cl_2) 2970, 2920, 2880, 2860, 1720 cm^{-1}; UV (EtOH) 212 nm (ε = 4,064) mass spectrum m/e 317 (M-57). Anal. Calcd for $C_{18}H_{34}SiO_6$: C, 57.67; H, 9.15. Found: C, 57.57; H, 8.96.



127

128

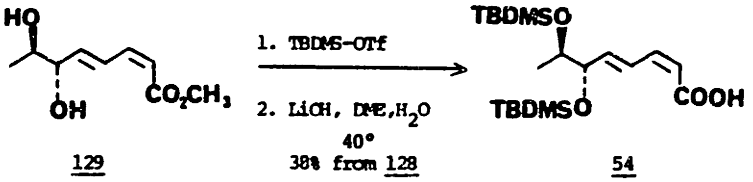
Diene acid 128 was prepared (57%) by a procedure identical to that outlined for the preparation of 121 from 120: R_f 0.5 (CH_2Cl_2, MeOH, 9:1); $[\alpha]_D^{21}$ + 1.5 (C =1.6, CH_2Cl_2); NMR (^{1}H. 250 MHz, $CDCl_3$) δ 8.00 (dd, J=15 Hz, 10 Hz, 1 H, H_4), 6.62 (t, J=10 Hz, 1 H, H_3), 6.05 (dd, J=15 Hz, 6 Hz, 1 H, H_5), 5.65 (d, J=10 Hz, 1 H, H_2), 4.75 (bs, 2 H, MEM), 4.19 (t, J=6 Hz, 1 H, H_6), 3.80-3.50 (m, 5 H, H_7, MEM), 3.39 (s, 3 H, MEM), 1.12 (d, J=6 H, 3 H, H_1), 0.90 (s, 9 H, t-Bu), 0.05 (s, 3 H, TBDMS), 0.03 (s, 3 H, TBDMS); IR (CH_2Cl_2) 3400-2500, 2920, 2880, 2850, 1720, 1685, 1635, 1595 cm^{-1}; UV (EtOH) 262 nm, (ε = 11,100).



128

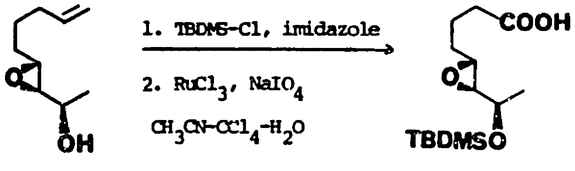
129

A solution of 128 (30 mg, 0.8 mmol) in MeOH containing Dowex 50W-X8 resin (210 mg) was heated to reflux for 5d. This mixture was cooled to ambient temperature, filtered through a sintered glass frit and concentrated *in vacuo* to leave 22 mg of crude 129 which was purified by flash chromatography (SiO_2, 10 x 190, mm, R_f .60, CH_2Cl_2, MeOH, 9:1), to afford 12.7 mg (86%) of pure 129: $[\alpha]_D^{21}$ - 36.6° (C = 1.27, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.58 (dd, J=15 Hz, 9 Hz, 1 H, H_4), 6.60 (t, J=9 Hz, 1 H, H_3), 6.09 (dd, J=15 Hz, 6 Hz, 1 H, H_5), 4.0-3.90 (m, 1 H), 3.72 (s, 3 H, -OMe), 2.40-2.10 (bs, 1 H, -OH), 1.80-1.60 (bs, 1 H, OH), 1.15 (d, J=6 Hz, 3 H, H_8); IR (CH_2Cl_2) 3680, 3580, 3040, 2980, 1710, 1640, 1600 cm^{-1}; mass spectrum m/e 169 (M-15).



To a solution of 129 (9 mg, .05 mmol) in CH_2Cl_2 (.25 mL) was added 2,6-lutidine (26 mg, .24 mmol) followed by TBDMS-OTf (39 mg, .147 mmol). This mixture was maintained at 25°C under N_2 for 1h, solvents removed *in vacuo* and the residue purified by preparativ layer chromatography (SiO_2, .25 mm, Et_2O, hexane 1:1, R_f 0.8) to yield 11 mg (51%) of the bis TBDMS ether: NMR (^1H, 250 MHz, $CDCl_3$) δ 7.40 (dd, J=15 Hz, 11 Hz, 1 H, H_4), 6.55 (t, J=11 Hz, 1 H, H_3), 5.01 (dd, J=15 Hz, 6 Hz, 1 H, H_5), 5.62 (d, J=11 Hz, 1 H, H_2), 3.98 (t, J=6 Hz, 1 H, H_6), 3.71 (s, 3 H, -OMe), 3.70-3.60 (m, 1 H, H_7), 1.12 (d, J=7 Hz, 1 H, H_1), 0.90 (s, 9 H, t-Bu), 0.83 (s, 9 H, t-Bu), 0.5-0.0 (m, 12 H, TBDMS).

This material was dissolved in a 3:1 mixture of DME : H_2O (0.5 mL) containing LiOH (3,2 mg, .158 mmol) and heated to 45°C for 4h. This mixture was diluted with CH_2Cl_2 (10 mL) and extracted with sat. $NH_4^+Cl^-$ (5 mL). The aqueous extract was washed with CH_2Cl_2 (4x20 mL) and the combined organic extracts were filtered through a cotton plug, concentrated *in vacuo* to leave 10.8 mg of crude 54 which was purified by prep plate chromatography (SiO_2, Et_2O, hexane, HCO_2H, 1:2:1%, R_f 0.6) to yield 7.3 mg of pure <u>54</u>: <u>m.p</u>. 76-78° (lit:77-79°);[40] $[\alpha]_D^{21}$ -22.3° (C = 1.28, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.48 (dd, J=15 Hz, 10 Hz, 1 H, H_4), 6.65 (t, J=10 Hz, 1 H, H_3), 6.10 (dd, J=15 Hz, 7 Hz, 1 H, H_5), 5.65 (d, J=10 Hz, 1 H, H_2), 3.98 (t, J=7 Hz, 1 H, H_6), 3.64 (dq, 7 Hz, 1 H, H_7), 1.13 (d, J=7 Hz, 3 H, H_8), 0.90 (s, 9 H, t-Bu), 0.85 (s, 9 H, t-Bu), 0.05-0.0 (m, 12 H, TBDMS); IR (CH_2Cl_2) 3070, 2980, 2890, 2880, 1730, 1695, 1640, 1600 cm^{-1}; UV (EtOH) 250 nm (ε = 11,400); mass spectrum m/e 355 (M-45).



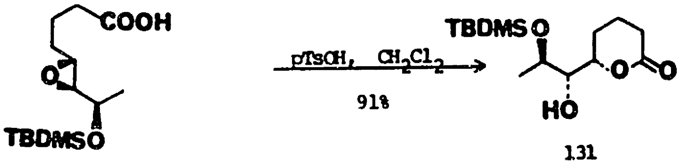
<u>123</u> <u>130</u>

Imidazole (2.40 g, 3.51 mmol) and tert-butyldimethylsilylchloride (3.53 g, 23.4 mmol) were added to a solution of epoxyalcohol (1.8 g, 11.7 mmol) in dimethylformamide (20 mL). This mixture was heated to 50°C under an atmosphere of nitrogen and then

was partitioned between ether (20 mL) and water (20 mL). The organic extract was washed with water (4x50 mL). The combined aqueous extracts were washed with ether (3x20 mL) and combined with the initial ether extracts, diluted with an equal volume of dichloromethane, filtered through cotton and concentrated <u>in vacuo</u> affording 4.3 g of a clear, colorless oil. The crude product was purified by flash column chromatography (SiO_2, 45x120 mm, hexane, 500 mL, Et_2O, hexane, 1:1 R_f 0.80) to afford 3.0 g (98%) of pure TBDMS ether: $[\alpha]_D^{21} = +4.6°$ (C = 7.0, CH_2Cl_2) NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.70 (m, 1 H, H_8), 6.03-5.93 (m, 2 H, H_9), 3.65 (dd, J=5 Hz, 1 H, H_2), 2.85-2.80 (m, 1 H, H_4), 2.59 (dd, J=5 Hz, 2.7 Hz, 1 H, H_3), 2.15-2.00 (m, 2 H, H_7), 1.60-1.50 (m, 4 H, H_5, H_6), 1.2 (d, J=5.9 Hz, 3 H, H_1), 0.85 (s, 9 H, t-Bu), .02 (s, 6 H, $Si(Me)_2$); IR

(CH_2Cl_2) 3020, 2930, 2850, 1640; mass spectrum m/e 213 (M-57); <u>Anal</u>. Calcd for $C_{15}H_{30}SiO_2$.

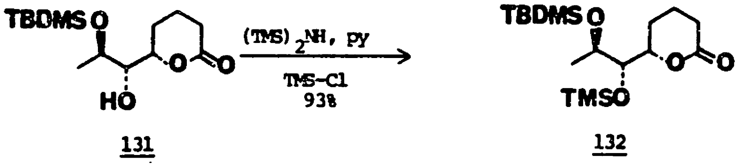
To a solution of 3.0 g (11.6 mmol) of the TBDMS ether in CH_3CN (29 mL), CCl_4 (29 mL) and H_2O (50 mL) was added solid $NaIO_4$ (11.3 g, 52.9 mmol). To this mixture was added $RuCl_3 \cdot 3H_2O$ (120 mg, 4%). The resulting biphasic mixture was stirred vigorously at 25°C for 7h. The resulting mixture was partitioned between CH_2Cl_2 (50 mL) H_2O (50 mL). Without being mixed, the phases were separated and the aqueous phase was washed with CH_2Cl_2 (2x50 mL). The combined extracts were filtered through a cotton plug and concentrated <u>in vacuo</u>. The resulting dark green oil was suspended in anhydrous ether (100 mL) and allowed to stand at 25°C for 30 min. This solution was filtered through a pad of celite (20 x 50 mm) and concentrated <u>in vacuo</u> to leave 3.22 g of a green oil (94% from <u>123</u>) containing ca. 10% of hydroxylactone <u>131</u>.



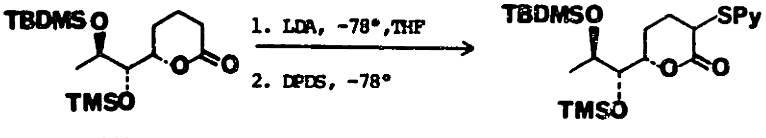
130

131

To a solution of 3.0 g (11.0 mmol) of carboxylic acid 130 in CH_2Cl_2 (100 mL) was added $pTsOH \cdot H_2O$ (320 mg). This mixture was maintained at 25°C for 3.5h, and extracted with 1/2 saturated aqueous $NaHCO_3$ (50 mL). The resulting emulsion was filtered through a cotton plug and concentrated to afford 4g of a mixture of crude product. This mixture was suspended in 200 mL of anhydrous CH_2Cl_2 and filtered through a pad of Celite. The filter cake washed with CH_2Cl_2 (3x100 mL) and concentrated *in vacuo* to afford crude 131 (3.6 g) which was purified by flash column chromatography (SiO_2, 50x180 mm, Et_2O, hexane, 2:1, R_f 0.45 to afford 2.95 g (91%) of pure 131: $[\alpha]_D^{21} = -5.0°$ (C = 2.39, CH_2Cl_2), NMR (^1H, 250 MHz, $CDCl_3$) δ 4.35-4.25 (m, 1 H, H_5), 4.01 (dd, J=5,6 Hz, 1 H, H_7), 3.62 (dd, J=6.4 Hz, 5.3 Hz, 1 H, H_6), 2.70-2.40 (m, 2 H, H_2), 2.30 (br s, 1 H, OH), 2.15-1.60 (m, 4 H, H_3, H_4), 1.15 (d, J=6.2, H_8), 0.85 (s, 9 H, tert butyl), .06 (s, 3 H, Si(Me)), .05 (s, 3 H, Si(Me)); IR (CH_2Cl_2) 3550, 2980, 2960, 2860, 1735, mass spectrum m/e 231 (M-57); Anal. Calcd. for $C_{14}H_{28}SiO_4$: C, 58.29; H, 9.78. Found: C, 57.99; H, 9.80.

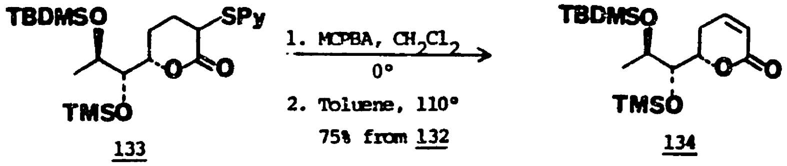


To a solution of 131 (300 mg, 1.03 mmol) in dry pyridine (1.5 mL) was added bishexamethyldisilazane (332 mg, 2.06 mmol) followed by addition of TMS-Cl (224 mg, 2.06 mmol). This mixture was maintained at 25°C under an atmosphere of dry nitrogen. After 20 min. reaction was quenched with brine (5 mL) and diluted with CH_2Cl_2 (20 mL). The phases were separated and the aqueous phase washed with CH_2Cl_2 (2x10 mL). The combined organic extracts were filtered through cotton, diluted with n-heptane (20 mL) and concentrated in vacuo to afford 350 mg (93%) of 132 as a colorless oil. In practice 132 was used without further purification. Analytically pure 132 could be obtained by preparative layer chromatography (SiO_2, 0.25 mm, Et_2O, hexane, 1:1, Rf .50): $[\alpha]_D^{21}$= -18.45 (C = 1.36, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 4.50 (dt, J=10.3, 3.7 Hz, 1 H, H_5), 3.75-3.65 (m, 1 H, H_7), 3.63 (dd, J=5.6, 3.7 Hz, 1 H, H_6), 2.61-2.30 (m, 2 H, H_2), 2.61-2.30 (m, 2 H, H_2), 1.65-1.98 (m, 4 H, H_3, H_4), 1.13 (d, J=5.6 Hz, 3 H, H_8), 0.84 (s, 9 H, tert butyl), 0.10 (s, 9 H, TMS), 0.04 (s, 3 H, MeSi), 0.01 (s, 3 H, MeSi); IR (CH_2Cl_2) 3025, 2960, 2935, 2895, 2860, 1730 cm^{-1}; mass spectrum m/e 345 (M-15), 303 (M-57); Anal. Calcd for $C_{17}H_{36}Si_2O_4$: C, 56.67; H, 10.06. Found: C, 56.90; H, 9.95.



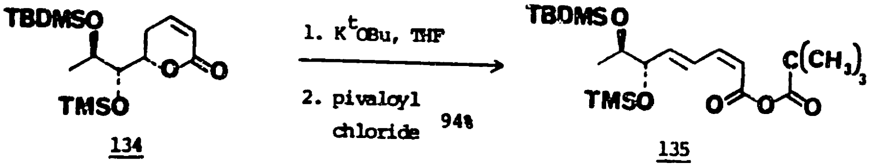
132 133

To a solution of 132 (350 mg, 0.96 mmol) in THF (3 mL) cooled to -78°C under N_2 was added a solution of LDA in THF (0.84 M, 2.3 mL, 1.93 mmol). After 1h, at -78° the enolate was quenched with a cold solution (-78°) of DPDS (424 mg, 1.93 mmol) in THF (2 mL). The resulting mixture was maintained at -78° for 1h, quenched (at -78°C) with saturated aqueous $NH_4^+Cl^-$ (2 mL) and extracted, after warming to 25°C, with CH_2Cl_2 (10 mL x 1). The combined organic extracts were filtered through a cotton plug and concentrated in vacuo to afford 774 mg of crude 133 as a mixture of diastereomeric sulfides (R_f .55, Et_2O, hexane 1:1). This mixture was used without further purification.

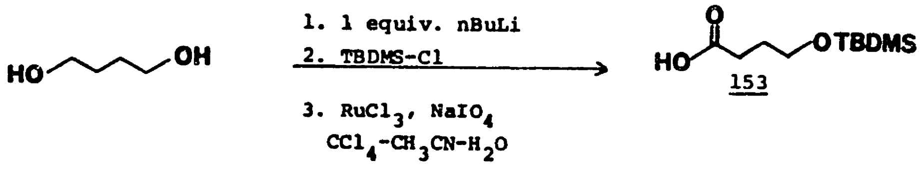


To a solution of the crude sulfenylation product (456 mg, 0.96 mmol, theoretical yield from <u>132</u>) in CH_2Cl_2 (10 mL) at 0°C was added a solution of MCPBA (430 mg, 2.2 mmol) in CH_2Cl_2 (10 mL). This mixture was maintained at 0°C for 30 min, diluted with CH_2Cl_2 (10 mL) and extracted with 1/3 saturated aqueous $NaHCO_3$ (2x20 mL). The aqueous phase was washed with CH_2Cl_2 (2x10 mL) and the combined organic extracts were filtered through cotton and concentrated <u>in vacuo</u> to afford 780 mg of a mixture of diastereomeric sulfoxides, (R_f .20, Et_2O, hexane 1:1). This mixture was used without further purification.

A solution of the diastereomeric sulfoxides in dry toluene (6 mL) was heated to reflux. After 30 min the mixture was cooled to ambient temperature and concentrated in vacuo to afford 707 mg of a pale yellow oil, which was purified by flash chromatography (SiO_2, 30x205 mm, Et_2O, hexane, 1:1, R_f 0.50) to afford 260 mg of pure <u>134</u> (75% from <u>132</u>); $[\alpha]_D^{21}$ = -85.9° (C = 1.62, CH_2Cl_2), NMR (^1H, 250 MHz, $CDCl_3$) δ 6.89 (ddd, J=2.1, 5.6, 10.1 Hz, 1 H, H_3), 5.97 (dd, J=2.6, 10.1 Hz, 1 H, H_2), 4.62 (dt J=11.6, 3.7 Hz, 1 H, H_5), 3.7-3.8 (m, 2 H, H_6, H_7), 2.58 (ddt, J=19.8, 11.6, 2.1 Hz, 1 H, $H_{4\alpha}$), 2.25 (ddd, J=19.8, 5.6, 3.7 Hz, 1 H, H_4), 1.15 (d, J=7.5 Hz, 3 H, H_8), 0.83 (s, 9 H, tert BuSi), 0.12 (s, 9 H, $Si(Me)_3$), .05 (s, 3 H, Si(Me)), .01 (s, 3 H, Si(Me)); IR (film) 2955, 2930, 2890, 2875, 1735; UV (EtOH), λ_{max} 217, ε = 2,650; mass spectrum m/e 343 (M-15), 301 (M-57); *Anal*. Calcd for $C_{17}H_{34}SiO_4$: C, 56.93; H, 9.55. Found: C, 57.14; H, 9.67.



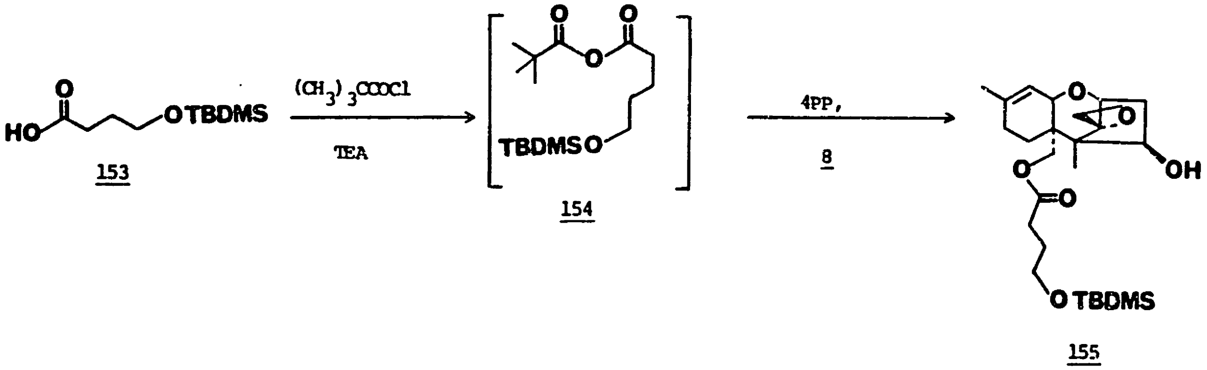
To a solution of 134 (68 mg, 0.19 mmol) in THF (0.8 mL) at 0°C was added a suspension of K^{t}OBu (23 mg, 0.21 mmol) in THF (1.4 mL). The resulting yellow solution was maintained under N_2 at 0°C. After 1h the intermediate potassium carboxylate was quenched with freshly distilled pivaloyl chloride (25 mg, 0.21 mmol). This mixture was maintained at 0°C for 20 min, warmed to ambient temperature and filtered (under nitrogen) through a bed of Florisil. The filter cake was washed with anhydrous THF (4x5 mL) and concentrated *in vacuo* to afford 79 mg of 135 (94%). This material was used without additional purification: $[\alpha]_D^{21} = -16.3°$ (C = 0.44, CH_2Cl_2) NMR (^1H, 250 MHz, $CDCl_3$) δ 7.43 (dd, J=15.5, 11.5, 1 H, H_4, H_4), 6.75 (t, J= 11.5 Hz, 1 H, H_3), 6.20 (dd, J=5.5, 15.5, 1 H, H_5), 5.70 (d, J=11.5 H, 1 H, H_2). IR (CH_2Cl_2) 2960, 2935, 2890, 2860, 1798, 1725, 1635, 1593. Mass Spectrum m/e 341 (M-101, $(CH_3)_3CO_2$)), 313, 101.



153

A solution of 1,2-butanediol (1.2 g, 13.5 mm) in THF (25 mL) was cooled to -78°C and nBuLi (12.9 mm) was added over a period of 10 min. This mixture was warmed to ambient temperature, maintained under N_2 for 13h, extracted with brine (2x10 mL) and concentrated to give 2.2g of crude mono TBDMS ether. This material was used without further purification: NMR (^{1}H, 60 MHz, $CDCl_3$) δ 3.7-3.6 (m, 4H), 3.1 (bs, 1 H, OH), 1.7-1.6 (m, 4 H), 1.0 (s, 9 H, tBu), 0.3 (s, 6 H, TBDMS).

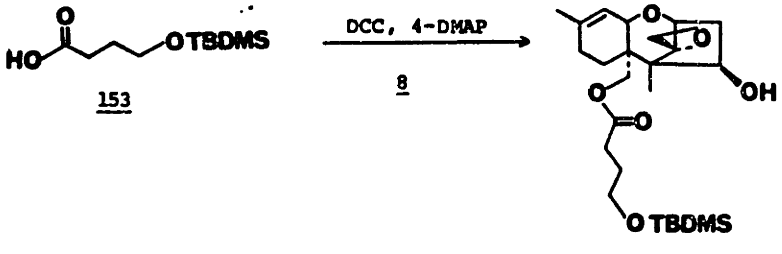
To a solution of this alcohol (192 mg, 0.95 mmol) in CH_3CN (1.8 mL), CCl_4 (1.8 mL) and H_2O (2.7 mL) was added $NaIO_4$ (612 mg, 2.87 mmol) followed by $RuCl_3 \cdot (H_2O)_3$ (10 mg, 2 mol %). This mixture was stirred vigorously at 25°C for 1h. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous phase was washed with CH_2Cl_2 (3x20mL) and the combined organic extracts were filtered through a cotton plus and concentrated to give 167 mg of crude 153. Purification of 153 was accompl by flash chromatography (SiO_2, 20x170 mm, Et_2O, hexane, H_2CO_2 (1:1:1%) R_f .6) to give 138 mg (66%) of pure <u>153</u>: NMR (^1H, 60 MHz, $CDCl_3$) δ 3.7 (t, J=6 Hz, 2 H, H_4), 2.4 (t, J=7 Hz, 2 H, H_2), 2.1-1.7 (m, 2 H, H_3), 0.90 (s, 9 H, tBu), 0.1 (s, 6 H, TBDMS); IR (CH_2Cl_2) 2920, 2800, 1710 cm^{-1}; Anal. Calcd for $C_{10}H_{22}SiO_3$: C, 45.09; H, 8.32. Found:



Method A:

To a solution of 153 (27 mg, 0.123 mmol) in THF (0.20 mL) was added triethyl amine (28 mg, 0.24 mmol), followed by pivaloyl chloride (16.5 mg, 0.137 mmol). This mixture was maintained at under nitrogen for 1.5 h. To this mixture was added a solution of verrucarol 8 (30 mg, 0.112 mmol) in THF (0.40 mL) and pyridine (128 mg, 1.62 mmol). The resulting mixture was maintained at 25°C under nitrogen for 76 h, concentrated *in vacuo* from heptane (2 x 15 mL) and purified by prep plate chromatography (SiO_2, 0.25 mm, Et_2O, CH_2Cl_2, 1:1, R_f .5) to afford 28 mg (56%) of pure 155.

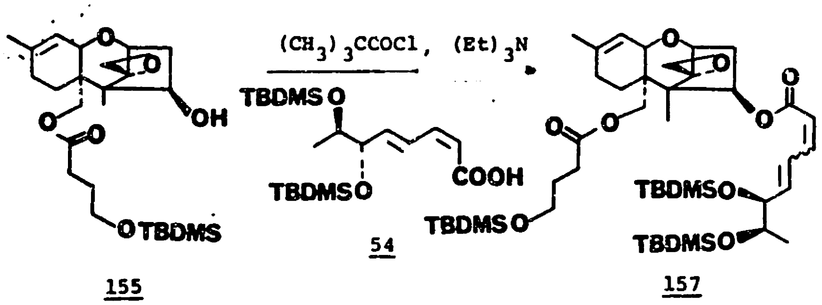
Method B:



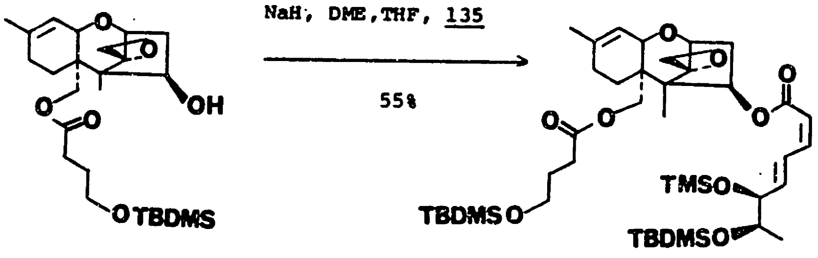
155

A solution of dicyclohexylcarbodiimide (DCC) (19 mg, 0.092 mmol) and 4-pyrrolidinopyridine (3 crystals) in CH_2Cl_2 (0.150 mL) was added to a solution of verrucarol 8 (12.3 mg, .46 mmol) and carboxylic acid 153 (12.1 mg, 0.054 mmol) in

CH_2Cl_2 (0.125 mL) and maintained at 25°C, under N_2, for 4.5 h. This mixture was filtered, the solids washed with CH_2Cl_2 (2 x 10 mL). The combined filtrate and washes were concentrated <u>in</u> <u>vacuo</u> and purified by prep plate chromatography (SiO_2, 0.25 mm, Et_2O, CH_2Cl_2, 1:1, R_f 0.5) to afford 15.2 mg (70%) of pure <u>155</u>: m.p. 83-84°C; $[\alpha]_D^{21}$ + 31.3° C (C = 1.12, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.42-5.35 (m, 1 H, H_{10}), 4.50-4.40 (m, 1 H, H_4), 4.12 (A of AB, J=11 Hz, 1H, H_{15a}), 3.88 (B of AB, J=11 Hz, 1 H, H_{15b}), 3.81 (d, J=5 Hz, 1 H, H_2), 3.65-3.55 (m, 3 H, $H_{4'}$, H_{11}), 3.10 (d, J=4 Hz, 1 H, H_{13a}), 2.79 (d, J=4 Hz, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$), 2.39 (t, J=8 Hz, 2 H, H_2), 2.01-1.71 (m, 8 H, H_7, H_8, $H_{3\beta}$, H_3', -OH), 1.70 (s, 3 H, H_{16}), 0.85 (s, 9 H, TBDMS), 0.81 (s, 3 H, H_{14}), 0.03 (s, 6 H, TBDMS); IR (CH_2Cl_2) 3680, 2960, 2880, 1735 cm^{-1}; mass spectrum m/e 466 (M^+).



To a solution of <u>54</u> (4.4 mg, 0.011 mmol) in CH_2Cl_2 (0.2 mL), under an atmosphere of N_2, was added triethylamine (2.8 mg, 0.027 mmol) followed by pivaloyl chloride (1.6 mg, 0.0132 mmol). This mixture was maintained at -25°C for 45 min and a solution of <u>155</u> (5.1 mg, 0.011 mmol) in CH_2Cl_2 (0.5 mL) containing several crystals of 4-dimethylaminopyridine (4-DMAP). After 20h the mixture was concentrated <u>in vacuo</u> and purified by prep plate chromatography (SiO_2, 0.25 mm, CH_2Cl_2, Et_2O, 1:1, R_f .6) to give exclusively (E,E)-<u>157</u> (contaminated with (E,E)-isomer of <u>54</u>) along with recovered <u>155</u> (3 mg, 60%). Data for (E,E)-<u>31</u>: NMR (^1H, 250 MHz, $CDCl_3$) δ 7.30 (dd, J=16 Hz, 11 Hz, 1 H, $H_{8'}$), 6.45 (dd, J=16 Hz, 11 Hz, 1 H, $H_{9'}$), 6.20-6.10 (m, 2 H, $H_{7'}$, H_4), 5.96 (d, J=16 Hz, 1 H, $H_{10'}$), 5.52-5.45 (m, 1 H, H_{10}), 3.12 (d, J=4 Hz, 1 H, H_{13a}), 2.81 (d, J=4 Hz, 1 H, H_{13b}), 2.48 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$), 1.71 (s, 3 H, H_{16}), 1.50 (d, J=7 Hz, 3 H, $H_{14'}$), 0.81 (s, 3 H, H_{14}).

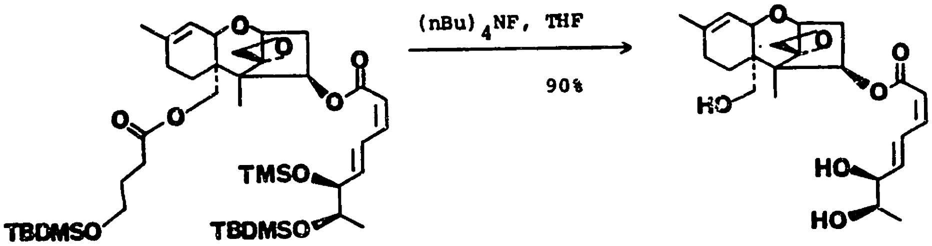


155

157 b

To a solution of NaH (7.7 mg, 0.321 mmol, oil free) in DME (0.5 mL) was added a solution of <u>155</u> (25 mg, 0.054 mmol) in DME (1.5 mL). This mixture was stirred at 25°C for 30 min and a solution of <u>135</u> (48 mg, 0.018 mmol) in DME (1 mL) was added. The resulting mixture was maintained at 25°C for 1.5 h, filtered through a bed of Florisil^R and concentrated <u>in vacuo</u> to afford crude <u>157b</u> (59 mg) which was purified by flash chromatography (SiO_2, Et_2O, hexane 1:1, R_f .40) to yield 24 mg (55%) of pure <u>157b</u>: $[\alpha]_D^{21}$ -3.25° (C = 1.20, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.49 (J=15 Hz, 11 Hz, 1 H, $H_{8'}$), 6.55 (t, J=11 Hz, 1 H, $H_{9'}$), 6.05 (dd, J=15 Hz, 7 Hz, 1 H, $H_{7'}$), 5.70-5.65 (m, 1 H, H_4), 5.65 (d, J=11 Hz, 1 H, $H_{10'}$), 5.46-5.40 (m, 1 H, H_{10}), 4.18 (A of AB, J=12 Hz, 1 H, H_{15a}), 4.05 (B of AB, J=12 Hz, 1 H, H_{15b}), 3.98 (t, J=7 Hz, 1 H, $H_{6'}$), 3.81 (d, J=5 Hz, 1 H, H_2), 3.75-3.60 (m, 4 H, H_{11}, $H_{4'}$, $H_{13'}$), 3.12 (d, J=4 Hz, 1 H, H_{13a}), 2.81 (d, J=4 Hz, 1 H, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H_{3d}), 2.39 (t, J=8 Hz, 1 H, $H_{2'}$), 2.05-1.60 (m, 7 H, H_7, H_8,

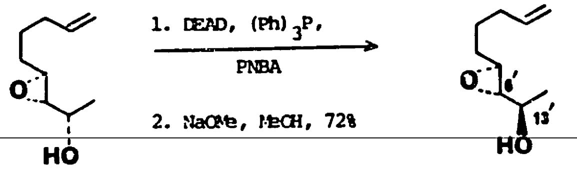
$H_{3'}$, $H_{3\beta}$), -.70 (s, 3 H, H_{16}), 1.12 (d, J=7 Hz, 3 H, $H_{14'}$), 0.85 (s, 18 H, TBDMS), 0.81 (s, 3 H, H_{14}), 0.15-0.0 (m, 21 H, -SiMe); IR (CH_2Cl_2) 2950, 2930, 2860, 1730, 1710 (shoulder), 1640, 1600 cm^{-1}; UV (MeOH) 262 nm (ε = 21,000) (Taken of <u>157b</u>); mass spectrum m/e 618 (M-188; -TMS, -TBDMS).



31

157

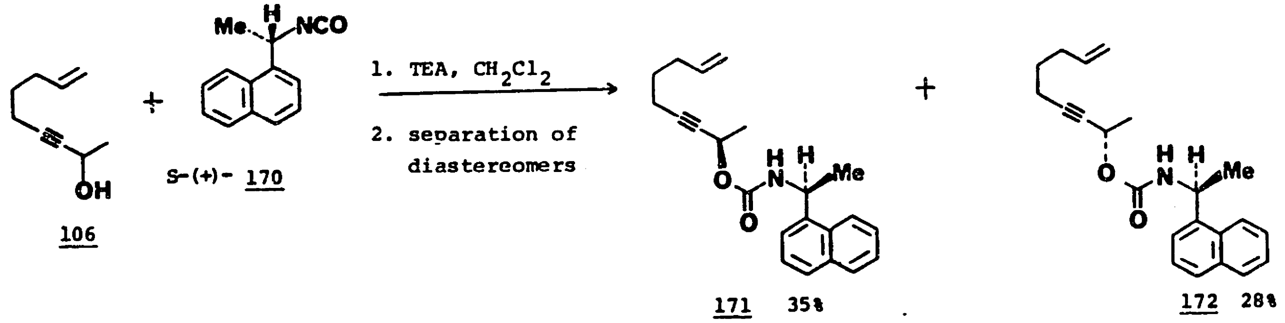
To a solution of <u>157b</u> (20 mg, 0.24 mmol) in THF (2 mL) was added $(nBu)_4F$ (0.119 mmol, 5 equiv). The resulting yellow solution was maintained at 25°C, under N_2, for 10 min, and quenched with sat. $NH_4^+Cl^-$ (2 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 x 20 mL). The combined organic extracts were diluted with CH_2Cl_2 (10 mL), filtered through a plug of cotton and concentrated <u>in vacuo</u> to leave 17 mg of a yellow oil. Pure <u>31</u> (9.1 mg, 90%) was obtained by flash column chromatography (SiO_2, 10 x 135 mm EtOAc (100%). R_f .25) which proved to be identical in all respects to a sample of natural trichoverrol B supplied by Professor Bruce B. Jarvis: $[\alpha]_D^{21}$ - 9.3° (C = 0.27, $CHCl_3$) (natural); $[\alpha]_D^{21}$ - 8.7° (C = 0.25, $CHCl_3$) synthetic); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.57 (dd, J=16 Hz, 11 Hz, 1 H, $H_{8'}$), 6.61 (t, J=11 Hz, 1 H, $H_{9'}$), 6.18-6.08 (m, 2 H, H_4, $H_{7'}$), 5.80 (d, J=11 Hz, 1 H, $H_{10'}$), 5.50-5.55 (m, 1 H, H_{10}), 4.30-4.20 (m, 1 H, $H_{6'}$), 4.95-4.60 (m, 5 H, H_2, H_{11}, H_{15}), 3.15 (d, J=5 Hz, 1 H, H_{13a}), 2.81 (d, J=5 Hz, 1 H, H_{13b}), 2.70-2.45 (m, 3 H, 2(-OH), H_{3a}), 2.15-1.90 (3 H, H_8, OH), 1.70 (s, 3 H, H_{16}), 1.60-1.50 (m, 2 H, H_7), 1.23 (d, J-6 Hz, 3 H, $H_{14'}$), 0.80 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3600, 3650-3200, 3050, 2985, 2940, 2880, 1690, 1640, 1600 cm^{-1}; UV (MeOH) 260 nm, (ε = 41,000); mass spectrum m/e 402 (M-18).



(-) <u>123</u>   <u>162</u>

Triphenylphosphine (1.24 g, 5.43 mmol) and para-nitrobenzoic acid (907 mg, 5.43 mmol) were added to a solution of epoxyalcohol (565 mg, 3.62 mmol) dry toluene (10 mL). To this solution was added diethylazodicarboxylate (922 mg, 5.07 mmol) and mixture stirred, under nitrogen atmosphere, at ambient temperature. After 1.5 h, the solvent was removed <u>in vacuo</u> leaving a heterogeneous mixture of a yellow oil and a white solid. The crude product was purified by flash column chromatography (SiO_2, 40x190 mm, Et_2O, hexane, 1:1, R_f .60), [Applied the crude mixture to column in dichloromethane (5 ml)], affording 1.03 g (93%) of a clear oil of the PNBA ester: $[\alpha]_D^{21}$ -35.5° (C = 0.84, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.28 (A of AB, J=8 Hz, 2 H), 7.18 (B of AB, J=8 Hz, 2 H), 5.82-5.69 (m, 1 H, H_8), 5.05-4.90 (m, 3 H, H_9, H_2), 2.99-2.95 (m, 1 H), 2.91-2.87 (m, 1 H), 2.12-2.00 (m, 2 H, H_7), 1.70-1.50 (m, 4 H, H_5, H_6), 1.42 (d, J=7 Hz, 3 H, H_1); IR (CH_2Cl_2) 3060, 2940, 2860, 1725, 1640, 1600 cm^{-1}; mass spectrum m/e 155 (M-150, $-C_7H_4NO_3$).

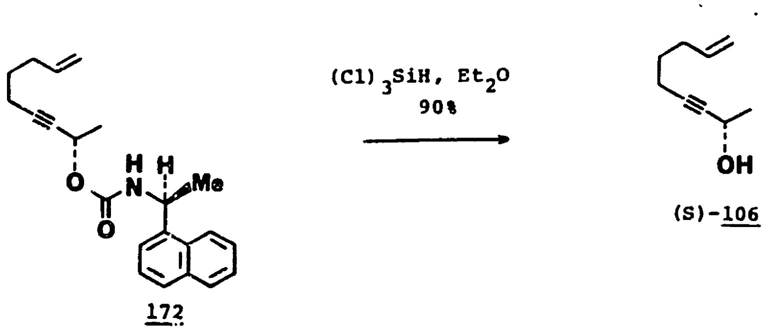
A solution of sodium methoxide in methanol (4 mL of a 0.4 <u>M</u> solution) was added to para-nitrobenzoate <u>162</u>. The resulting solution was stirred at ambient temperature. After 30 min several drops of 1M HCl was added to lower the pH to approximately 6. This mixture was partitioned between ether (30 mL) and 1/3 saturated aqueous NaCl solution. Phases were separated and the aqueous phase was extracted with ether (4x30 mL). The ether extracts were diluted with an equal volume of CH_2Cl_2 filtered through a cotton plug and concentrated in vacuo to afford an off-white solid. Crude product was purified by flash column chromatography (SiO_2, 40x200 mm, Et_2O, hexane, 1:1, R_f .20) to afford 416 mg (80%) of pure <u>162</u>: $[\alpha]_D^{21}$ = -12.2°(C =0.38, CH_2Cl_2); NMR (^1H 250 MHz, $CDCl_3$) δ 5.85-5.69 (m, 1 H, H_8), 5.03-4.92 (m, 2 H, H_9), 3.68-3.58 (m, 1 H, H_2), 2.88 (m, 1 H, H_4), 2.70 (dd, J=4.61, 2.49 Hz, 1 H, H_3), 2.18 (m, 2 H, H_7), 1.89 (d, J=5.39, 1 H, OH), 1.55 (m, 4 H, H_5, H_6), 1.25 (d, J=6.5, 3 H, H_1); IR (CH_2Cl_2) 3590, 3480, 3050, 2975, 2935, 2865, 1640 cm^{-1}; mass spectrum m/e 111 (M-45, CH_3COH); <u>Anal</u>. Calcd for $C_9H_{16}O_2$: C, 68.96; H, 10.52. Found: C, 68.80; H, 10.64.



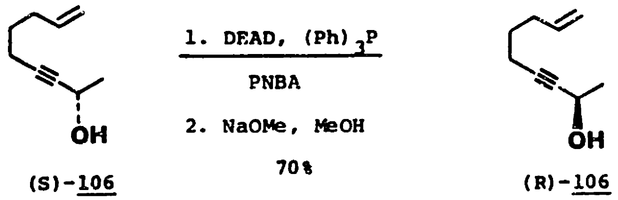
To a solution of 106 (2.56 g, 18.6 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (9.5 mL, 68.2 mmol) followed by isocyanate 170 (4.75 g, 24.1 mmol). This mixture was heated to reflux under N_2 for 17h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (100 mL). The aqueous phase was washed with CH_2Cl_2 (2x30 mL) and the combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to leave 5.5 g of a gray oil. Flash column chromatography (SiO_2, 40x200 mm, Et_2O, hexane, 1:4, R_f .25) afforded a mixture of pure diastereomers 171 and 172, 4.76 g (76%). These diastereomers were separated by repeated flash chromatography (SiO_2, 90x250 mm, Et_2O, hexane, 1:5) afforded 1.86 g (35%) of pure 171, (R_f 0.65, Et_2O, hexane, 1:5, 3 developments) and 1.74 g (32%) of pure 172, (R_f 0.55, Et_2O, hexane 1:5, 3 developments). 171: $[\alpha]_D^{21}$ + 47.1° (C = 1.13, CH_2Cl_2), NMR (^1H, 250 MHz, $CDCl_3$) δ 8.15 (d, J=8 Hz, 1 H), 7.85 (d, J=8 Hz, 1 H), 7.75 (d, J=8 Hz, 1 H), 7.60-7.50 (m, 4 H), 5.82-5.60 (m, 2 H,

H_8, H_2), 5.50-5.40 (m, 1 H), 5.20-5.10 (m, 1 H), 5.05-4.95 (m, 2 H, H_9), 2.25-2.05 (m, 4 H, H_5, H_7), 1.80-1.45 (m, 8 H, H_1, H_6, CH_3-); IR (CH_2Cl_2) 3660, 3430, 3040, 2850, 1710 cm^{-1}.

<u>172</u>: $[\alpha]_D^{21}$ - 40.9° (CH_2Cl_2, 1.4); NMR (^1H, 250 MHz, $CDCl_3$) δ 8.15 (d, J=8 Hz, 1 H), 7.85 (d, J=8 Hz, 1 H), 7.75 (d, J=8 H, 1 H), 7.60-7.50 (m, 4 H), 5.82-5.60 (m, 2 H, H_8, H_2), 5.50-5.40 (m, 1 H), 5.20-5.10 (m, 1 H), 5.05-4.95 (m, 2 H, H_9), 2.25-2.05 (m, 4 H, H_5, H_7), 1.80-1.45 (m, 8 H, H_1, H_6, CH_3-); IR (CH_2Cl_2) 3430, 3040, 2980, 2940, 1715 cm^{-1}.

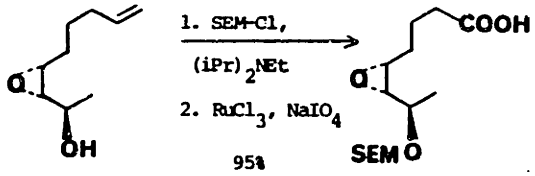


To a solution of 172 (1.74 g, 5.2 mmol) in Et_2O (150 mL) was added triethylamine (5.32 g, 52.6 mmol) and trichlorosilane (3.56 g, 26.3 mmol). The resulting white slurry was stirred at 25°C under a nitrogen atmosphere for 16h, cooled to 0°C and sat. $NH_4^+Cl^-$ was added slowly with vigorous stirring. The resulting solids were filtered, washed with Et_2O (4x50 mL), concentrated *in vacuo* (1.42 g) and chromatographed (SiO_2, 40x200 mm, Et_2O, hexane 1:1) to yield 640 mg (90%) of pure (S)-106: $[\alpha]_D^{21}$ - 19.7° (C = 1.31, CH_2Cl_2). (R)-106 was prepared by a completely analogous procedure $[\alpha]_D^{21}$ + 19.2° (C = .91, CH_2Cl_2).



To a solution of (S)-106 (203 mg, 1.47 mmol) in toluene (8 mL) was added triphenylphosphine (575 mg, 2.20 mmol) followed by para-nitrobenzoic acid (PNBA) (368 mg, 2.20 mmol) and diethylazodicarboxylate (DEAD) (376 mg, 2.05 mmol). This mixture was maintained under nitrogen at 25°C for 1h, concentrated in vacuo to yield crude product which was purified by flash chromatography (SiO_2, 30x230 mm, Et_2O, hexane, 2:1, R_f .55) to afford 378 mg (90%) of pure p-nitrobenzoate: $[\alpha]_D^{21}$ + 1.30 (C = 3.3, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 8.28 (A of AB, J=9 Hz, 1 H), 8.20 (B of AB, J=9 Hz, 1 H), 5.82-5.62 (m, 2 H, H_2,H_7), 5.04-4.92 (m, 2 H, H_9), 2.28-2.07 (m, 4 H, H_5, H_7), 1.65-1.55 (m, 5 H, H_1, H_6).

p-Nitrobenzoate (370 mg, 1.28 mmol) was dissolved in 0.4 M NaOMe, MeOH (3 mL) and stirred at 25°C for 20 min. This mixture was neutralized (ca pH 6) with 1N HCl, diluted with CH_2Cl_2 (10 mL), extracted with brine (10 mL) filtered through cotton and concentrated in vacuo to give a crystalline solid (methyl p-nitrobenzoate). This material was triturated with pentane (4x50 mL), concentrated in vacuo and purified by flash chromatography (SiO_2, 30x190 mm, Et_2O, hexane, 3:1, R_f 0.4) to give 125 mg (70% from (S)-<u>106</u>) of pure (R)-<u>106</u> (>95% ee, Mosher ester analysis).



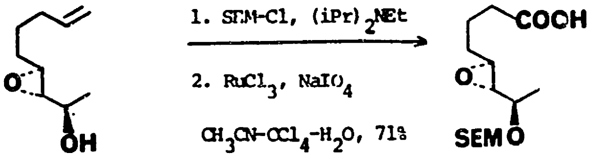
116

173

To a solution of 116 (414 mg, 2.65 mmol) in CH_2Cl_2 (15 mL) was added diisopropylethyl amine (1.7 g, 13.25 mmol) followed by SEM-Cl (885 mg, 5.30 mmol). This mixture was maintained at 25°C for 16h, then was diluted with CH_2Cl_2 (20 mL) and extracted with 1/3 saturated $NaHCO_3$ (2x10 mL). The combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to afford 1.0 g of crude product which was purified by flash column chromatography (SiO_2, 30x190 mm, Et_2O, hexane, 1:3, R_f .4) to yield 719 mg (95) of pure material: $[\alpha]_D^{21}$ + 43.3° (C = .66, CH_2Cl_2); NMR (^1H, 250 MHz, CDCl3) δ 5.85-5.70 (m, 1 H, H_8), 5.02-4.90 (m, 2 H, Hg), 4.87 (A of AB, J=7 Hz, 1H, $-OCH_2O-$), 4.71 (B of AB, J=7 Hz, 1 H, $-OCH_2O-$), 3.75-3.50 (m, 3 H, H_2, SEM), 2.91-2.85 (m, 2 H, H_3, H_4), 2.15-2.01 (m, 2 H, H_7), 1.70-1.30 (m, 4 H, H_5, H_6), 1.20 (d, J=6 Hz, 3 H, H_1), 0.92 (t, J=7 Hz, 2 H, SEM), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 3040, 2960, 1640 cm^{-1}; mass spectrum m/e 213 (M-73); Anal. Calcd for $C_{15}H_{30}SiO_3$: C, 62.88; H, 10.55. Found: C, 63.10; H, 10.84.

To a solution of this material (719 mg, 2.5 mmol) in CCl_4-CH_3CN-H_2O (5 mL, 5 mL, 7.5 mL) was added $NaIO_4$ (2.4 g, 11.3

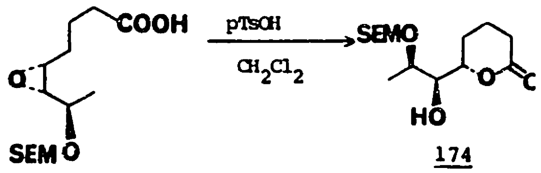
mmol) followed by 20 mg of $RuCl_3$. This heterogeneous mixture was stirred vigorously for 5h at 25°C, diluted with CH_2Cl_2, (20 mL) and extracted with water (10 mL). The aqueous phase was washed with CH_2Cl_2 (3x10 mL) and the combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to give 760 mg (98%) of acid 173 which also contained ca. 10% of hydroxylactone 174. This mixture was used without further purification: $[\alpha]_D^{21}$ + 28.6° (C = .44, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 10.1-9.5 (bs, 1 H, OH), 4.83 (A of AB, J=8 Hz, 1 H, $-OCH_2O-$), 4.79 (B of AB, J=8 Hz, 1 H, $-OCH_2O-$), 3.70-3.40 (m, 3 H, H_2, SEM), 2.95-2.85 (m, 2 H, H_3, H_4), 2.50-2.30 (m, 2 H, H_7), 1.90-1.30 (m, 4 H, H_5, H_6), 1.18 (d, J=7 Hz, 3 H, H_1), 0.90 (t, J=9 Hz, 2 H, SEM), -.04 (s, 9 H, SEM); IR (CH_2Cl_2) 3500-2500, 3040, 2960, 1710 cm^{-1}.



162 163

Carboxylic acid 163 was prepared in a manner completely analogous to that described for the preparation of 173 from 116: SEM ether, 95% after chromatography (SiO_2, Et_2O, hexane, 1:1, R_f .65); $[\alpha]_D^{21} = +11.2°$ (C = 1.2, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.85-5.68 (m, 1 H, H_8), 5.03-4.93 (m, 2 H, H_9), 4.77 (A of AB, J=13.7 Hz, 1 H, $-OCH_2O-$), 4.73 (B of AB, J=13.7 Hz, 1 H, $-OCH_2O-$), 3.71-3.49 (m, 3 H, H_2, SEM), 2.80-2.70 (m, 2 H, H_3, H_4), 2.15-2.03 (m, 2 H, H_7), 1.60-1.50 (m, 4 H, H_5, H_6), 1.22 (d, J=6.7 Hz, 3 H, H_1), 0.91 (t, J=8.6 Hz, 3 H, SEM), 0.0 (s, 9 H, TMS); IR (CH_2Cl_2) 3050, 2950, 2900, 1640 cm^{-1}; mass spectrum m/e 213 (M-73, TMS); Anal. Calcd for $C_{15}H_{30}SiO_3$: C, 62.88; H, 10.55. Found: C, 63.19; H, 10.79.

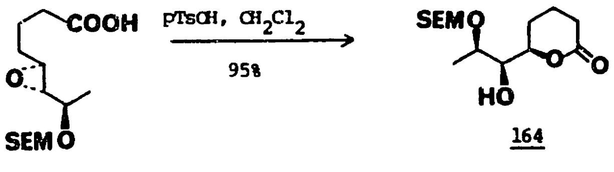
163: $[\alpha]_D^{21} = +15.0°$ (C = 1.13, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 4.79 (A of AB, J=6.8 Hz, 1 H, OCH_2O), 4.68 (B of AB, J=6.8 Hz, 1 H, OCH_2O), 3.70-3.40 (m, 3 H, H_2, SEM), 2.80-2.70 (m, 2 H, H_3, H_4), 2.39 (t, J=7.4 Hz, H_7), 1.80-1.48 (m, 4 H, H_5, H_6), 1.19 (d, J=5.97 Hz, 3 H, H_1), 0.90 (t, J=8.55 Hz, 2 H, SEM), -.02 (s, 9 H, SEM); IR (CH_2Cl_2) 3400-2500, 3050, 2975, 2900, 1713 cm^{-1}.



173

174

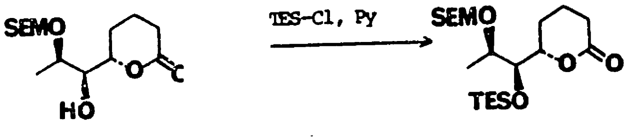
To a solution of 173 (760 mg, 2.5 mmol) in CH_2Cl_2 (12 mL) was added pTSOH (14 mg, 3 mol%). This mixture was stirred at 25°C for 3h, diluted with CH_2Cl_2 (20 mL), extracted with 1/3 saturated NaHCO3 (1 x 10 mL). The aqueous extract was washed with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to leave 617 mg (81%) of a dark green oil. In practice this material was used without further purification. Analytically pure 174 was obtained by preparative layer chromatography (SiO_2, .25 mm, Et_2O (100%), R_f .30): $[\alpha]_D^{21}$ - 28.1° (C = 1.05, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.71 (m, 2 H, $-OCH_2O-$), 5.30-5.40 (m, 1 H, H_5), 4.87 (quintet, J=7 Hz, 1 H, H_7), 3.70-3.35 (m, 4 H, H_6, -OH, SEM), 2.38-2.65 (m, 2 H, H_2), 2.05-1.75 (m, 4 H, H_3, H_4), 1.23 (d, J=7 Hz, 3 H, H_8), 0.92 (t, 8 Hz, 2 H, SEM), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 3680, 3580, 3400, 2960, 2890, 1735 cm^{-1}; mass spectrum m/e 289 (M-15); Anal. Calcd for $C_{14}H_{28}SiO_5$: C, 55.23; H, 9.27. Found: C, 54.99; H, 9.08.



163

164

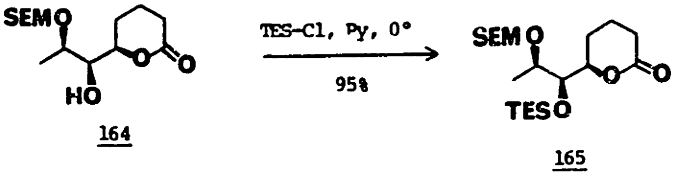
Hydroxylactone 164 was prepared (95%) by an analogous procedure for that described for the preparation of 174 from 173: R_f .30, Et_2O (100%); $[\alpha]_D^{21}$ - 41.01° (C = 4.93, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 4.70 (m, 2 H, $-OCH_2O-$), 4.31-4.20 (m, 1 H, H_5), 4.05-3.95 (m, 1 H, H_7), 3.62-3.55 (m, 2 H, SEM), 3.41-3.36 (m, 1 H, H_6), 2.75-2.34 (m, 3 H, H_2, -OH), 2.13-1.60 (m, 4 H, H_3, H_4), 1.23 (d, J=7 Hz, 3 H, H_1), 0.95-0.85 (m, 2 H, SEM), -.05 (s, 9 H, SEM); IR (CH_2Cl_2) 3700-3500, 3040, 2960, 1730 cm^{-1}; mass spectrum m/e 289 (M-15).



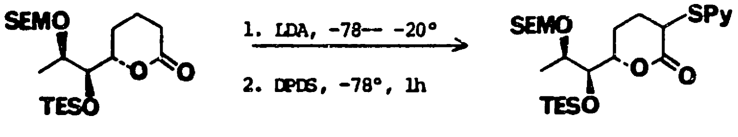
174

175

To a solution of 174 (617 mg, 2.03 mmol) in pyridine (5 mL) was added triethylsilyl chloride (TES-Cl), (612 mg, 4.06 mmol) which was maintained at 25° under an atmosphere of nitrogen for 2h. This mixture was diluted with CH_2Cl_2 (30 mL) and extracted with H_2O (20 mL). After the resulting emulsion separated (ca 10 min.) the phases were separated and the aqueous phase washed with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were filtered through a plug of cotton and concentrated *in vacuo*. The resulting green oil was concentrated from n-heptane (2 x 20 mL) to remove residual pyridine to leave 1.26 g of crude 175. This material was purified by flash chromatography (SiO_2, 40 x 190 mm, Et_2O, hexane, 2:1, R_f .55) to afford 630 mg (58% from 116) of pure 175: $[\alpha]_D^{21}$ + 9.7° (C = 1.52, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.70 (A of AB, J=7 Hz, 1 H, $-OCH_2O-$), 5.61 (B of AB, J=7 Hz), 5.41-5.32 (m, 1 H, H_5), 4.85-4.73 (m, 1 H, H_7), 4.61-4.52 (m, 3 H, H_6, SEM), 2.61-2.30 (m, 2 H, H_2), 2.00-2.59 (m, 4 H, H_3, H_4), 1.23 (d, J=7 Hz, 3 H, H_8), 1.00-0.05 (m, 11 H, TES, SEM), 0.70-0.51 (m, 6 H, TES), -0.1 (s, 9 H, SEM); IR (CH_2Cl_2) 2960, 2880, 1735 cm^{-1}; mass spectrum m/e 403 (M-15).



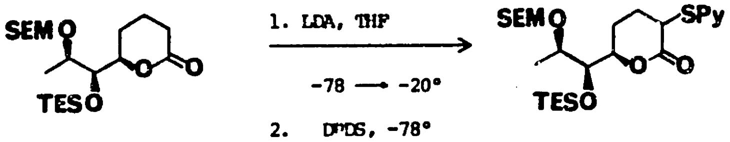
Diprotected lactone 165 was prepared (95%) by a procedure analogous to that described for the preparation of 175 from 174: R_f .45 (Et_2O, 100%). $[\alpha]_D^{21}$ + 26.4° (C = .44, CH_2Cl_2), NMR (^1H, 250, $CDCl_3$) δ 4.69-4.72 (m, 2 H, $-OCH_2O-$), 4.45-4.35 (m, 1 H, H_5), 3.87-3.49 (m, 4 H, H_6, H_7, SEM), 2.62-2.30 (m, 2 H, H_2), 2.00-1.75 (m, 4 H, H_3, H_4), 1.15 (d, J=7 Hz, 3 H, H_1), 1.00-.90 (m, 11 H, SEM, TES), 0.70-0.59 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 3050, 2960, 2880, 1730, cm^{-1}; mass spectrum m/e 361 (M-57); Anal. Calcd for $C_{20}H_{42}Si_2O_5$: C, 57.37; H, 10.11. Found: C, 57.64; H, 10.37.



175

176

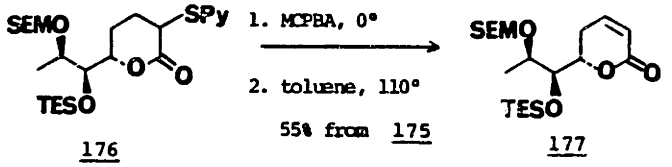
To solution of 175 (418 mg, 1.00 mmol) in THF (4 mL) at -78°C under an atmosphere of N_2 was added LDA (2.0 mmol, 0.65 M in THF prepared and titrated immediately before use). This mixture was maintained at -78°C for 10 min then warmed to -20°C for 1h. The resulting pale yellow solution was recooled to -78°C and a solution of 2,2'-dipyridyldisulfide (DPDS) (440 mg, 2.0 mmol) in THF (4 mL), precooled to -78°C, was added rapidly in one portion. This mixture was maintained at -78°C for 1h, quenched with 1 ml of sat. $NH_4^+Cl^-$, warmed to ambient temperature, diluted with CH_2Cl_2 (10 mL) and washed with water (10 mL). The aqueous phase was washed with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts filtered through a cotton plug and concentrated *in vacuo* to leave 970 mg of a yellow oil which consisted of ca. 80% 176 as a mixture of diastereomers and 20% of 175. This material was used without purification.



165

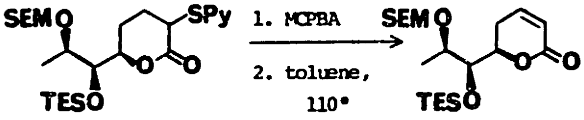
166

Lactone 166 was prepared by a procedure analogous to that described for the preparation of 176 from 175, to afford 30% of 166 and 60% of recovered 165. These materials were separated by flash chromatography (SiO_2, Et_2O, hexane, 2:1, R_f 0.8 (sulfide diastereomers), R_f 0.7 (165).



To a cold (0°C) solution of crude 176 (1.00 mmol, theory) in CH_2Cl_2 (6 mL) was added a solution of MCPBA (88% titrated) (396 mg, 2.0 mmol) in CH_2Cl_2 (6 mL). This mixture was maintained at 0°C for 1h, diluted with CH_2Cl_2 (20 mL) and extracted with 1/3 saturated $NaHCO_3$ (10 mL x 2). The combined organic extracts were filtered through cotton, concentrated *in vacuo* (905 mg) and purified by flash chromatography (SiO_2, 30x200 mm, Et_2O, (100%), R_f .40) to afford 340 mg of the corresponding diastereomeric sulfoxides and 31 mg of unsubstituted lactone 175. Data for diastereomeric sulfoxides: NMR (^1H, 250 MHz, $CDCl_3$) δ 8.65-8.55 (m, 1 H, α-py), 8.00-7.90 (m, 2 H, β-py), 7.40-7.30 (m, 1 H, γ-py), 4.80-4.70, 2 H, SEM, appears as doubled AB pattern), 4.55-4.20 (m, 1 H, H_5), 4.25-4.18 (m, 1 H), 3.80-3.70 (m, 1 H), 3.65-3.40 (m, 3 H), 2.8-1.3 (m, 4 H, H_3, H_4), 1.28-1.18 (m, 3 H, H_8), 1.00-1.85 (m, 11 H, SEM, TES), 0.70-0.55 (m, 6 H, TES), 0.01--0.01 (m, 9 H, SEM).

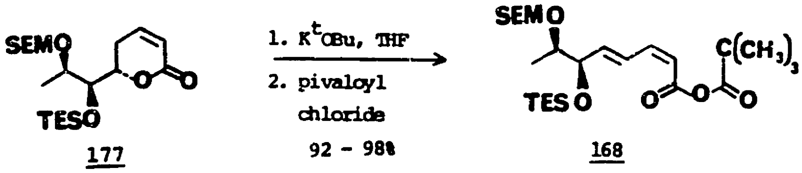
A solution of this sulfoxide material (335 mg, 0.62 mmol) in dry toluene (5 mL) was heated to reflux for 2 h and the solvent concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 30x200 mm, Et_2O (100%), R_f .80) to give 228 mg (89%, 75% from 173) of pure 177: $[\alpha]_D^{21}$ -64.61° (C = 1.17, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 6.80-6.70 (m, 1 H, H_3), 5.97 (bd, J=10 Hz, 1 H, H_2), 4.71 (A of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4.65 (B of AB, J=7 Hz, 1 H, $-OCH_2O-$), 4,52-4.45 (m, 1 H, H_5), 4.83 (quintet, J=6 Hz, 1 H, H_7), 4.73-4.67 (m, 1 H, H_6), 4.58 (t, J=9 Hz, 2 H, SEM), 2.50-2.40 (m, 2 H, H_4), 1.24 (d, J=6 Hz, 3 H, H_8), 1.00-0.85 (m, 11 H, TES, SEM), 1.75-1.60 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 2970, 2880, 1720 cm^{-1}; UV (EtOH) 205 nm (ε = 4,100); mass spectrum m/e 401 (M-15); Anal. Calcd for $C_{20}H_{40}Si_2O_5$: C, 57.65; H, 9.67. Found: C, 56.95; H, 10.21.



166 26% from 165 167

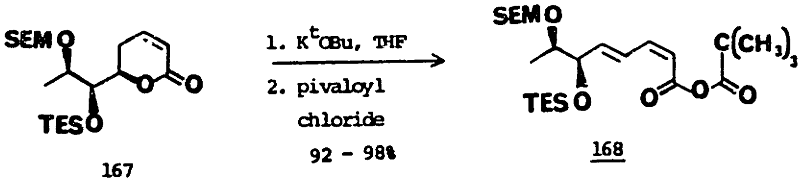
Enone 167 was prepared (77%) by a procedure analogous to that described for the preparation of 177 from 176.

167: R_f .67, Et_2O (100%); $[\alpha]_D^{21}$ + 67.8° (C = .45, CH_2Cl_2); NMR (^1H, 250 MHz, CDCl3) δ 6.91-6.83 (m, 1 H, H_3), 5.96 (dd, J=10 Hz, 3 Hz, 1 H, H_2), 4.71-4.69 (m, 2 H, $-OCH_2O-$), 4.60-4.50 (m, 1 H, H_5), 3.97-3.91 (m, 1 H, H_6), 3.80-3.50 (m, 3 H, H_7, SEM), 2.80-2.65 (m, 1 H, H_{4a}), 2.37-2.20 (m, 1 H, H_{4b}), 1.15 (d, J=7 Hz, 3 H, H_8), 1.00-0.87 (m, 11 H, TES, SEM), 0.70-0.60 (m, 6 H, TES), 0.0 (s, 9 H), SEM); IR (CH_2Cl_2) 3050, 2960, 2880, 1720 cm^{-1}; UV (EtOH) 208 nm (ε = 4,200); mass spectrum m/e 359 (M-57).



To a solution of 177 (23 mg,0.05 mmol) in THF (0.2 mL) at 0°C was added a solution of KtOBu (7.8 mg, 0.07 mmol) in THF (0.5 mL) which was maintained at 0°C, under N_2 for 45 min. To this yellow solution was added pivaloyl chloride (8.4 mg, 0.70 mmol), the resulting mixture maintained at 0°C under N_2 for 30 min and filtered through a bed of Florisil^R under an atmosphere of N_2. The filter cake was washed with Et_2O (100%) (3 x 10 mL) and concentrated *in vacuo* to give 27 mg (98%) of 168. This material was used without further purification: $[\alpha]_D^{21}$ + 53.7° (C = 0.8, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.52 (dd, J=15 Hz, 11 Hz, 1 H, H_4), 6.73 (t, J=11 Hz, 1 H, H_3), 6.22 (dd, J=15 Hz, 6 Hz, 1 H, H_5), 5.61 (d, J=11 Hz, 1 H, H_2), 4.70 (s, 2 H, $-OCH_2O-$), 4.32 (t, J=6 Hz, 1 H, H_6), 3.72 (dq, J=6 Hz, 1 H, H_7), 3.60-3.50 (m, 2 H, SEM), 1.23 (s, 9 H, t-Bu), 1.08 (d, J=6 Hz, 3 H, H_8), 0.90-0.85 (m, 11 H, TES, SEM), 0.70-0.65 (m, 6 H, TES), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 2950, 2880, 1795, 1725, 1635, 1590 cm^{-1}; mass spectrum m/e 428 (M-72).

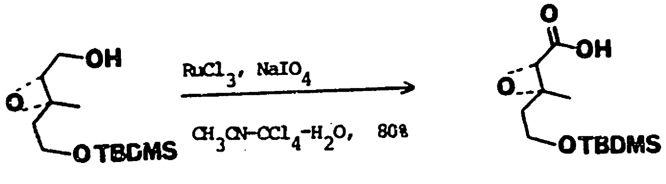
194 (diene acid): NMR (^1H, 250 MHz, $CDCl_3$) δ 7.55 (dd, J=16 Hz, 10 Hz, 1 H, H_4), 6.69 (t, J=10 Hz, 1 H, H_3), 6.15 (dd, J=16 Hz, 6 Hz, 1 H, H_5), 5.66 (d, J=10 Hz, 1 H, H_2), 4.70 (s, 2 H, $-OCH_2O-$), 4.32 (t, J=6 Hz, 1 H, H_6), 3.72 (dq, J=6 Hz, 1 H, H_7), 3.65-3.58 (m, 2 H, SEM), 1.08 (d, J=6 Hz, 3 H, H_8), 1.00-0.8 (m, 11 H, SEM, TES), 0.68-0.50 (m, 6 H, TES), 0.0 (s, 9 H, SEM); UV (EtOH 262 nm (ε = 12,800); mass spectrum m/e 372 (M-44); Anal. Calcd for $C_{20}H_{40}O_5Si_2$; C, 57.65; H, 9.67. Found: C, 57.80; H, 9.41.



167

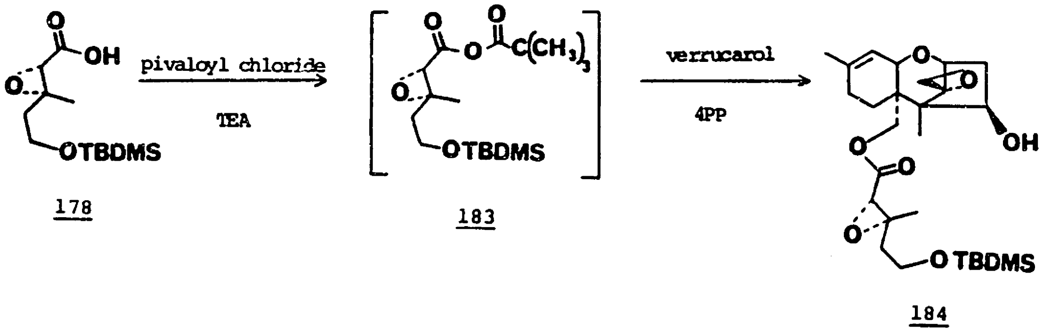
168

Mixed anhydride was prepared by the identical procedure described for the conversion of <u>177</u> to <u>168</u> (95%).



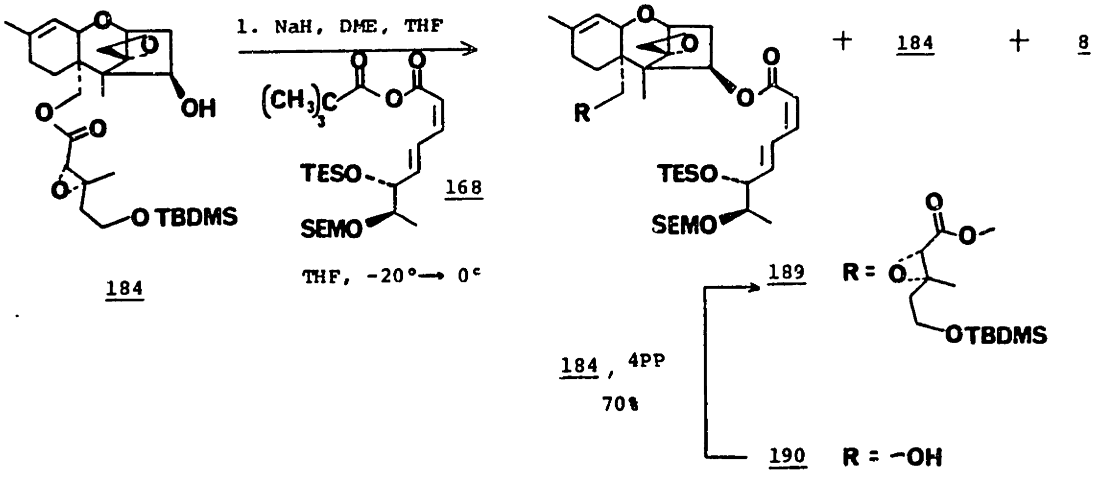
182 178

A solution of 182[41a] (46 mg, .186 mmol) in CCl_4 (.37 mL), CH_3CN (.37 ml) and H_2O (.56 mL) containing $NaIO_4$ (137 mg, .65 mmol) and $RuCl_3$ (1 mg, 2 mol%) was stirred vigorously at 25°C for 4h diluted with CH_2Cl_2 (10 mL) and the phases separated. The organic phase was filtered through a cotton plug and concentrated to afford 37 mg (76%) of crude 178: $[\alpha]_D^{21}$ + 14.4° (c .84, $CHCl_3$); NMR (^1H 250 MHz, $CDCl_3$) δ 3.74 (t, J=6 Hz, 2 H, $H_{5'}$), 3.53 (s, 1 H, $H_{2'}$), 1.98 (dt, J=14 Hz, 6 Hz, 1 H, $H_{4'a}$), 1.74 (dt, J=14 Hz, 6 Hz, 1 H, $H_{4'b}$); IR (film) 3600-2500, 2956, 2928, 2858, 1752, 1732 cm^{-1}.



To a solution of 178 (138 mg, 0.531 mmol) in CH_2Cl_2 (1.5 mL) was added triethylamine (124 mg, 1.22 mmol) followed by pivaloyl chloride (74 mg, 0.612 mmol). The resulting mixture was maintained, under a N_2 atmosphere, at 25°C for 1.5 h and verrucarol 8 (103 mg, 0.387 mmol) was added as a solution in CH_2Cl_2 (3 mL) containing 4-pyrrolidinopyridine (6 mg, 0.04 mmol). This mixture was kept at 25°C under N_2 for 2 h, concentrated *in vacuo* and purified by flash chromatography (SiO_2, 30 x 160 mm, Et_2O, CH_2Cl_2 1:1, R_f 0.20) to afford 116 mg (59%) of pure 184, in addition 17 mg of verrucarol (R_f 0.1), 17 mg of diester (R_f 0.6) and 12 mg of C(4) monoester (R_f 0.4) were recovered. Data for 184: mp 93-94°C; $[\alpha]_D^{21}$ -29.8° (C = 1.29, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 5.45-5.35 (m, 1 H, H_{10}), 4.50-4.40 (m, 1 H, H_4), 4.22 (A of AB, J=13 Hz, 1 H, H_{15a}), 4.00 (B of AB, J=13 Hz, 1 H, H_{15b}), 3.81 (d, J=5 Hz, 1 H, H_2), 3.69 (t, J=5 Hz, 2 H, $H_{5'}$), 3.56 (bd, J=5 Hz, 1 H, H_{11}), 3.48 (s, 1 H, $H_{2'}$), 3.10 (d, J=4 Hz, 1 H,

H_{13a}), 2.78 (d, J=4 Hz, 1 H, H_{13b}), 2.57 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$), 2.02-1.72 (m, 7 H, $H_{4'}$, H_7, H_8, $H_{3\beta}$), 1.70 (s, 3 H, H_{16}), 1.38 (s, 3 H, $H_{12'}$), 1.20 (d, J=7 Hz, $H_{14'}$), 0.85 (s, 9 H, TBDMS), 0.81 (s, 3 H, H_{14}), 0.03 (s, 6 H, TBDMS); IR (CH_2Cl_2) 3580, 2940, 2860, 1750 cm^{-1}; mass spectrum m/e 508 (M^+); Anal. Calcd for $C_{27}H_{44}SiO_4$: C, 63.74; H, 8.72. Found: C, 63.53; H, 8.76.



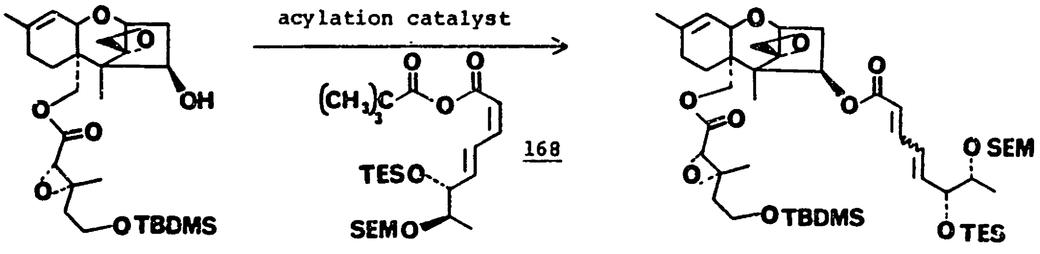
A solution of 184 (5 mg, 0.009 mmol, concentrated from toluene 2 x before use) and 168 (9 mg , 0.02 mmol) in a DME, THF mixture (1:1, 0.5 mL) was added to a suspension of NaH (1.1 mg, 0.047 mmol) in DME (0.2 mL) at -20°C under an atmosphere of N_2. This mixture was maintained at -20°C under N_2 for 30 min, warmed to 0°C for 12 hr, neutralized with AcOH, THF, H_2O (3:1:1) (0.02mL), and concentrated *in vacuo* from heptane yielding crude 189 which was purified by prep plate chromatography (SiO_2, 0.25 mm, Et_2O, hexane, 2:1, R_f .45) to afford 0.9 mg (ca. 10%) of pure 189 along with 1.1 mg (20%) of 190 and 1 mg (20%) of recovered 184 and unreclaimed verrucarol 8. 189: $[\alpha]_D^{21}$ + 32.8° (C = 1.0, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.50 (dd, J=15 Hz, 11 Hz, 1 H, H_8'), 6.57 (t, J=11 Hz, 1 H, H_9'), 6.05 (dd, J=15 Hz, 7 Hz, 1 H, H_7'), 5.65 (d, J=11 Hz, 1 H, H_{10}'), 5.75-5.68 (m, 1 H, H_4), 5.45-5.40 (m, 1 H, H_{10}), 4.75-4.68 (m, 2 H, SEM), 4.31-4.13 (m, 3 H, H_6'), H 15), 3.81 (d, J=5Hz, 1 H, H_2), 3.71-3.55 (m, 6 H, H_{13}', H_{11},

H_{5}', SEM), 3.50 (s, 1 H, H_{2}'), 3.13 (d, J=4 Hz, 1 H, H_{13a}), 2.80 (d, J=4 Hz, 1 H, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$, 2.08-1.70 (m, 7 H, H_{4}', H_{7}, H_{8}, $H_{3\beta}$), 1.70 (bs, 3 H, H_{16}), 1.37 (s, 3 H, H_{12}'), 1.09 (d, J=7 Hz, 3 H, H_{14}'), 1.00-0.85 (m, 20 H, SEM, TES, tBu), 0.81 (s, 3 H, H_{14}), 0.59 (q, J=8Hz, 6 H, TES), 0.05-0.00 (m, 18 H, TBDMS, SEM); IR (CH_2Cl_2) 2970, 2880, 1750, 1710, 1640, 1600 cm^{-1}, UV (EtOH) 262 nm (ε = 25,400), mass spectrum m/e 804 ($M-Me_3SiCHCH_2$), HRMS Calcd for $C_{47}H_{82}Si_3O_{11}$ m/e 906.516, Found m/e

<u>190</u>: NMR (^1H, 250 MHz, $CDCl_3$) δ 7.57 (dd, J=15 Hz, 11 Hz, H_{8}'), 6.60 (t, J=11 Hz, 1 H, H_{10}'), 6.20-6.02 (m, 2 H, H_{4}, H_{7}'), 5.69 (d, J=11 Hz, H_{10}'), 5.55-5.45 (m, 1 H, H_{10}), 4.71 (s, 2 H, SEM), 4.30 (t, J=6 Hz, 1 H, H_{6}'), 4.00 (d, J=5 Hz, 1 H, H_{2}), 3.81-3.05 (m, 9 H, H_{2}, H_{11}, H_{15}, H_{5}', H_{13}', SEM), 3.13 (d, J=4 Hz, 1 H, H_{13a}), 2.95 (bt, J=6 Hz, 1 H, -OH), 2.79 (d, J=4 Hz, 1 H, H_{13b}), 2.57 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$), 2.18-1.95 (m, 7 H, H_{4}', H_{7}, H_{8}, $H_{3\beta}$), 1.70 (bs, 3 H, H_{16}), 1.10 (d, J=7 Hz, 3 H, H_{14}'), 0.98-0.89 (m, 11 H, SEM, TES), 0.81 (s, 3 H, H_{14}), 0.61 (q, J=8 Hz, 6 H, TES), 0.00 (s, 9 H, SEM).

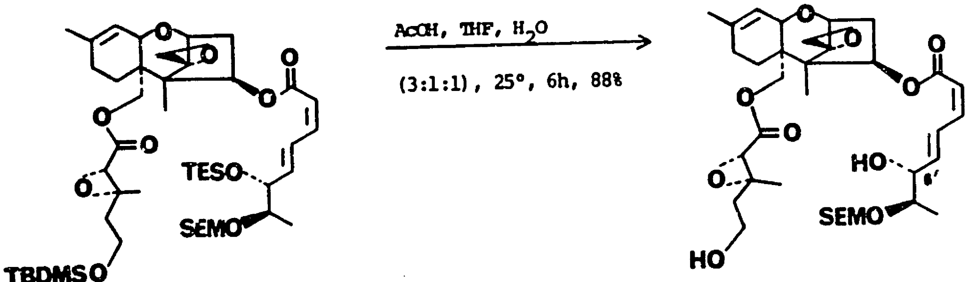
To a solution of acid <u>178</u> (3.5 mg, 0.013 mmol) in CH_2Cl_2 (0.05 mL) was added triethylamine (4.5 mg, 0.045 mmol) followed by pivaloyl chloride (2 mg, 0.015 mmol). The resulting mixture was maintained, under N_2, at 25°C for 1 h and <u>190</u> (2 mg, 0.003 mmol) was added as a solution in CH_2Cl_2 (0.2 mL) containing 0.2 mg of 4-pyrrolidinopyridine. At

22 h this mixture was concentrated *in vacuo* and purified by prep plate chromatography (SiO_2, 0.25 mm, Et_2O, hexane, 2:1, R_f .55) to afford 1.9 mg (70%) of pure **189**.



184 — 168 (CH_2Cl_2) — 139 (Z,E), 192 (E,E)

To a solution of 184 (32 mg, 0.063 mmol) in CH_2Cl_2 (0.8 mL) containing 4-pyrrolidinopyridine (0.52 mg, 5 mol %) was added a solution of 168 (35 mg, 0.07 mmol) in CH_2Cl_2 (1.0 mL) and maintained at 25°C under N_2. After 7 d the crude reaction mixture was concentrated *in vacuo* and purified by prep plate chromatography (SiO_2, 0.25 mm, Et_2O, hexane, 2:1, R_f 0.40) to afford 10 mg (17%) of a 3:1 mixture of 189: 192, respectively. These isomers could be separated by prep plate chromatography (SiO_2, 0.25 mm, EtOAc, hexane, 5:1, 5 developments, 189 R_f 0.55; 192 R_f 0.48) to afford 4 mg (7%) of 189 and 1 mg (1%) of 192. Also isolated from the first chromatography was 18 mg (50%) of 184. Data for 192: NMR (^1H, 250 MHz, $CDCl_3$) δ 7.28 (dd, J=15 Hz, 11 Hz), 6.40 (dd, J=15 Hz, 11 Hz, 1 H, $H_{9'}$), 6.20 (dd, J=15 Hz, 5 Hz, 1 H, $H_{8'}$), 5.88 (J=15 Hz, 1 H, $H_{10'}$), 5.75-5.65 (m, 1 H, H_4), 5.45-5.40 (m, 1 H, H_{10}), 4.70 (s, 2 H, SEM), 4.32 (bt, J=5 Hz, 1 H, $H_{6'}$), 4.28 (A of AB, J=12 Hz, 1 H, H_{15a}), 4.18 (B of AB, J=12 Hz, 1 H, H_{15b}), 3.83 (d, J=5 Hz, 1 H, H_2), 3.75-3.65 (m, 6 H, H_{11}, H_5', H_{13}', SEM) 3.50 (s, 1 H, H_2'), 3.33 (d, J=4 Hz, 1 H, H_{13a}), 2.81 (d, J=4 Hz, 1 H, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, $H_{3\alpha}$), 2.10-1.70 (m, 7 H, H_4', H_7, H_8, $H_{3\beta}$), 1.70 (bs, 3 H, H_{16}), 1.38 (s, 3 H, H_{12}'), 1.05 (d, J=6 Hz, 3 H, H_{14}'), 1.00-0.85 (m, 20 H, SEM, TES, TBDMS), 0.82 (s, 3 H, H_{14}), 0.60 (q, J=8 Hz, 6 H, TES), 0.05-0.00 (m, 18 H, TBDMS, SEM).



189

195

A solution of 189 (8 mg, 0.008 mmol) in a mixture of AcOH, THF, H_2O (3:1:1) (0.40 mL) was stirred at 25°C for 6 h and concentrated *in vacuo* from n-heptane (2 x 10 mL) to afford crude 195. This material was purified by prep plate chromatography (SiO_2, 0.25 mm, EtOAc (100%), R_f0.4) to afford 5.3 mg (88%) of pure 195: $[\alpha]_D^{21}$ + 32.4° (C = 0.53, CH_2Cl_2); NMR (^1H, 250 MHz, $CDCl_3$) δ 7.62 (dd, J=15 Hz, 11 Hz, 1 H, H_8'), 6.60 (t, J=11 Hz, 1 H, H_9'), 6.11-5.95 (m, 2 H, H_7', H_4), 5.68 (d, J=11 Hz, 1 H, H_{10}'), 5.50-5.40 (m, 1 H, H_{10}), 4.72 (s, 2 H, SEM), 4.32 (A of AB, J=13 Hz, H_{15a}), 4.18-4.09 (m, 2 H), 3.84 (d, J=4 Hz, 1 H, H_2), 4.80-4.40 (m, 7 H), 3.58 (s, 1 H, H_2'), 3.15 (d, J=4 Hz, 1 H, H_{13a}), 2.82 (d, J=4 Hz, 1 H, H_{13b}), 2.55 (dd, J=16 Hz, 8 Hz, 1 H, H_{3d}) 2.18-1.80 (m, 7 H, H_4', H_7, H_8, $H_{3\beta}$), 1.70 (bs, 3 H, H_{10}), 1.40 (s, 3 H, H_{12}'), 1.16 (d, J=7 Hz, 3 H, H_{14}'), 0.91 (t, J=8 Hz, 2 H, SEM), 0.81 (s, 3 H, H_{14}), 0.0 (s, 9 H, SEM); IR (CH_2Cl_2) 3680, 3600-3300, 2970, 2890, 1735, 1720 (shoulder), 1680, 1600 cm^{-1}; UV (EtOH)

262 nm (ε = 19,500); mass spectrum (sample did not volitilize).

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

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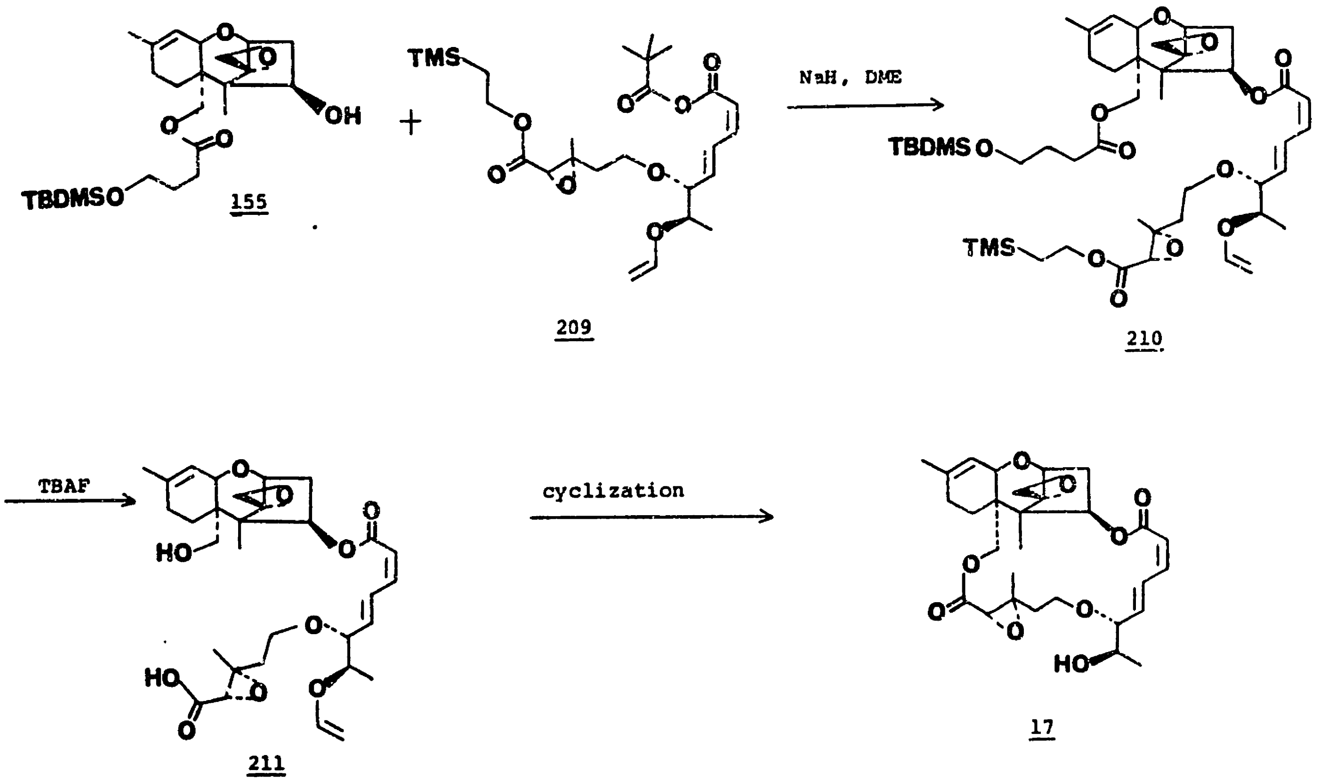

155 209 210 211 17

masking the C(15) acid fragment followed by lactonization and deprotection would yield the natural product.

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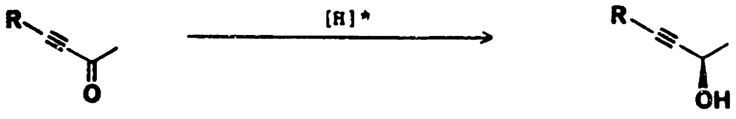

i   ii

R	Reagent	Optical Purity (ee)
n-C_4H_9	BINAL-H[60d]	84%
H	LiAlH$_4$, N-methylephedrine[60e]	79%
Ph	Midland Reagent[60f]	72%
tert-Butyl	Midland Reagent[60f]	73%

(b) Optically active (R)-2,2'-binapthol was purchased from Aldrich Chemical Co., $[\alpha]_D^{20}$ + 35.8° (C .87,THF), lit. $[\alpha]_D^{20}$ + 34.3 (C 1.0 THF)^{63c}; (c) Kyba, E.P.; Gokel, G.W.; de Jong, F.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Kaplan, L.; Soga, G.D.Y.; Cram, D.J. J. Org. Chem. 1977, 42, 4173.

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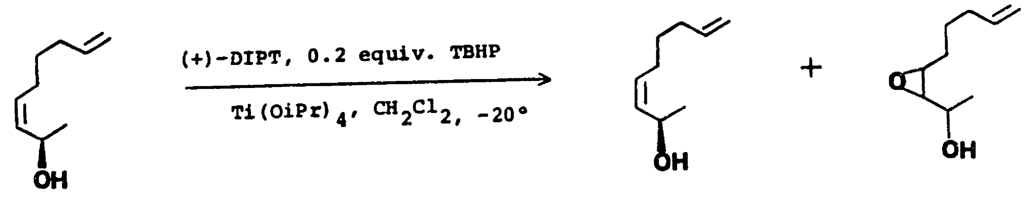

(+)-115
(64% ee)

(+)-115
(64% ee)
88%

protocol were not successful.^{59b}

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74. We observed that it was important that intermediate 157 be chromatographed prior to the deprotection step, otherwise, a significant amount of deacylation occurred.

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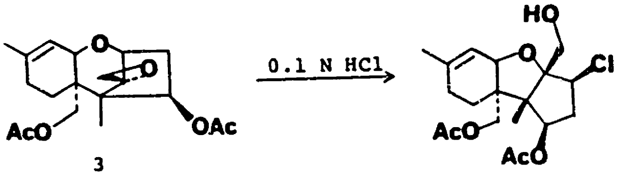
76. For example, the trichothecene nucleus rearranges to the apotrichothecene skeleton in 0.1N HCl. We suspect that



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15

a similar rearrangement would also occur with weak Lewis acids.

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85. In addition we found that this oxidation was sensitive to scale, with best results realized in small scale reactions (50 mg of 182 appears to be an optimum scale). Marked decrease in yield were obtained in larger scale experiments (e.g. a 200 mg scale reaction afforded 178 in only 30% yield). Similar results were observed by Blizzard, who used $KMnO_4$, 18-crown-6, in benzene ("purple benzene") for this oxidation.[41a]

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

87. In general, α-heterosubstituted esters are hydrolyzed much more readily than the corresponding unsubstituted ester. For an extensive review on the kinetics of ester hydrolysis and formation see: Kirby in "Comprehensive Chemical Kinetics", 1977, vol. 10, 57. American Elsevier, New York.

88. Identical results were obtained from a reaction in which the NaH was used from a can freshly opened under a N_2 atmosphere.

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

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