AN ABSTRACT OF THE THESIS OF

CURTIS LEE KIRKEMO for the degree of DOCTOR OF PHILOSOPHY

in CHEMISTRY presented on December 18, 1975

Title: APPROACHES TO THE SYNTHESIS OF POLYKETIDES. VERMICULINE.

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Abstract approved: _____
Dr. James D. White

An approach to the generation of polyketides was investigated, which involved ozonolysis of 6,7-cyclopenteno-1,4,5,8-tetrahydro-2-methoxy-3-methylnaphthalene (26), to produce what is believed to be polyketide 27. Compound 26 was formed by the following sequence: Diels-Alder addition of 1,2-dimethylenecyclopentane and 2-methoxy-3-methylbenzoquinone (29) afforded adduct 30 which was reduced with lithium aluminum hydride to diol 31, followed by dehydration with phosphorus oxychloride to 32 and subsequent lithium-ammonium reduction to produce 26.

The synthesis of vermiculine (63) was studied. Hagemann's ester was converted to alcohol 113 by the action of isopropenyl acetate and p-toluenesulfonic acid followed by reduction of the resulting mixture with sodium borohydride in aqueous dioxane. Reduction of 113 with lithium aluminum hydride produced diol 115 which was oxidized with manganese dioxide to aldehyde 117. Reaction of 117

with the anion of triethyl phosphonoacetate followed by acetylation of the resulting product (98) gave diester 99. Epoxidation of 99 with m-chloroperbenzoic acid yielded 105, which was hydrolyzed to diol 106 by the action of aqueous perchloric acid. The diol was cleaved with lead tetraacetate in pyridine and ethyl acetate to produce the protected vermiculinic acid 107. Ketalization of 107 with ethylene glycol followed by saponification of the esters yielded hydroxy acid 110. Attempts to cyclize 110 were unsuccessful. A route to the noncyclic dimer was developed starting from 98. Bromoacetylation of 98 followed by an Arbusov reaction with trimethylphosphite gave phosphonate 127, which was condensed with aldehyde 117 to afford dimer 128. Epoxidation of 128 with m-chloroperbenzoic acid followed by hydrolysis of the bisepoxide (129) with aqueous perchloric acid produced pentol 130. Lead tetraacetate cleavage of 130 gave the protected vermiculinic acid dimer (131).

Approaches to the Synthesis of Polyketides. Vermiculine.

by

Curtis Lee Kirkemo

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Typed by Clover Redfern for Curtis Lee Kirkemo

To my family and friends

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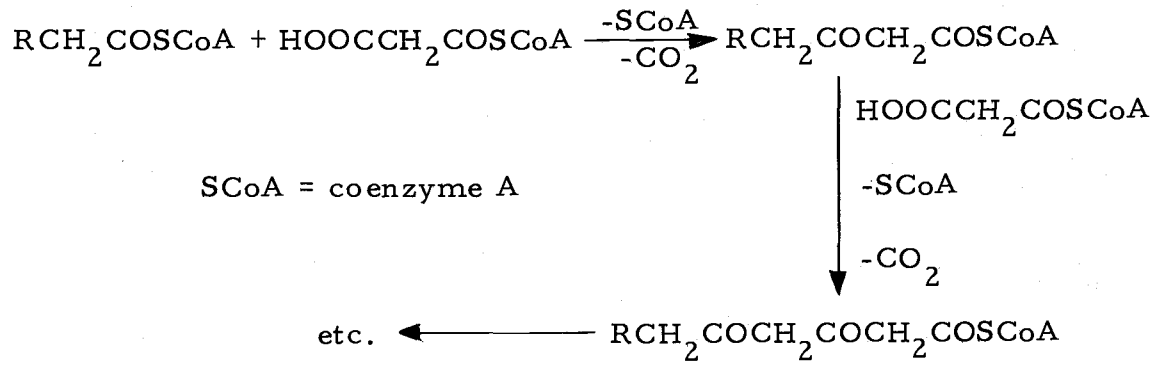
APPROACHES TO THE SYNTHESIS OF POLYKETIDES. VERMICULINE.

I. INTRODUCTION: β-POLYKETIDES

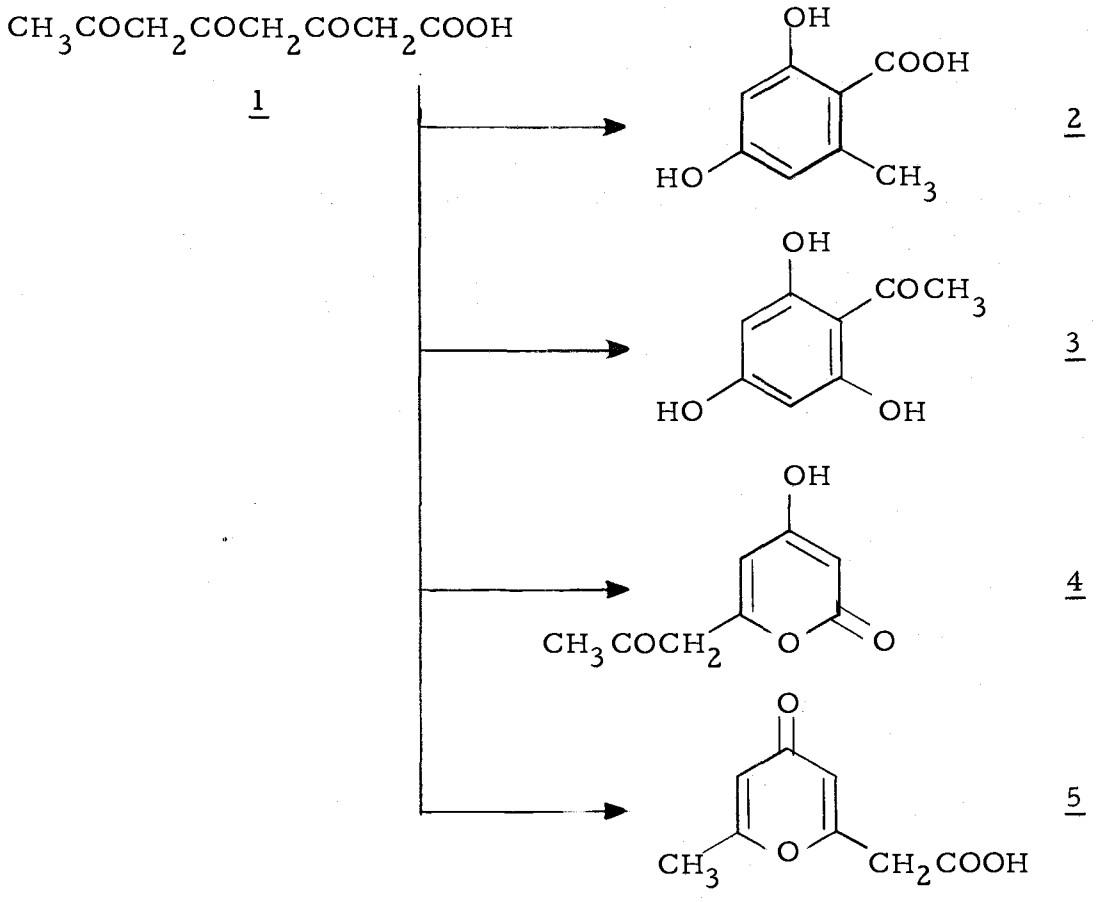
The polyacetate (acyl polymalonate) hypothesis has had great success over the last 20 years in explaining and predicting the biogenesis of naturally occurring, aromatic compounds, leading to its acceptance as a major biosynthetic pathway (1, 2). First proposed by J.N. Collie in 1907 (3), it remained little known until 1953, when A.J. Birch published the first of a series of papers in which he developed the theory (4). Robert Robinson was also an early worker in the field, and published an expanded version of Collie's hypothesis in 1955 (5).

The basic tenet of the polyacetate theory is that certain aromatic natural products are derived from chains of alternating methylene and carbonyl functions (polyketides). These are in turn produced by multiple condensations of enzyme-bound malonic acid, as shown below.



The polyketide chains are most probably enzyme-bound, and are of varying length up to 20 carbons (corresponding to ten "acetates"). The aromatic compounds are produced by a variety of condensation pathways, principally by intramolecular aldol and Claisen condensations of the polyketide. The cyclic intermediate so formed, then undergoes tautomeric shifts and/or dehydrations to give a condensed metabolite. A simple example would be the four modes of condensation possible for a polyketide chain composed of four acetate units as shown in Scheme 1.

Scheme 1.



Aldol condensation of 1 will ultimately yield orsellinic acid (2), while Claisen condensation will afford acetylphloroglucinol (3). Two other modes of cyclization will produce pyrones 4 and 5. Compounds 2, 3, and 4 are known metabolites, while 5 is found in nature only in decarboxylated form.

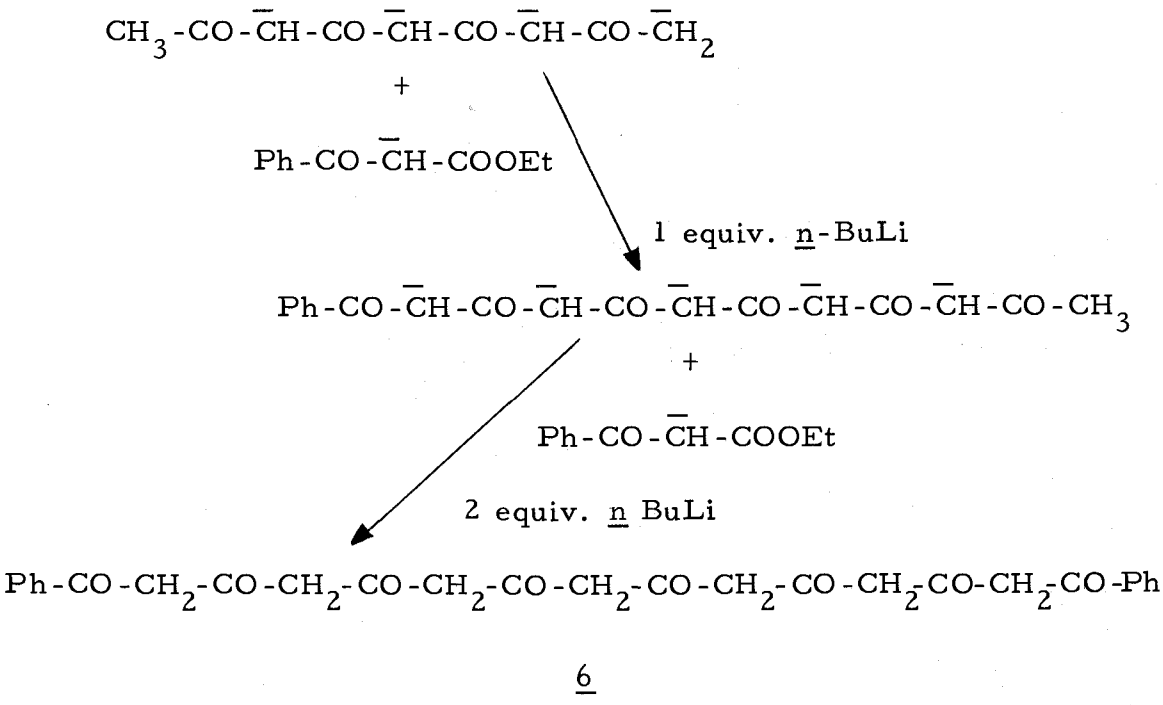
Verification of the polyacetate theory has been carried out using suitable precursors, synthesized with appropriate isotopic labels (generally carbon-14). These precursors have been fed to growing organisms, and the extent of incorporation measured, and the position of the labels in a large number of secondary metabolites compared to that predicted by theory (1). Experimental results have amply supported the theory, leading to its use in some cases to predict structures for newly discovered natural products (1, 2).

The synthesis of polyketides for continuing biosynthetic studies and as synthetic precursors to complex natural products is of great interest, and was the objective of this work. While many groups have worked toward this goal, the synthesis, characterization, and condensation of polyketide chains have proved to be extremely difficult. The principal synthetic problem lies in the increasing reactivity and consequent instability of polyketides as the number of "acetate units" increases.

Thus far, T. M. Harris and his co-workers (6) have enjoyed the most success in polyketide synthesis. Their approach is based on the

observed fact that, when the polyanion of a β-polyketo system is generated, the terminal position is the most nucleophilic and reacts selectively with alkylating agents, acylating agents, or carbon dioxide. Using this fact, they have succeeded in preparing polyketides and polyketoacids with as many as eight ketone units. The synthesis of the octaketone 6 shown in Scheme 2 demonstrates their approach (7).

Scheme 2.



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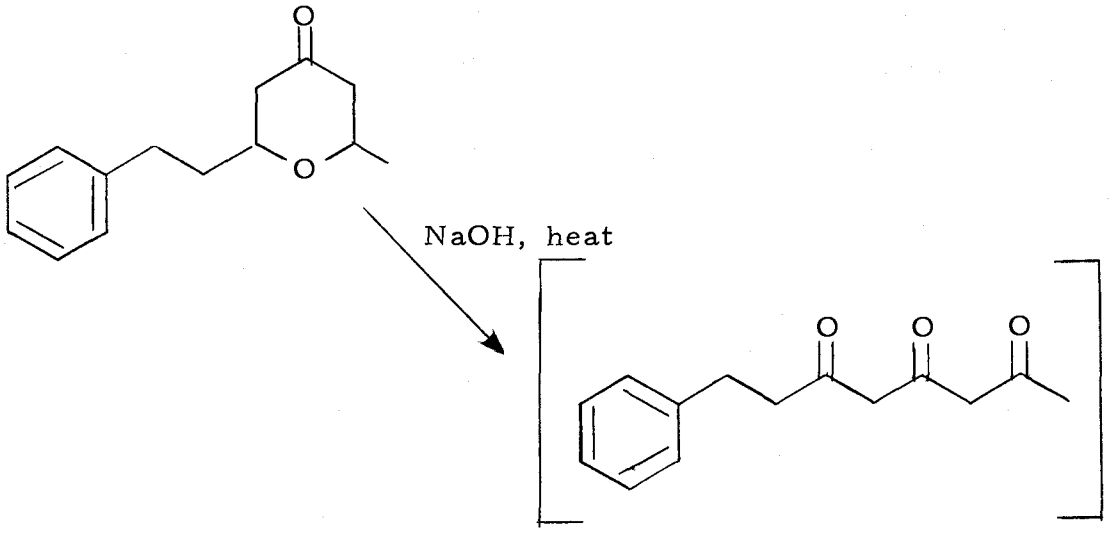
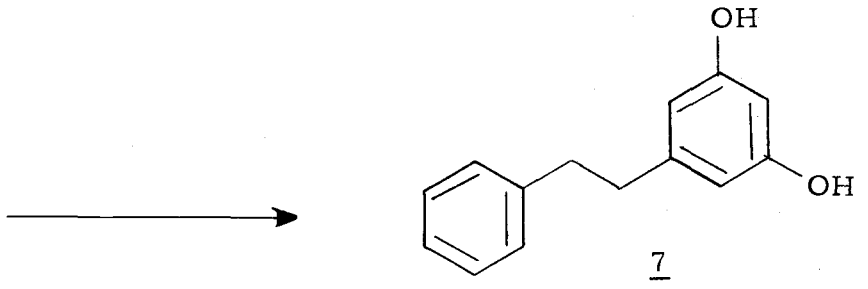
While the yield of 6 is low, the method is of considerable value considering the complexity of the problem and the small number of steps involved. This approach has the distinction of being the only method to date which allows isolation and purification of the larger

polyketides. The octaketide 6 was purified on acidic silica gel and proved to be a crystalline product (mp 101-109°C), though a mixture of many keto and enol forms.

The most serious limitation of the Harris scheme is its inability as presently formulated to easily generate a polyketide with a differentiated "head" (methyl) and "tail" (carboxyl). Many of the common cyclization pathways leading to condensed metabolites via polyketides in nature are thus precluded for the Harris intermediates.

The strategy which has been adopted by most workers is to prepare the β-diketone functions in a masked form, and then unmask them in one step late in the sequence. The approach developed first by Birch (8) and used principally by T. Money and A.I. Scott (9) constructs masked polyketide systems with the β-diketone units protected in the form of a pyrone ring. Birch used this method to synthesize the naturally occurring dihydropinosylvin (7).





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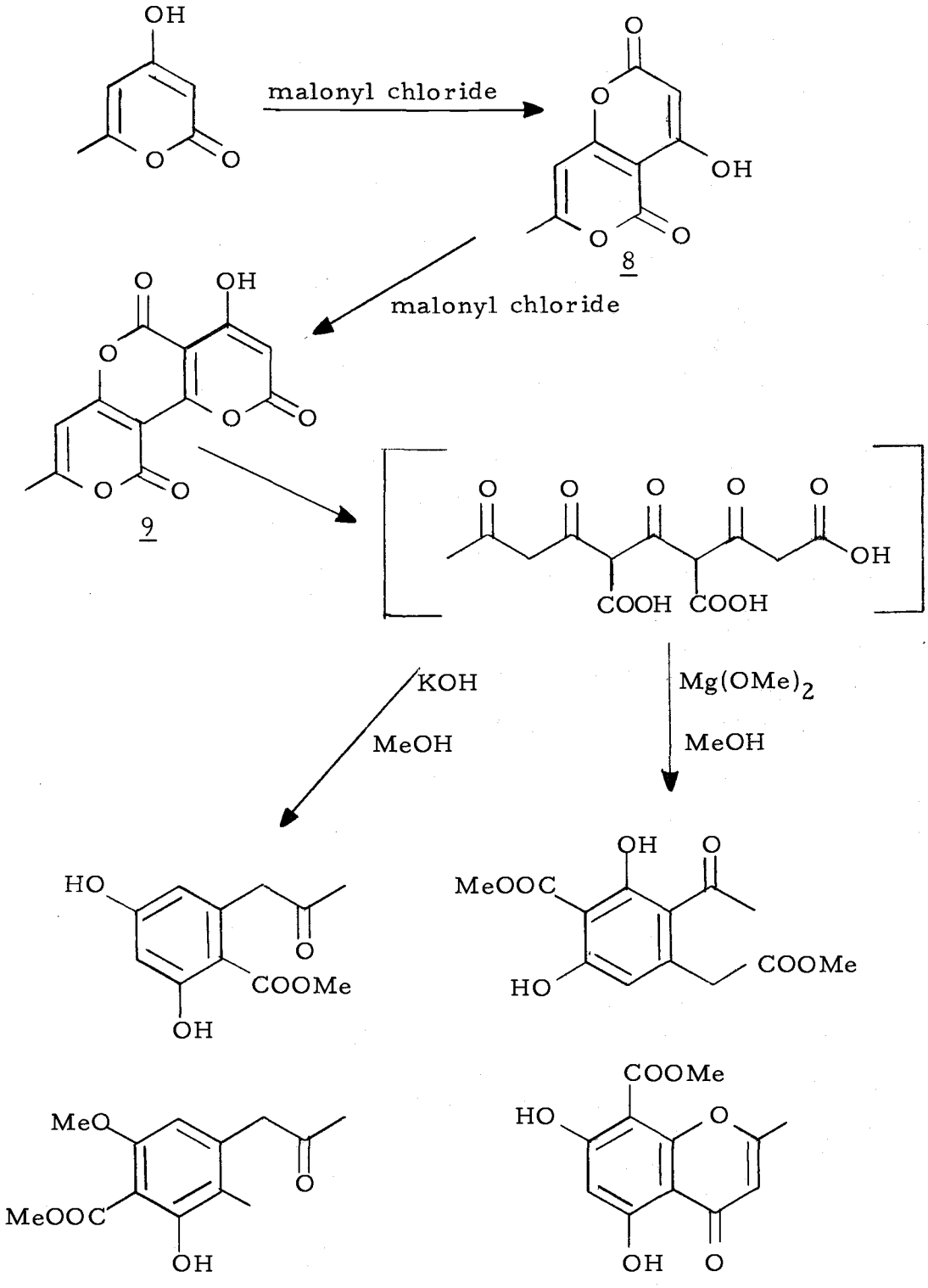
Dihydropinosylvin

Money, Scott and their co-workers have extended the pyrone approach to systems which, at least in theory, would lead to polyketides of almost any chain length. An example is given in Scheme 3, in which triacetic acid lactone is converted to dipyrone 8, and finally to tripyrone 9 by reaction with malonyl chloride. Tripyrone 9 has been converted to aromatic products by various reagents (10).

While Money and Scott have had some success with condensed pyrone systems, it appears that the upper limit for successful opening to the polyketide intermediate may be the tripyrone 9 (a tetraketoacid equivalent). An attempt to carry the approach beyond this stage led to the synthesis of bis-pyranopyrandione 10, which is a protected heptaketodiacid (11). This structure, as has any system larger than the tetraketoacid equivalent 9, yielded only products resulting from partial opening of the polypyrone structure.

Scheme 3.


OH
malonyl chloride
O
O
OH
O
O
8
malonyl chloride
O
OH
O
O
O
O
9
O
O
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O
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OH
COOH
COOH
KOH
MeOH
Mg(OMe)2
MeOH
HO
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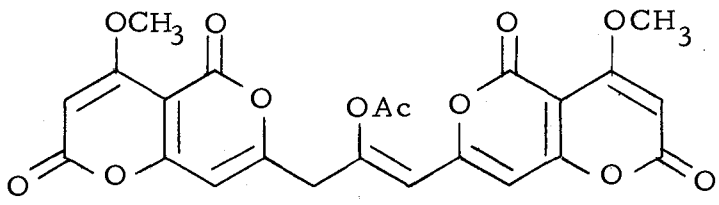

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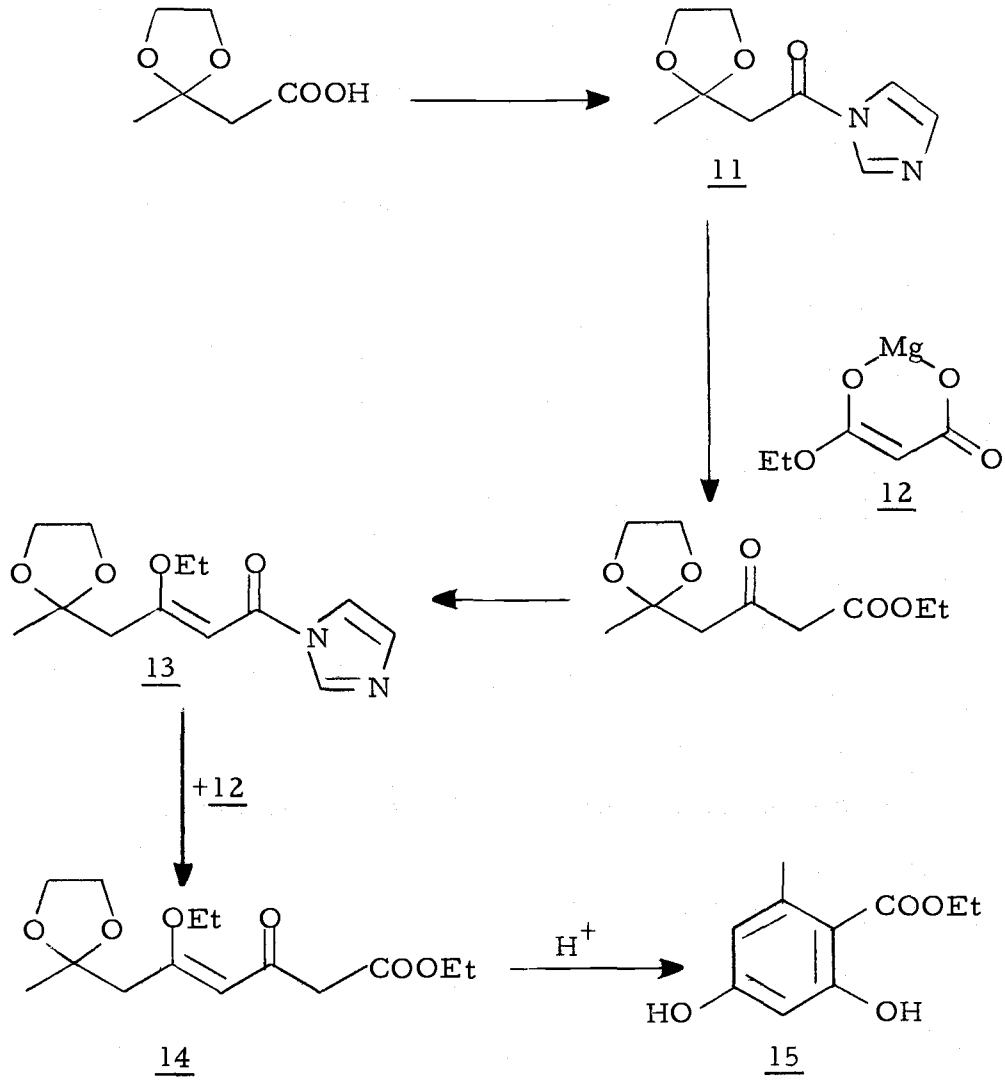
To a large extent, the problems with the pyrone approach stem from the basic or acidic conditions which are required to open the pyrone rings. These conditions tend to produce degradation products, initially, via retro-Claisen condensations and decarboxylations. The smaller system, where degradation is not as much of a problem, give condensed products which appear to be derived from polyketides, though the polyketides themselves have not been isolated.

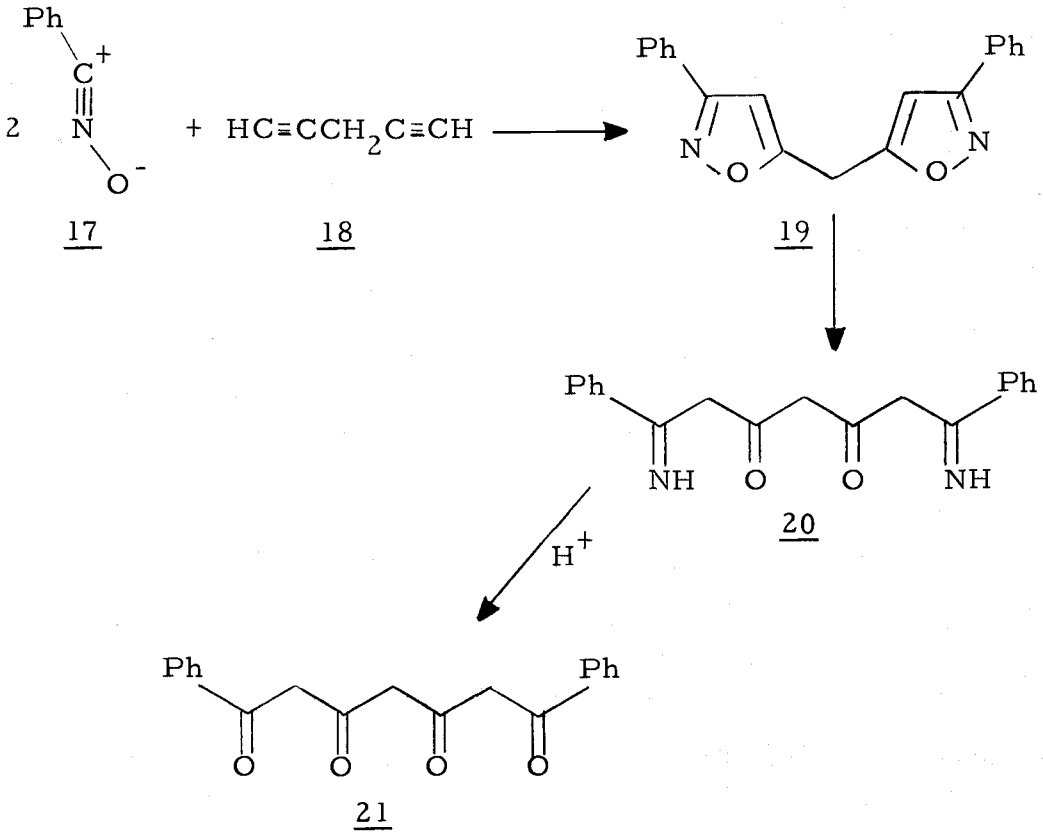
In 1966, G Bram (12) obtained a protected triketoacid (14) by the potentially useful reaction of protected acyl imidazoles 11 and 13 (Scheme 4) with the magnesium chelate of monoethyl malonate (12). Upon acidification, this produced ethyl orsellinate (15), presumably through the intermediacy of the unisolated triketoester. The limits of this scheme have not been established.

Scheme 4.



Based on the observation that isoxazoles are known to undergo nitrogen-oxygen bond cleavage upon mild reduction, G. Casnati and co-workers (13) were able to produce tetraketone 21 by the 1,3-dipolar cycloaddition of two equivalents of phenylnitrile oxide (17) with diethynylmethane (18). Reduction of 19 to the diimino compound 20

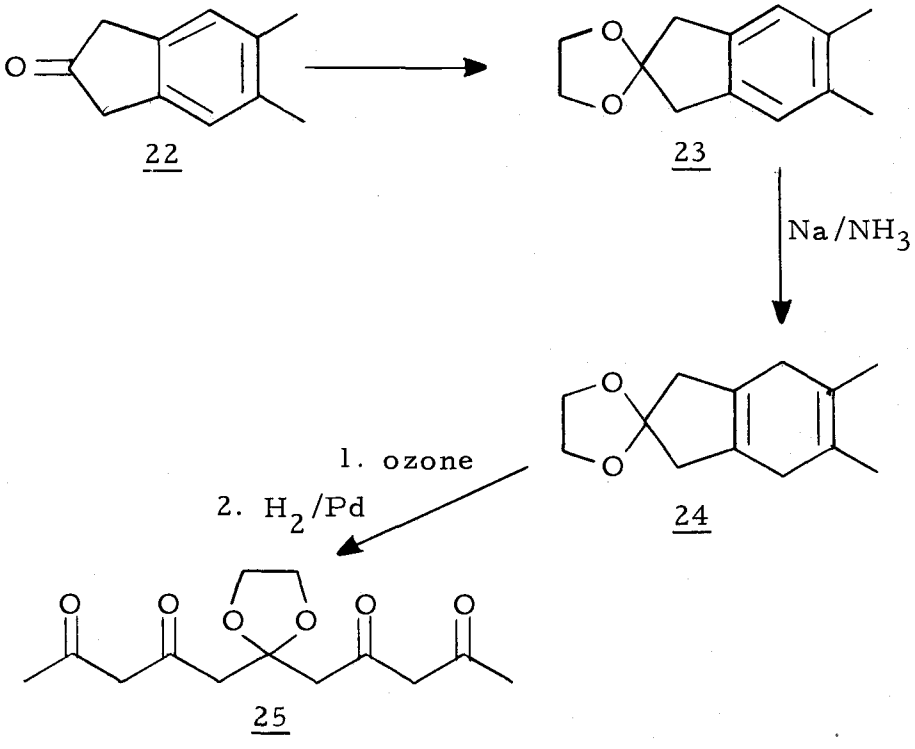
followed by mild acidic hydrolysis, gave the desired tetraketo product (21).



After initially working with pyrone systems, Birch, in 1963, published a paper (14) in which he described an attempted synthesis of polyketides by a new approach. This scheme involved the oxidative cleavage of 1,4-dihydroaromatic systems which are obtained by dissolving metal reduction (Birch reduction) of the corresponding aromatic systems. In an attempt to produce a pentaketide, he prepared 24 from 5,6-dimethylindan-2-one (22) by ketalization and

subsequent dissolving metal reduction (Scheme 5). Ozonolysis of the dihydroindane 24 gave what was believed to be compound 25. Birch was never able to isolate this product in a pure state, nor could he prepare any crystalline derivatives or aromatic condensation products. His results did, however, indicate the possible presence of the polyketide derivative. Ultraviolet spectral data, elemental analysis, a positive ferric chloride test, and the isolation of acetone and acetic acid from basic cleavage products were cited as evidence for the formation of a β-polycarbonyl compound.

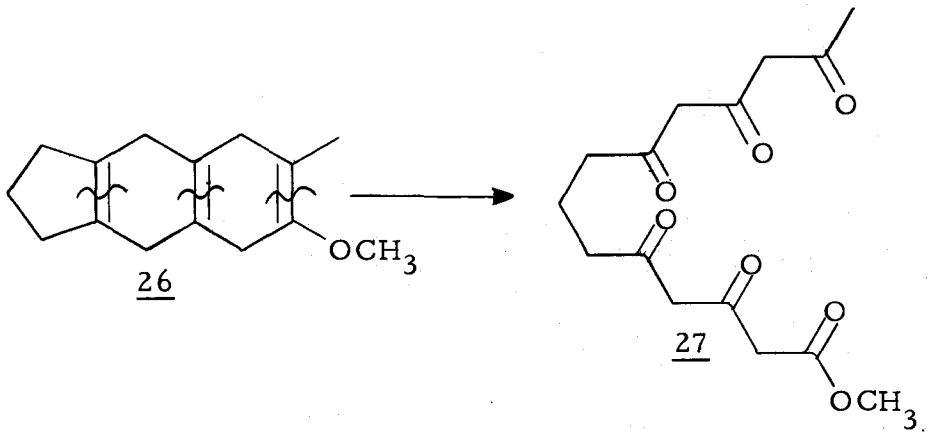
Scheme 5.



Because of the possibilities which ozonolytic cleavage of 1,4-dihydrobenzene systems held for the synthesis of large polyketides, and because this scheme, in principle, affords a means for producing polyketides with distinguishable "heads" and "tails", it was decided to reexamine and, if possible, extend the approach pioneered by Birch. The details and results of the work are given in the following sections.

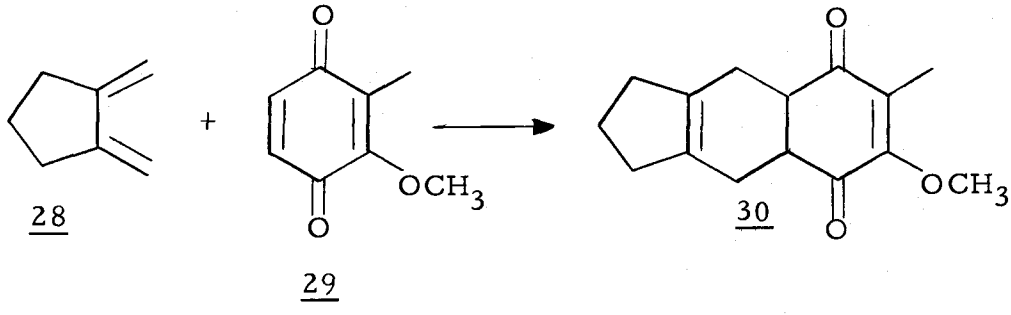
II. DISCUSSION AND RESULTS: β-POLYKETIDES

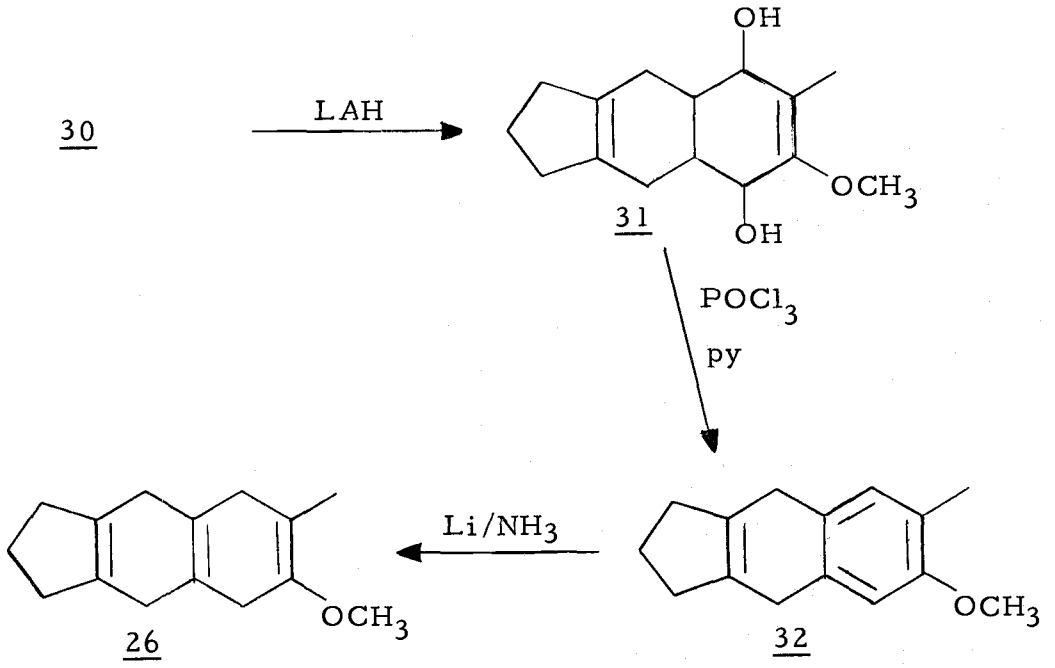
The tetrahydronaphthalene 26 appeared to be a suitable substrate on which to test the approach to polyketide synthesis originally envisioned by Birch (14). Oxidative cleavage of 26 would be expected to yield a modified polyketide (27), in which a ketone carbonyl at C-7 is replaced by a mtheylene group, and the termini are differentiated as methyl and ester functions.



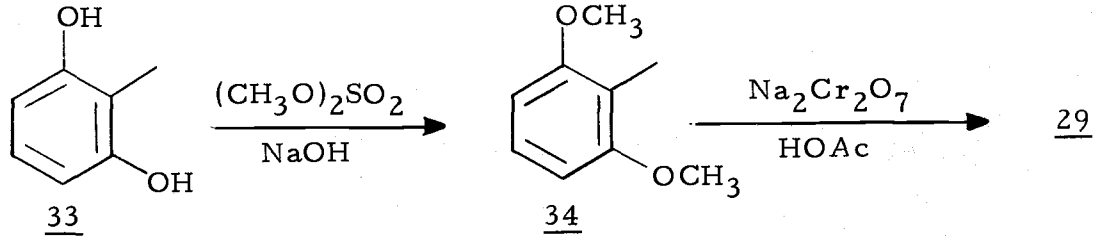
Scheme 6 shows the route which led to 26.

Scheme 6.

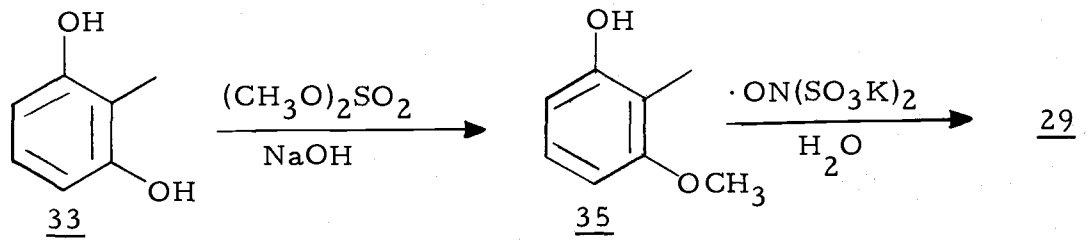




A literature search showed that 2-methoxy-3-methylbenzoquinone (29) had been previously prepared (15) from the commercially available 2-methylresorcinol (33) by conversion to 2,6-dimethoxytoluene (34) and subsequent oxidation to the desired quinone 29 using sodium dichromate in glacial acetic acid.



Because of the need for large quantities of the quinone (29), and the low yield involved in the dichromate oxidation step (20%), another route was sought. Fremy's salt (16) (potassium nitrosodisulfonate), a mild oxidant, has been used successfully to form quinones from phenols (16). This suggested the route shown below.



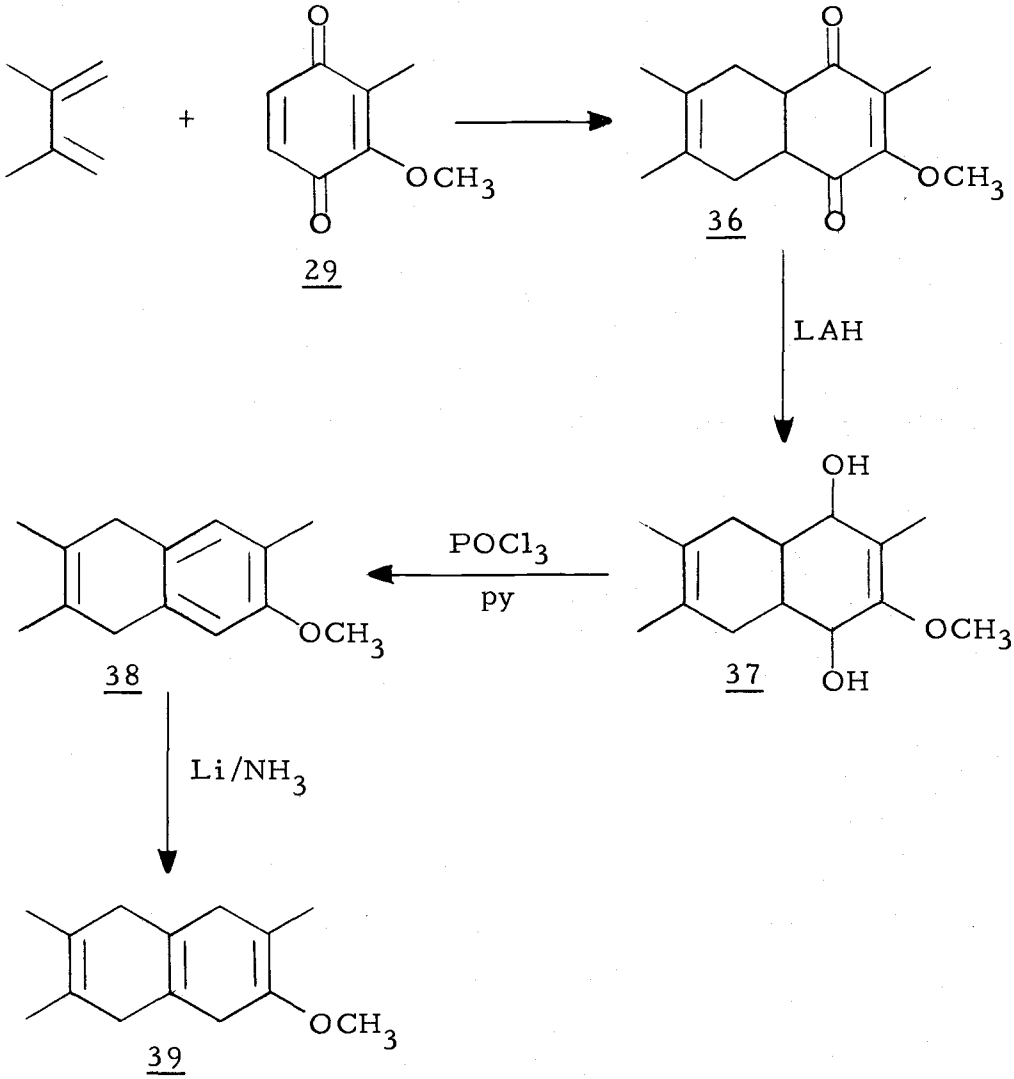
3-Methoxy-2-methylphenol (35) was prepared by the reaction of 2-methylresorcinol (33) with dimethyl sulfate and one equivalent of sodium hydroxide (17). Phenol 35 was converted to the desired quinone 29 in 42% yield by treatment in water with Fremy's salt.

With quinone 29 readily accessible, model studies (Scheme 7) were undertaken to develop the experimental procedures required to prepare 26.

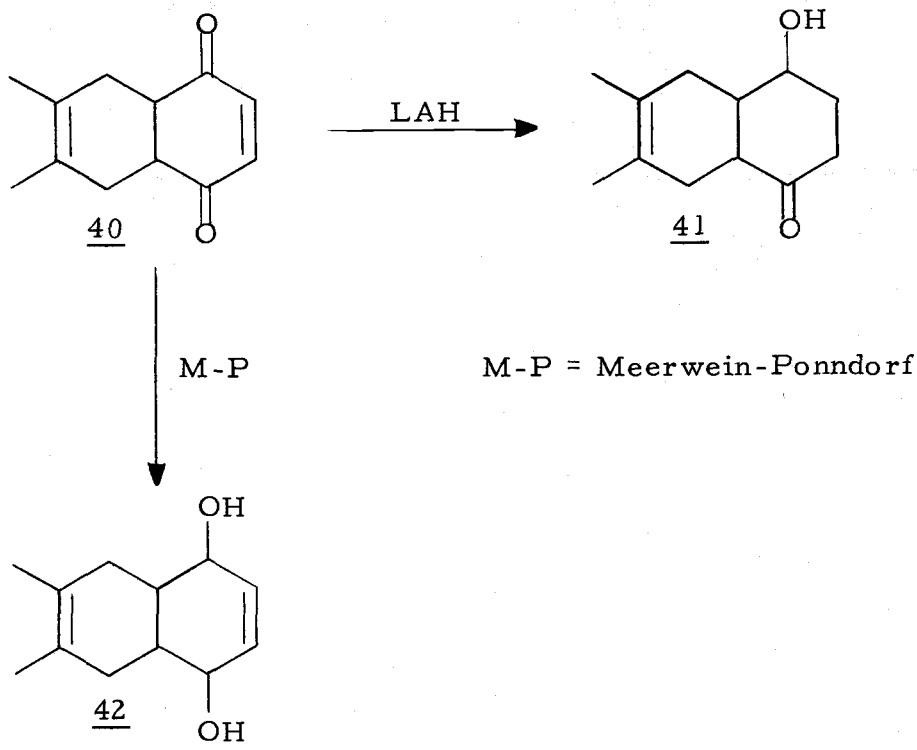
The Diels-Alder reaction of quinone 29 and 2,3-dimethylbutadiene produced a 72% yield of crystalline adduct 36 as the only isolated product. The preference for cycloaddition at the less substituted double bond of the quinone is in accord with previously reported regioselectivity in the Diels-Alder reaction of quinones (18).

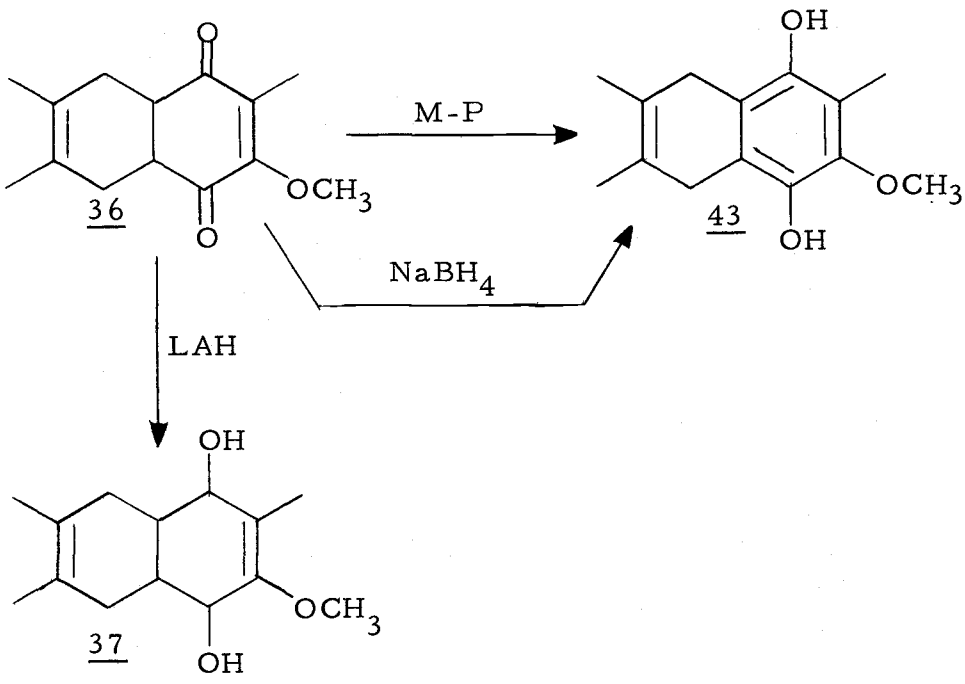
Attempted reduction of 36, using lithium aluminum hydride at 0°C, gave only a 22% yield of the diol 37. By comparison, Birch and co-workers (14) had attempted the reduction of 40 with lithium aluminum hydride and had obtained only the ketoalcohol 41, arising from a 1,2-reduction and a 1,4-reduction of the diketone.

Scheme 7.



Meerwein-Ponndorf reduction conditions (aluminum isopropoxide and 2-propanol), which do not promote 1,4-reduction are known to convert 40 to 42 in good yield (14). Applying Meerwein-Ponndorf conditions to adduct 36, however, produced mainly 5,8-dihydro-1,4-dihydroxy-2-methoxy-3,6,7-trimethylnaphthalene (43). This same product (43) was obtained in 93% yield using sodium borohydride in 2-methyl-2-propanol. Evidently, in each case the alkali catalyzed tautomerization to the stable naphthalenoid system (43) proceeds more rapidly than reduction of the diketone (36).



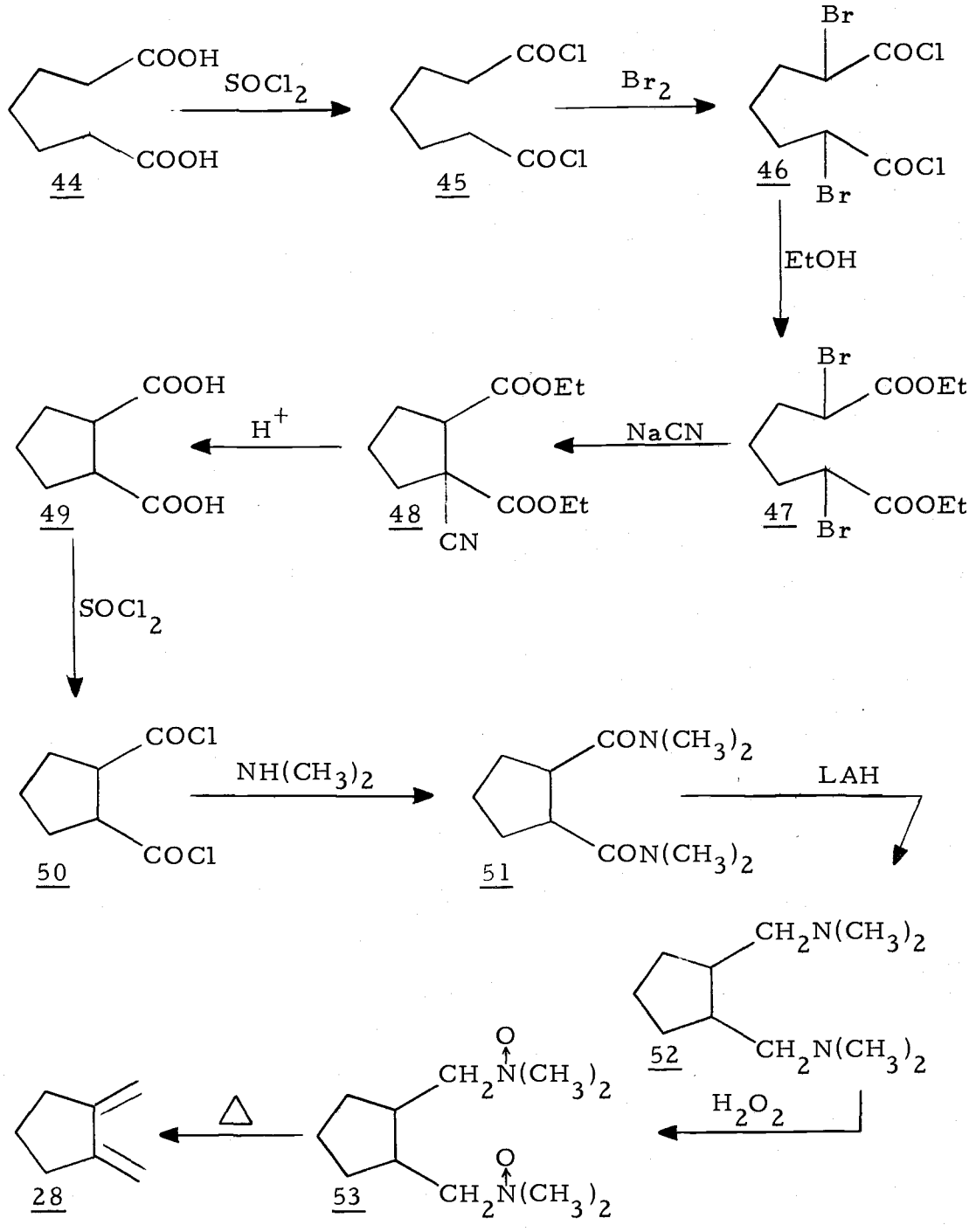


Having obtained the desired diol (37) in low yield using lithium aluminum hydride, this method was again studied, and by carrying out the reaction at -50°C the yield, of 37 was improved to 82%.

Diol 37 was converted smoothly to crystalline 5,8-dihydro-2-methoxy-3,6,7-trimethylnaphthalene (38) by a bis dehydration with phosphorus oxychloride in pyridine. Birch reduction of 38 in tetrahydrofuran completed the model sequence, producing 1,4,5,8-tetrahydro-2-methoxy-3,6,7-trimethylnaphthalene (39) in 74% yield.

Following completion of the synthesis of model system 39, work was directed toward preparation of 26. For this, a necessary starting material is 1,2-dimethylenecyclopentane, which was prepared by the route illustrated in Scheme 8 (19,20).

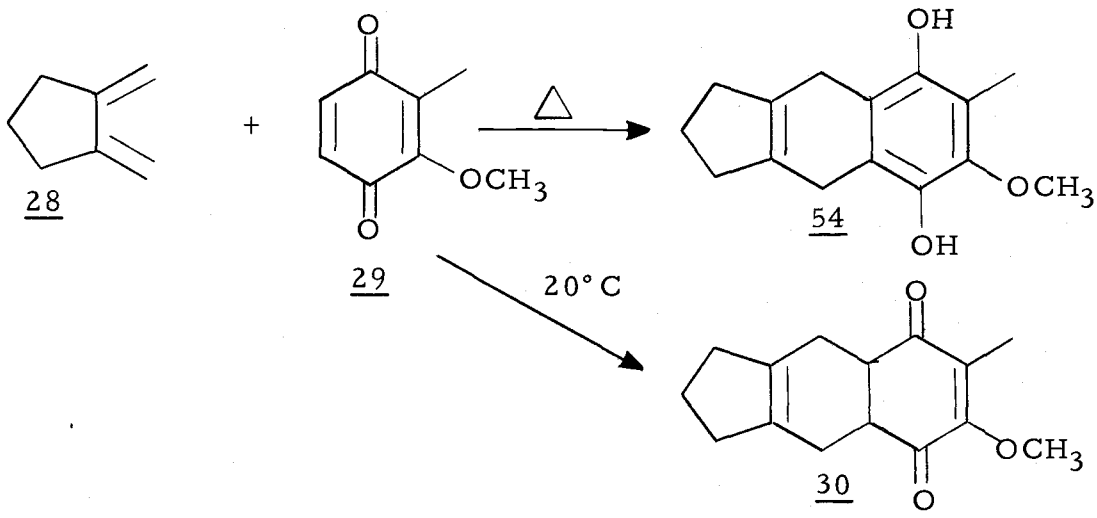
Scheme 8.


COOH
COOH
44
$SOCl_2$
COCl
COCl
45
Br_2
Br
COCl
COCl
Br
46
EtOH
Br
COOEt
COOEt
Br
47
NaCN
COOEt
COOEt
CN
48
H^+
COOH
COOH
49
$SOCl_2$
COCl
COCl
50
$NH(CH_3)_2$
$CON(CH_3)_2$
$CON(CH_3)_2$
51
LAH
$CH_2N(CH_3)_2$
$CH_2N(CH_3)_2$
52
H_2O_2
O
$CH_2\overset{\uparrow}{N}(CH_3)_2$
O
$CH_2\overset{\uparrow}{N}(CH_3)_2$
53
△
28

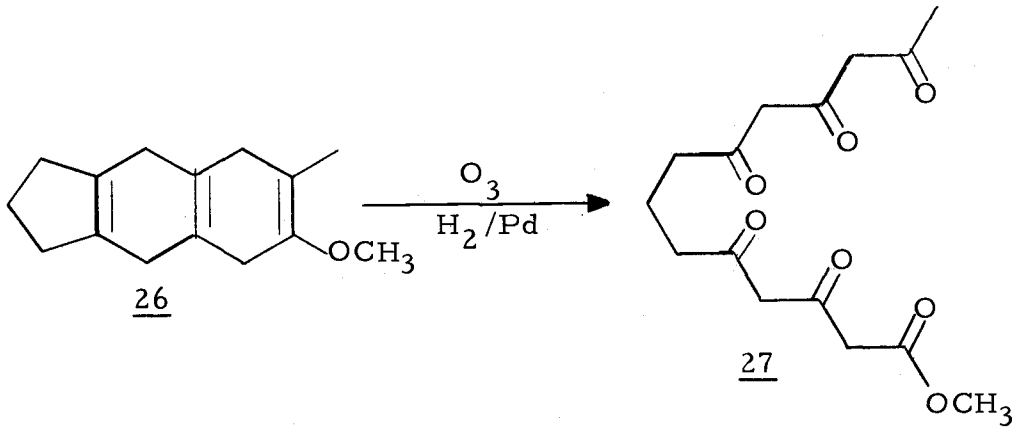
Pimelic acid 44 was converted to its acid chloride 45 by the action of thionyl chloride, and then to ethyl α, α' dibromopimelate (47) by sequential addition of bromine followed by ethanol. Using the method of Fuson and Cole (19), treatment of 47 with sodium cyanide in ethanol caused cyclization to ethyl 1-cyano-1,2-cyclopentanedicarboxylate (48). Acid hydrolysis of 48 gave crystalline 1,2-cyclopentane-dicarboxylic acid (49).

The diacid 49 was converted to the diene by the method of Bartlett and co-workers (20). This involved formation of 1,2-cyclopentanedicarboxylic acid chloride 50, which was converted to diamide 51 by reaction with dimethylamine. Reduction of 51 with lithium aluminum hydride gave diamine 52. Finally, the diamine was oxidized with 30% hydrogen peroxide to the diamine oxide 53, which was pyrolyzed (Cope elimination) to 1,2-dimethylenecyclopentane (28).

With both addends secured, the Diels-Alder addition of 28 and 29 was attempted using the conditions worked out for the model system 36. Upon heating at 65°C for eight hours, the very dark solution produced only a low yield of hydroquinone 54. However, when the reaction was run at room temperature for 16 hours, the desired adduct was obtained.

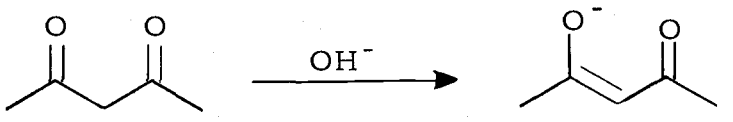


Reduction of 30 with lithium aluminum hydride at -60° C gave the diol (31) in 68% yield. This was converted to 6,7-cyclopenteno-1,4,5,8-tetrahydro-2-methoxy-3-methylnaphthalene (26) with phosphorus oxychloride in pyridine followed by lithium-ammonia reduction. Ozonolysis of 26 was carried out in methylene chloride at -78° C, and was followed by reductive cleavage of the ozonide with hydrogen and palladium on charcoal. After filtration and removal of the solvent a yellow oil remained.



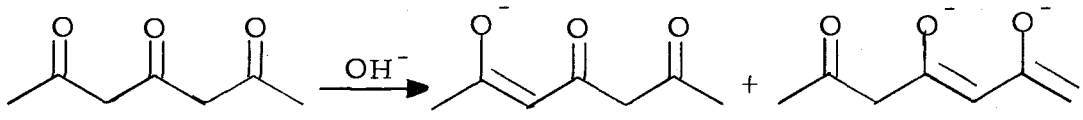
Thin-layer chromatography on silica gel, in a variety of solvents showed the product to be very complex. The infrared spectrum of the product showed strong carbonyl stretching centered at 1730 cm^{-1} and broad hydroxyl stretching at 3500 cm^{-1}. A positive reaction with aqueous ferric chloride (a test for enolic or phenolic hydroxide) supports the presence of enolic β-dicarbonyl function. NMR showed two singlets at 3.67 and 3.80 (1:3), both of which correspond to the expected shift of a methylene in a β-diketone. The shifts would also be correct for the methyl group of a methyl ester. While suggesting that a β-polyketide (as a mixture of enolic forms) had been produced, this information did not establish conclusively the structure of this polyketide.

Acetylacetone (55) shows ultraviolet absorption in water at 274 nm. Birch found that this shifts to 293 nm upon the addition of sodium hydroxide (14). The shift was attributed to the formation of enolate anion 56.



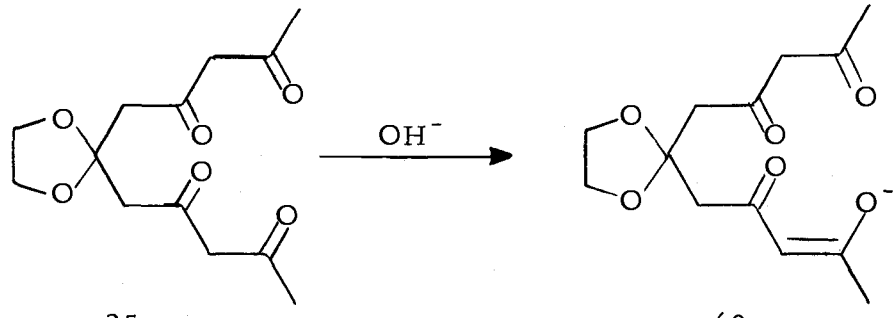
55 56

In aqueous sodium hydroxide, diacetylacetone (57) showed a similar ultraviolet absorption at 295 nm, plus a smaller absorption at 342 nm. The 295 nm absorption was attributed to the monoanion 58 and the 342 nm absorption was believed to be derived from a small amount of dianion 59 (14).



57 58 59

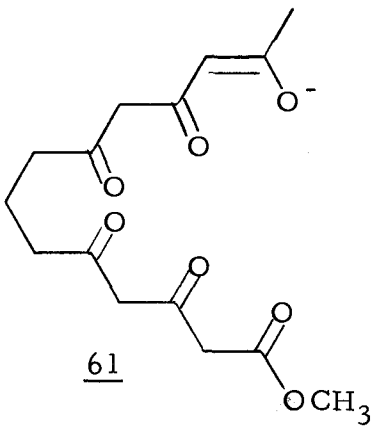
Upon treatment of this ozonolysis product (25) with aqueous sodium hydroxide in methanol, Birch obtained a similar ultraviolet absorption at 294 nm, which he felt resulted from 60.



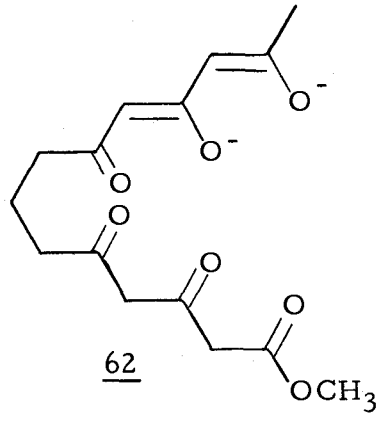
25 60

The ozonolysis product 27 gave ultraviolet data which corresponds well to both Birch's ozonolysis product 25 and to diacetylacetone (57) (Table I). In neutral solution the ultraviolet spectrum showed an absorption at 273 nm, which shifts to 298 nm with the

addition of 3N sodium hydroxide. There was also a small shoulder at 358 nm. These could, by analogy to diacetylacetone, be attributed to mono and dianions 61 and 62.



61



62

Table I. Comparative ultraviolet data for polyketides.

Compound	Neutral	In Base (Anions)	
Acetylacetone (55)[a]	274 nm	293 nm	
Diacetylacetone (57)[a]	-	295 nm	342 nm
Compound 25[a]	-	294 nm	
Compound 27	273 nm	298 nm	358 nm

[a]From reference 14.

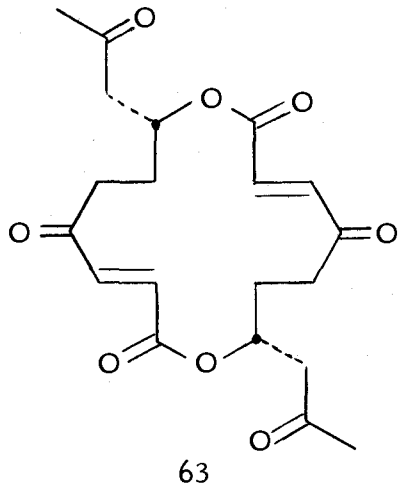
If the 358 nm absorption is due to a dianion then this would be strong evidence that 27 is being formed, since there is no other readily accessible product which could form a dianion. All attempts to prepare crystalline derivatives of the ozonolysis product 27 failed,

as did attempts to effect cyclization to an aromatic system.

In conclusion, it appears that ozonolysis does give a product which has many of the properties expected from a β-polyketide. The fact that no aromatic condensation products or derivatives have been isolated in either Birch's work or this study is a cause for concern and further study.

III. INTRODUCTION: VERMICULINE

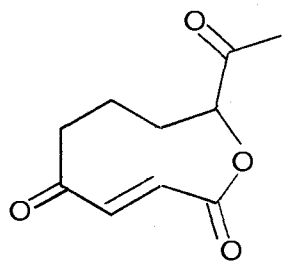
Vermiculine is a C-20 dilactone macrolide (Figure 1) which was first reported in 1972 by Fuska, Nemec, and Kuhr (21). It is found as a crystalline (mp 175-177°C) metabolite of Penicillium vermiculatum Dangeard, and shows antibacterial activity against Gram-positive bacteria and weak activity against yeasts. A later paper by Fuska and co-workers (22) showed that vermiculine also displays cytotoxic effects against Ehrlich ascites carcinoma, lymphadenoma L-5178, and sarcoma 37 cells; thus, the macrolide is of interest as a possible cancerostatic agent.



63

Figure 1. Vermiculine (absolute stereochemistry not implied).

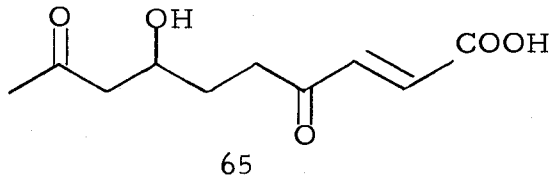
The structure 64 originally assigned to vermiculine by Sedmera and co-workers (23) was based on an erroneous molecular weight assignment and misinterpretation of mass spectroscopic fragmentation data.



64

Chemical studies by Boeckman (24), as a prelude to an attempted synthesis of vermiculine, led him to question the unusual nine-membered, cyclic structure (which would contain a highly-strained, trans double bond) proposed by Sedmera. The uncertainty was eliminated by means of an X-ray crystallographic structure determination, carried out by Clardy and Fayos (24). This established the structure of vermiculine as 63.

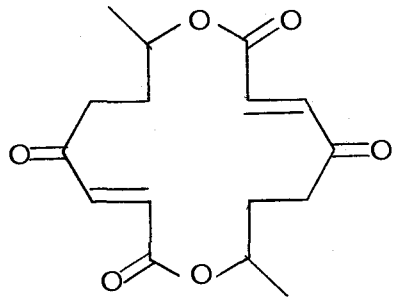
The macrolide ring of vermiculine is the result of a diesterification of two identical (as yet unisolated) C-10 hydroxyacid units (vermiculinic acid (65)).



65

While the absolute stereochemistry of vermiculine is not known, the structure determination did indicate that both vermiculinic acid subunits possess the same configuration at the hydroxyl group. Thus, vermiculine is optically active ($[\alpha]_0^{20}$ -12.5), with the acetonyl side chains in a cis relationship.

The structure of vermiculine is closely related to that of pyrenophorin (66), a metabolite of the fungi Pyrenophora avenae and Stemphylium radicinum (25). Both substances contain the same 16-membered dilactone ring system, but differ with respect to side-chains (66 possesses cis oriented methyl substituents in place of acetonyl appendages in 63).

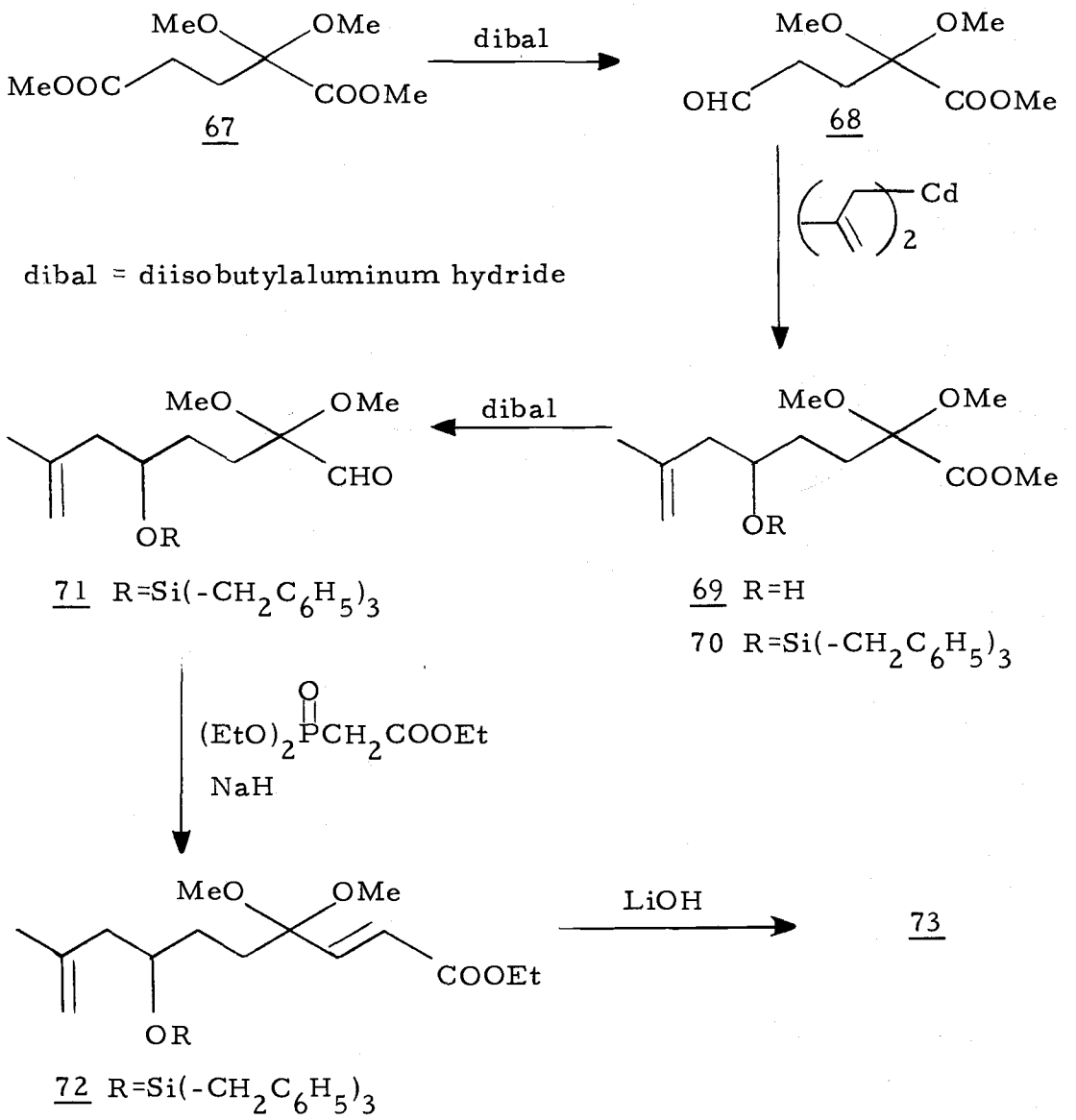


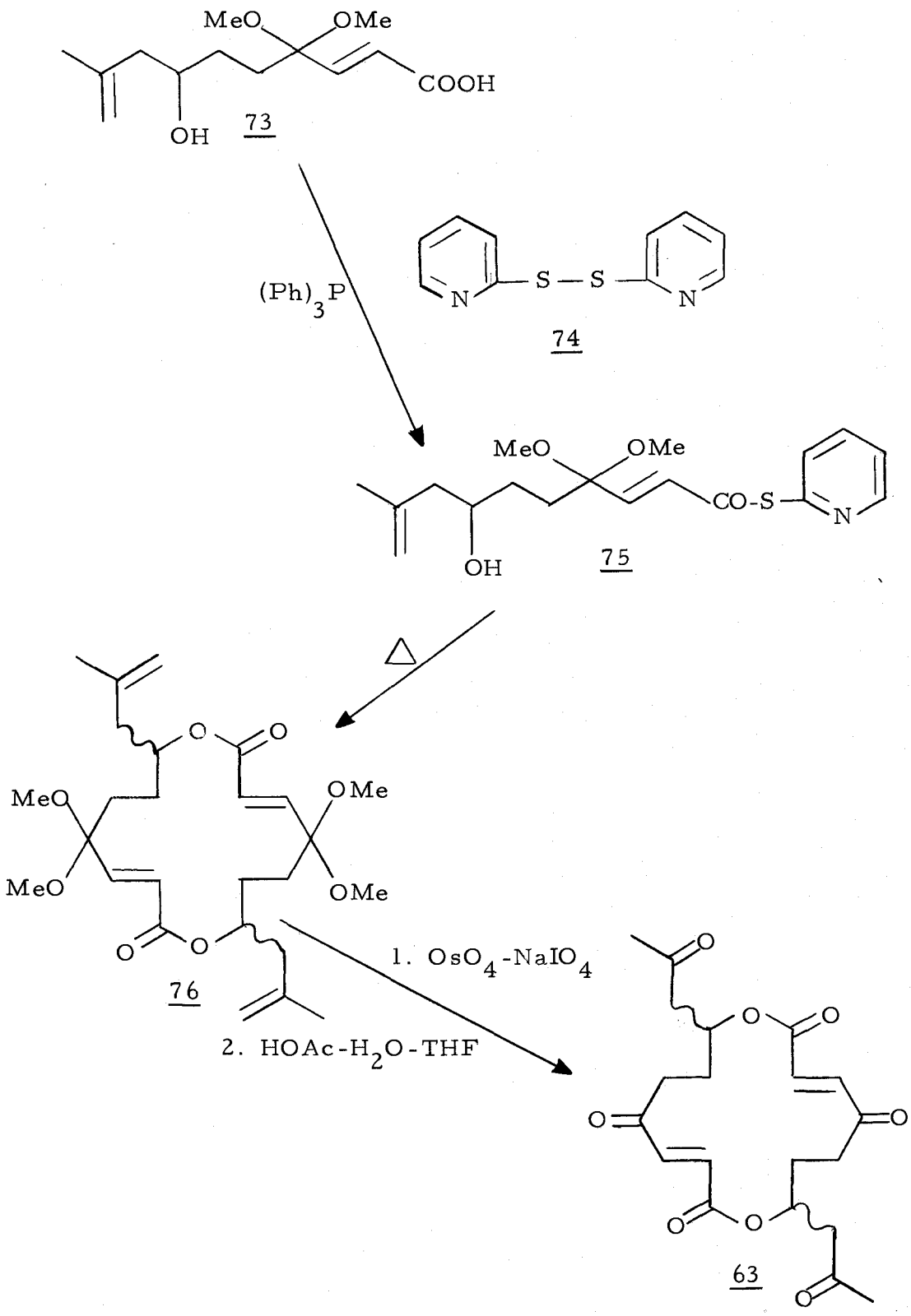
66

Corey and co-workers (26) have recently reported a synthesis of 63, the first part of which involves the synthesis of hydroxy acid 73 as shown in Scheme 9. Selective reduction of 67 with diisobutylaluminum hydride gave the aldehyde 68 in 50% yield. The reaction of 68 with dimethallyl cadmium afforded alcohol 69, which was protected as

the tribenzylsilyl ether 70. Reduction of 70 with diisobutylaluminum hydride, followed by a Wadsworth-Emmons reaction with the anion of triethyl phosphonoacetate gave 72 (94% from 70), which was converted to 73 by the action of lithium hydroxide in aqueous methanol.

Scheme 9.




MeO
OMe
COOH
OH
73
(Ph)3P
S — S
N
N
74
MeO
OMe
CO-S
N
OH
75
△
O
O
MeO
OMe
MeO
OMe
O
O
76
1. OsO4-NaIO4
2. HOAc-H2O-THF
O
O
O
O
O
O
63

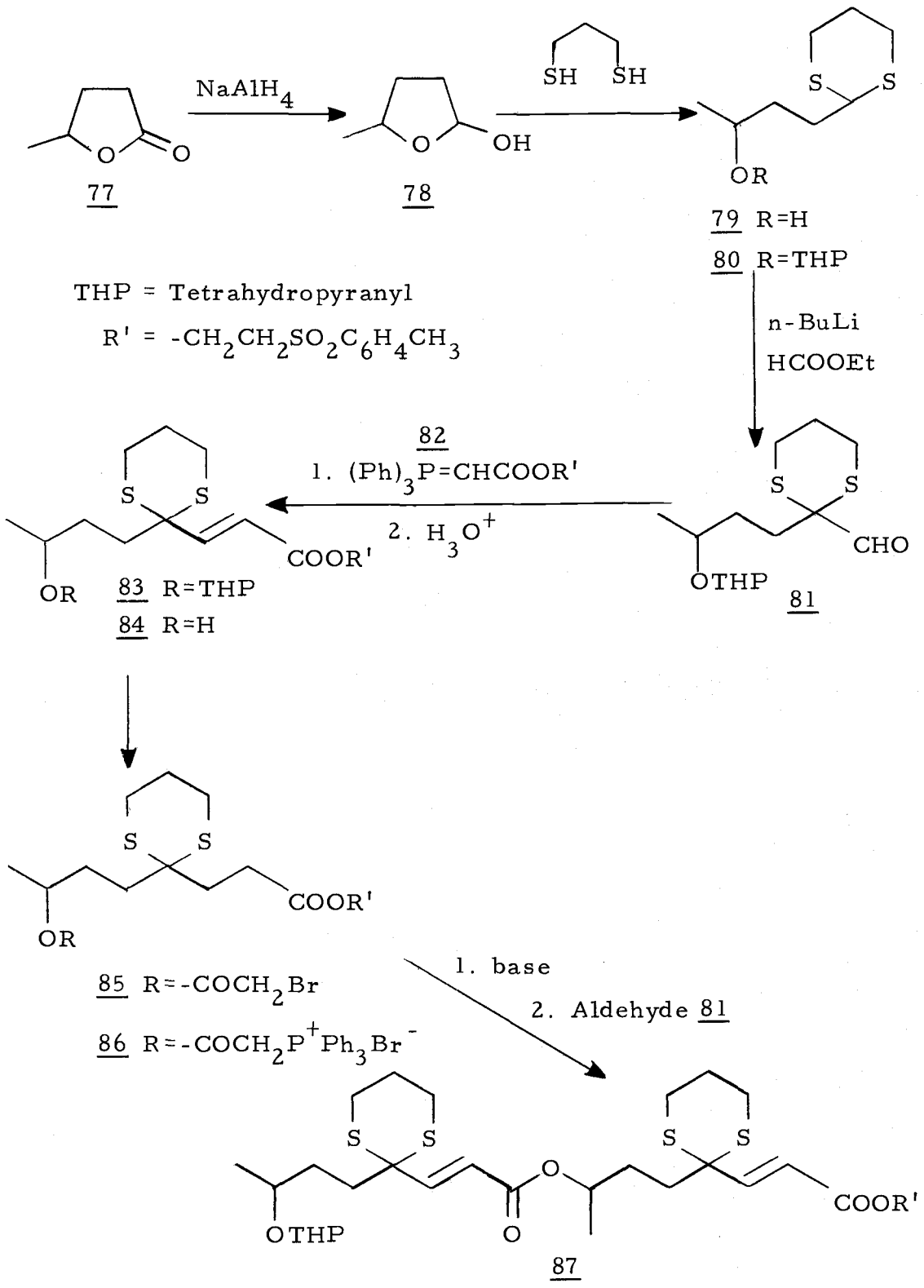
The cyclization of two equivalents of 73 to the macrolide 76 was accomplished by first forming the pyridine thiolester 75 (77%, 2, 2'-dipyridyl disulfide and triphenylphosphine). Heating adduct 75 at high dilution in refluxing xylene, gave a 30% yield of 76 as a 1:1 mixture of cis and trans isomers. Corey envisions this last reaction as occurring via a "double activation", whereby reactivity of the carboxyl group is enhanced by the use of the thiolester and nucleophilicity of the alcohol is improved by hydrogen bonding to the pyridine nitrogen. The reacting entities are supposedly held in close proximity by means of an intramolecular complex.

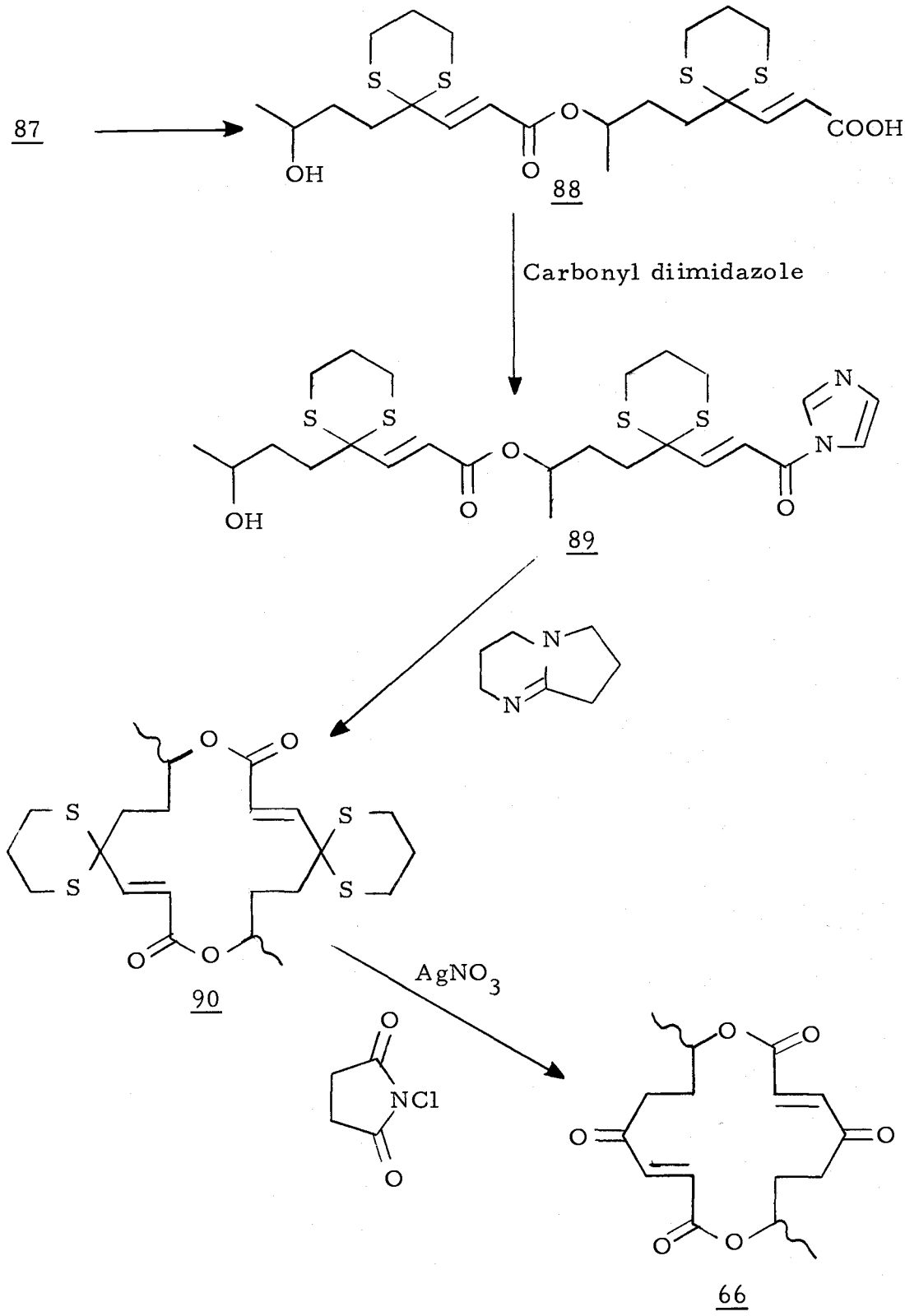
The Corey synthesis was completed by oxidative cleavage of the two methylene groups of 76 with osmium tetroxide and sodium periodate, followed by deketalization to racemic vermiculine and its meso form.

The similarities between vermiculine and pyrenophorin (66) obviously make a successful approach to the latter of interest in the planning of a synthesis of 63. Raphael's synthesis of pyrenophorin is shown in Scheme 10 (25).

Reduction of γ-valerolactone (77) with sodium aluminum hydride gave lactol 78, which was converted to dithiane 79 by the action of 1, 3-propanedithiol and boron trifluoride-etherate. Protection of the alcohol as its tetrahydropyranyl ether 80 was followed by conversion to aldehyde 81 with n-butyl lithium and ethyl formate. The aldehyde

Scheme 10.

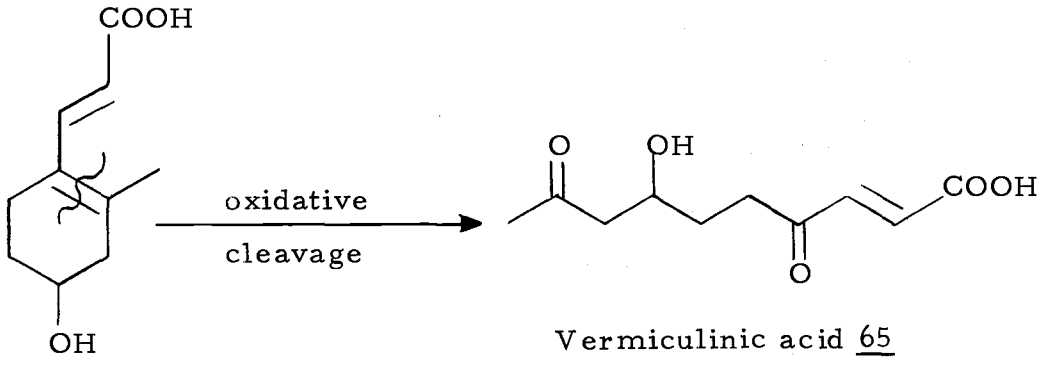

NaAlH4
77
78
79 R=H
80 R=THP
THP = Tetrahydropyranyl
R' = -CH2CH2SO2C6H4CH3
n-BuLi
HCOOEt
82
1. (Ph)3P=CHCOOR'
2. H3O+
81
83 R=THP
84 R=H
85 R=-COCH2Br
86 R=-COCH2P+Ph3Br-
1. base
2. Aldehyde 81
87


87
S
S
S
S
O
COOH
OH
O
88
Carbonyl diimidazole
S
S
S
S
N
N
O
OH
O
O
89
N
N
S
S
S
S
O
O
O
O
90
AgNO3
NCl
O
O
O
O
O
O
O
O
66

(81) was allowed to react with phosphonium ylide 82 to give adduct 83. This compound was converted to phosphorane 86 by sequential deprotection of the alcohol, formation of the bromoacetate 85, and reaction of the later with triphenylphosphine. Addition of aldehyde 81 to the ylide generated from 86 gave dimer 87. The alcohol was then unmasked and the terminal ester was cleaved by means of 1,5-diazabicyclo[4.3.0] non-5-ene in benzene to yield 88. Lactonization of 88 to 90 was effected by activation of the acid as the imidazolide 89 with N,N-carbonyldiimidazole, followed by treatment with 1,5-diazabicyclo[4.3.0] non-5-ene to give 90. Regeneration of the ketone functions using N-chlorosuccinimide and silver nitrate gave a 1:1 mixture of racemic pyrenophorin (66) and its meso form. The following section presents the results of work directed toward a synthesis of vermiculine, which is conceptually different from the approaches devised by Raphael and by Corey to this C-16 diolide system.

IV. DISCUSSION AND RESULTS: VERMICULINE

The synthesis of vermiculine divides logically into two phases; synthesis of a monomeric unit related to vermiculinic acid (65), followed by lactonization of two hydroxy acid components to the diolide. Previous work directed towards the synthesis of β-polyketides by oxidative cleavage of cyclohexenes suggested that the 1,6-diketone functionality of vermiculinic acid might be generated by means of a similar fragmentation process, involving an appropriately substituted cyclohexene precursor. The initial approach to vermiculine (63), via 65, was predicated on this concept and is described below.



Vermiculinic acid 65

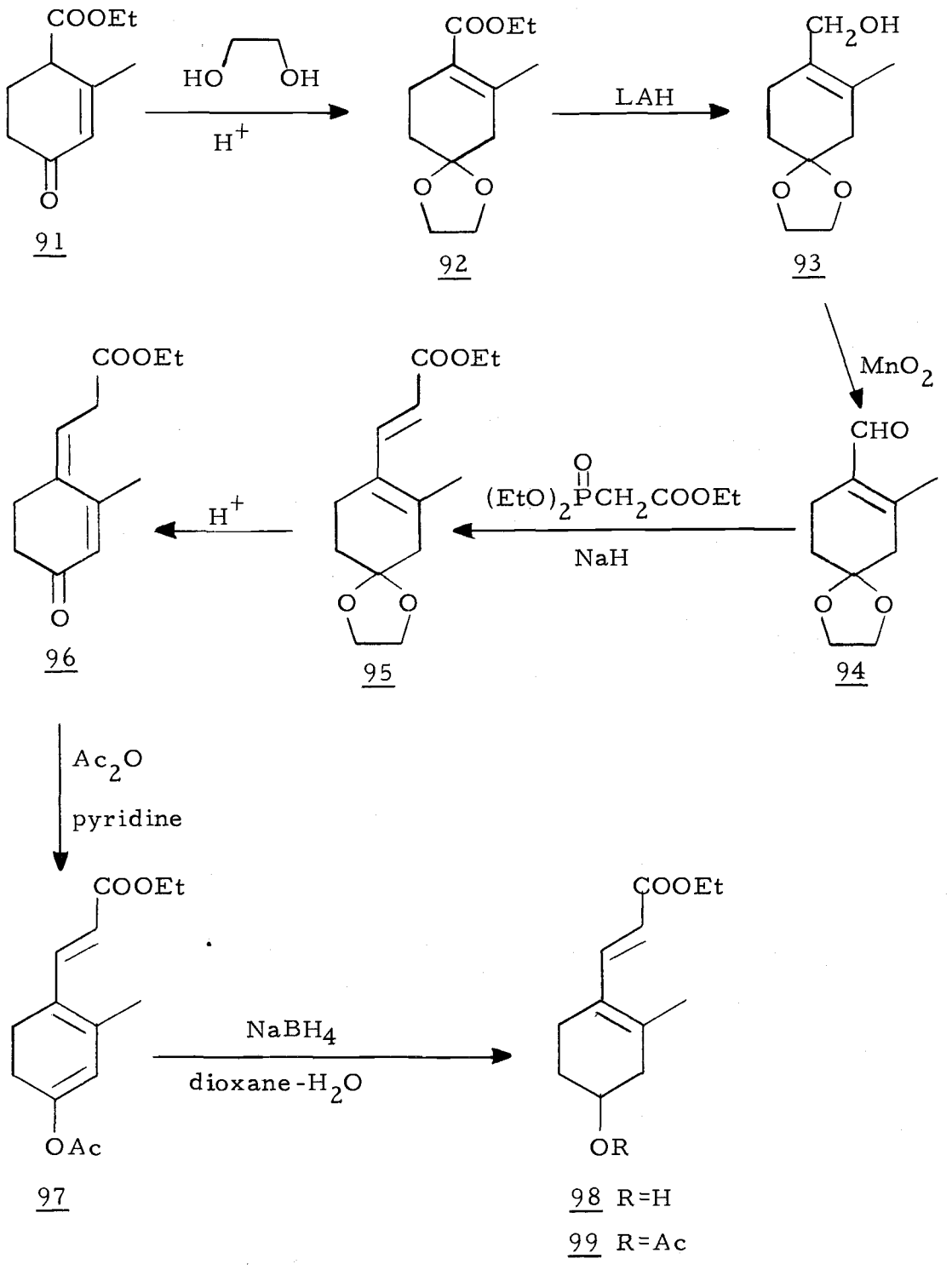
Hagemann's ester (91) appeared to be an especially attractive starting material since, in addition to a preformed cyclohexene ring, it also contains functionality well suited for the synthesis of diene 98. The essential transformations to be accomplished would then be (a) migration of the double bond to the tetrasubstituted position,

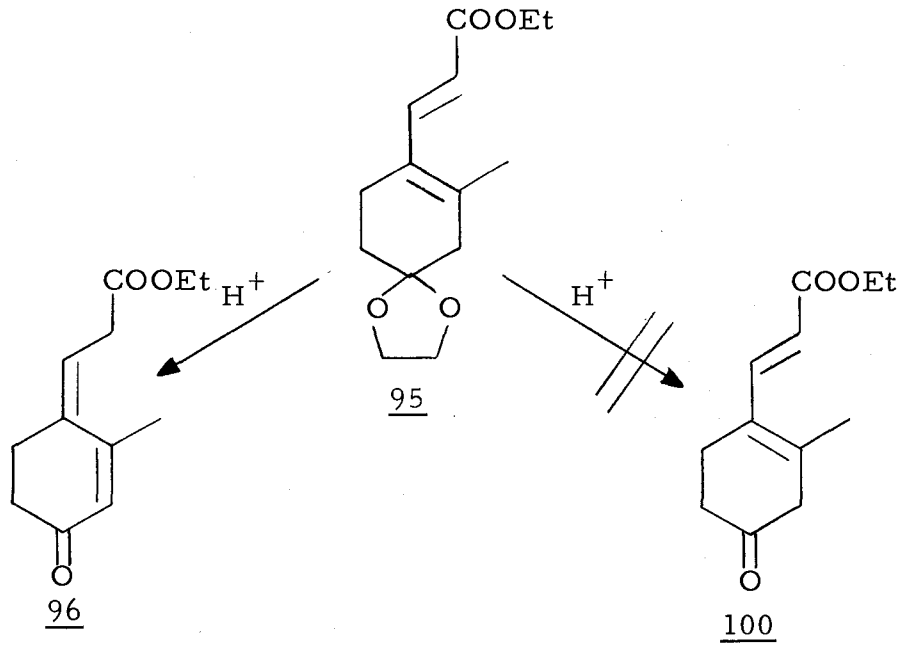
(b) reduction of the ketone to an alcohol, and (c) extension of the carboxyl function by two carbons to give an $\alpha, \beta, \gamma, \delta$-unsaturated ester. Scheme 11 depicts the synthesis pathway leading from 91 to the key intermediate 99.

Schaffner has shown that ketalization of Hagemann's ester is accompanied by an acid-catalyzed shift of the double bond, giving 92 in 76% yield (27). Reduction of 92 with lithium aluminum hydride converted the ester into allylic alcohol 93 in 84% yield. Activated manganese dioxide (28), a reagent known to selectively oxidize allylic alcohols to aldehydes or ketones, was successfully employed to convert 93 to aldehyde 94. Attempts to effect a two-carbon homologation of 94 by means of a Knoevenagel condensation with malonic acid proved fruitless (28). The use of the Wittig reaction (29) was investigated, but the phosphonate modification (30), using the anion of triethyl phosphonacetate was found to produce 95 in significantly better yield (86%).

It had been hoped that 95 could be converted to 100 by deketalization, and thence to 98 by reduction of the ketone. Deketalization under a variety of conditions, however, produced only conjugated ketone 96.

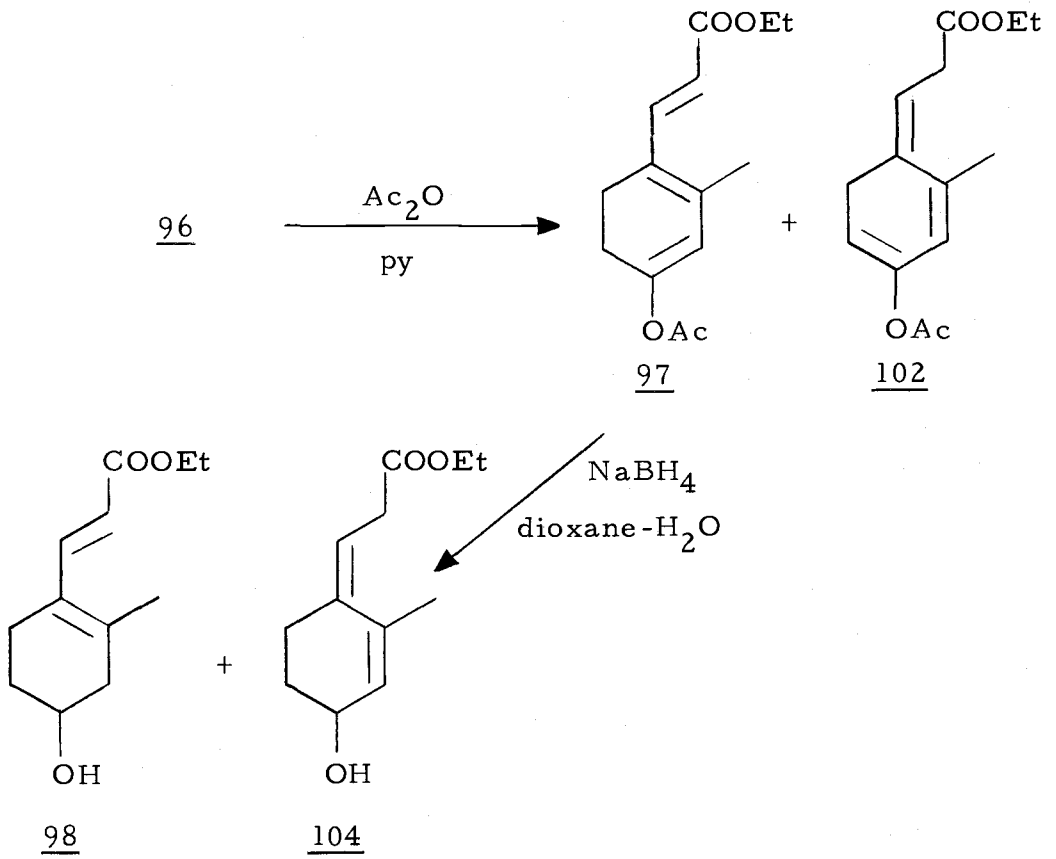
Scheme 11.


COOEt
HO OH
H+
91
92
LAH
CH2OH
93
MnO2
CHO
94
(EtO)2PCH2COOEt
NaH
95
H+
96
Ac2O
pyridine
97
NaBH4
dioxane-H2O
OAc
OR
98 R=H
99 R=Ac



The problem of double bond isomerization was circumvented by the reduction of enol acetate 97 (31) with sodium borohydride in the presence of water. The reaction proceeds via initial hydrolysis of the enol acetate by hydroxide, followed by tautomerization to the ketone, and reduction of the latter at a rate faster than the double bond migrates. Treatment of 96 with acetic anhydride in pyridine gave enol acetates 97 and 102 as a 1:1 mixture (~75%). Attempts to enhance the proportion of 97 by acid catalyzed enol acetate formation, using perchloric acid and acetic anhydride, or with isopropenyl acetate and p-toluenesulfonic acid, resulted in unuseable mixtures. Reduction of the mixture of 97 and 102 with sodium borohydride in aqueous dioxane gave alcohols 98 and 104, which could be separated by column chromatography. Alcohol 98 was then protected as its acetate (99) by

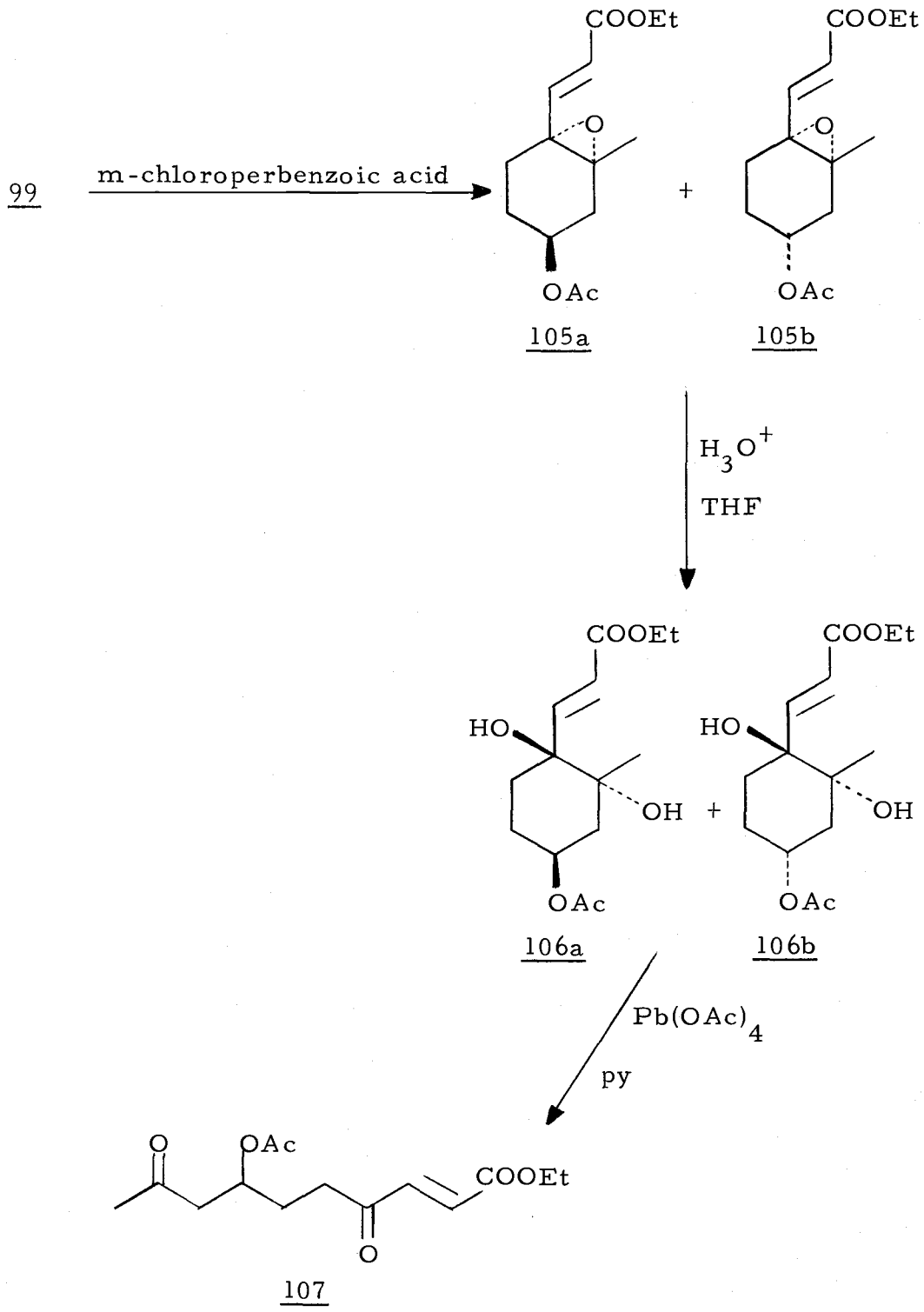
reaction with acetic anhydride in pyridine.



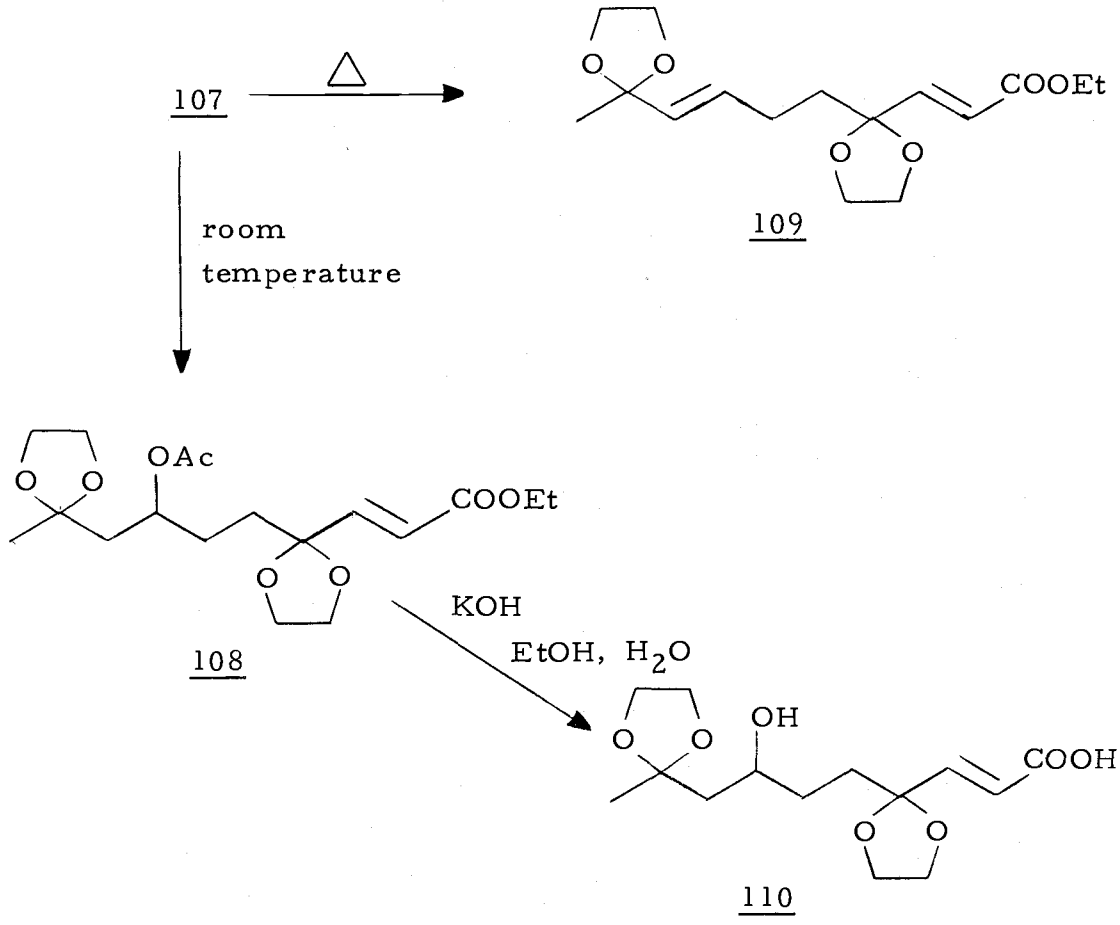
At this point, an oxidative cleavage of the cyclohexene double bond of 99 would have produced vermiculinic acid (65), as its acetate and ethyl esters. Cleavage of 99 with ozone was ruled out because of the unselective attack at double bonds which this reagent typically exhibits (32). Osmium tetroxide (33) and ruthenium tetroxide (34), both of which have been extensively used for oxidative cleavage of olefins were also eliminated since they invariably give poor yields with tetrasubstitured double bonds. On the other hand, m-chloroperbenzoic acid reacts readily and often selectively with electron-rich,

tetrasubstituted alkenes. Moreover, in 98, the α, β-unsaturated linkage, which is in most direct conjugation with the ester, should be particularly slow to epoxidize (35). In fact, treatment of 98 with m-chloroperbenzoic acid gave the desired epoxide 105 in 96% yield. Spectroscopic examination of the product by NMR showed it to be a 2: 1 mixture of the two possible diastereomers.

Attempted hydrolysis of 105 using 1% perchloric acid in aqueous tetrahydrofuran at room temperature produced only starting material after 24 hours. Successful diol formation was found to require refluxing the epoxide in a mixture of 3% perchloric acid and aqueous tetrahydrofuran for 45 minutes. These conditions gave 106 (89%) as a separable mixture of 106a and 106b. Diol 106 was converted to the protected vermiculinic ester 107 by oxidation with lead tetraacetate in pyridine (36) and ethyl acetate for 20 minutes. The reaction, under these conditions, was almost quantitative, but a pronounced drop in yield occurred as reaction time was extended, due to further oxidation of the product with lead tetaacetate. Other oxidizing agents, such as sodium periodate (37) and manganese dioxide (38), both of which are known to effect glycol cleavage, gave no reaction with 106. The lack of reactivity in these cases is probably due to the trans disposition of the glycol moiety, a consequence of the diaxial opening of epoxide 105. Formation of a cyclic intermediate is thus prohibited.


99
m-chloroperbenzoic acid
COOEt
O
OAc
105a
+
COOEt
O
OAc
105b
H_3O^+
THF
COOEt
HO
OH
OAc
106a
+
COOEt
HO
OH
OAc
106b
$Pb(OAc)_4$
py
O
OAc
COOEt
O
107

Diketone 107 was converted to diketal 108 in order to avoid elimination of the sensitive β-acetoxyketone in subsequent steps. This was accomplished by allowing 107 to stand at room temperature with ethylene glycol in the presence of p-toluenesulfonic acid as catalyst. The use of refluxing benzene to azeotropically remove water, which is formed in this ketalization, resulted in product 109 derived from elimination of the acetoxyl group. Saponification of 108 with potassium hydroxide in aqueous ethanol at room temperature, for 24 hours produced vermiculinic acid diketal 110 in 83% yield.

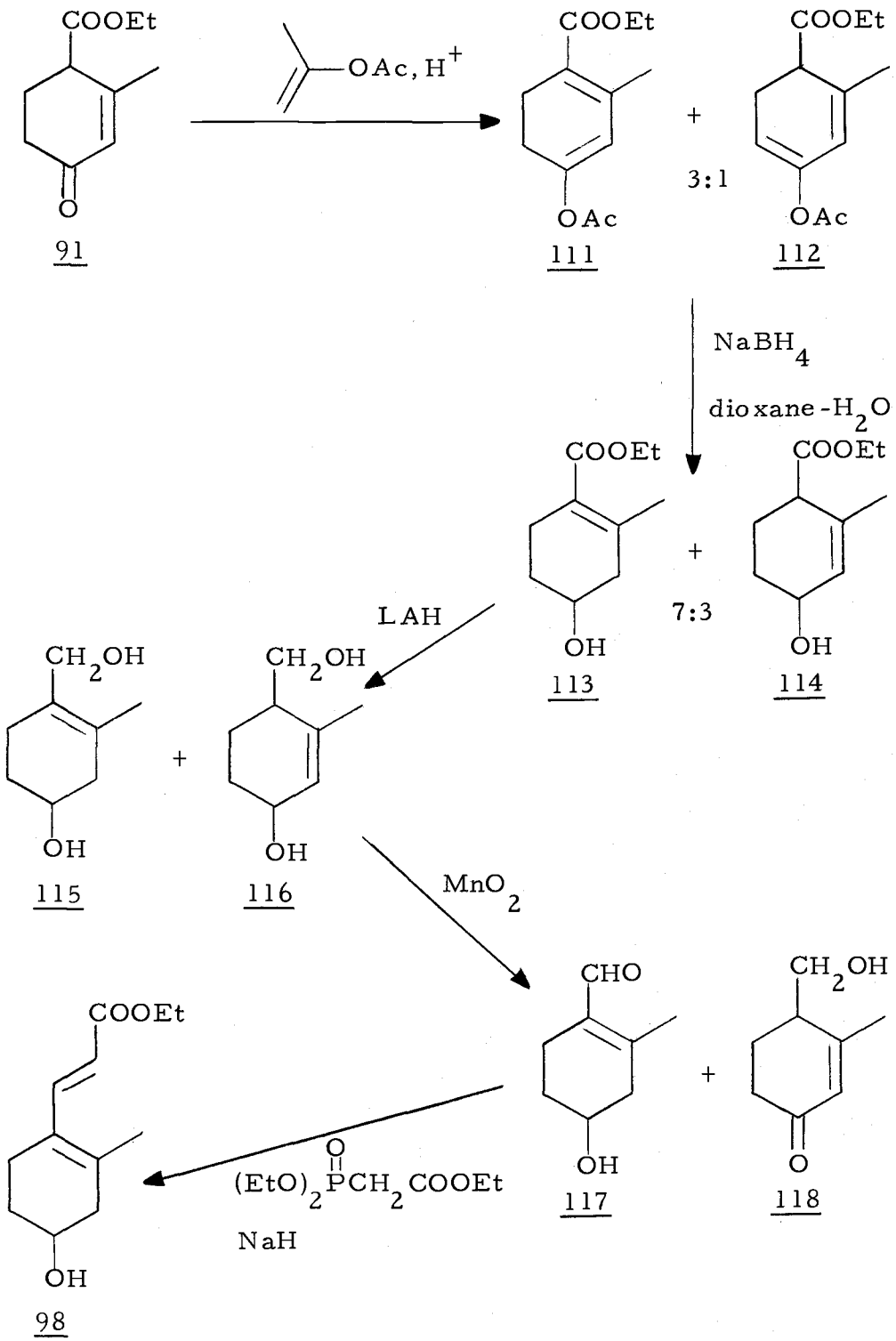


A major difficulty associated with the route outlined above is the low yield (40%) encountered in the formation of enol acetate 97. In order to circumvent this problem, a new approach was developed in which Hagemann's ester (91) was converted to 113 via reduction of enol acetate 111. This new pathway, shown in Scheme 12, was used as the principal route to 98.

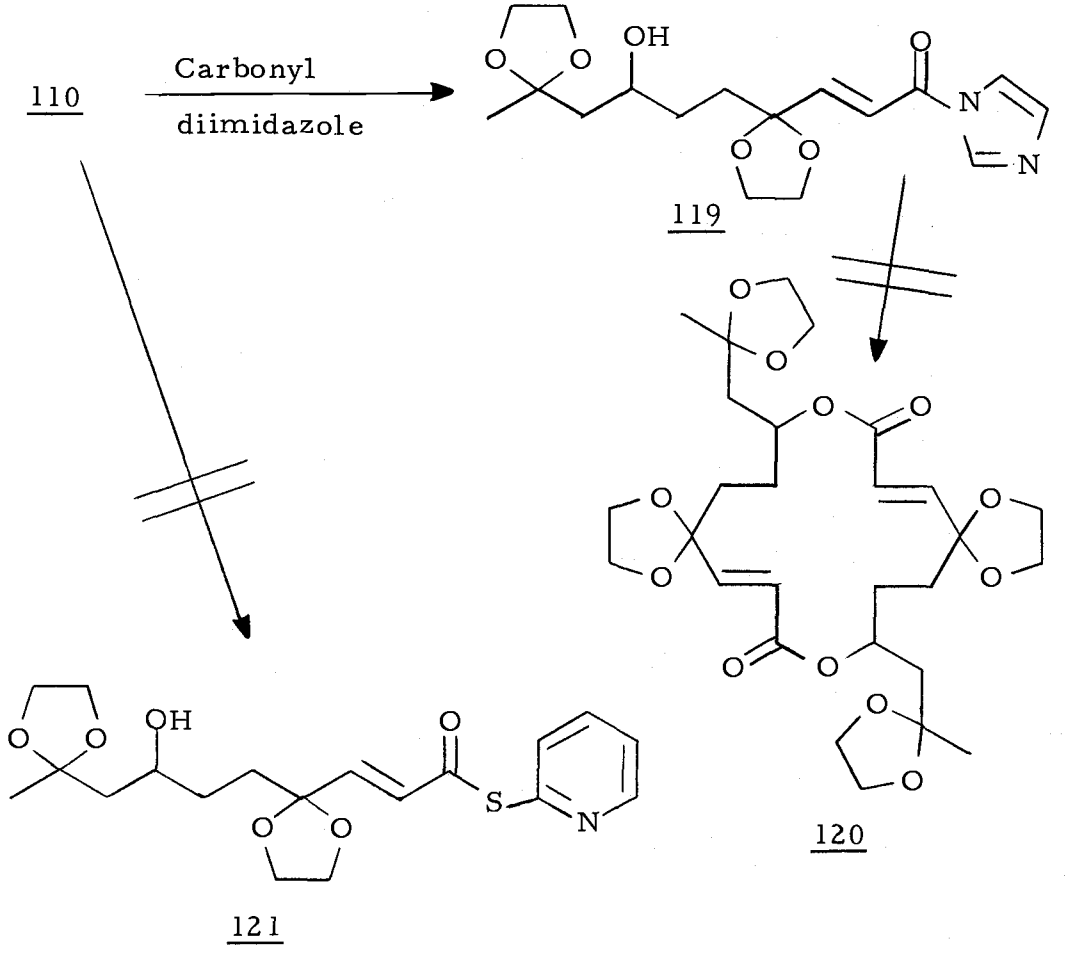
Enol acetylation of Hagemann's ester was carried out using isopropenyl acetate (39) and p-toluenesulfonic acid as catalyst. This gave the desired product 111, admixed with 112, in a 3:1 ratio. Reduction of the mixture with sodium borohydride in aqueous dioxane furnished an inseparable mixture of alcohols 113 and 114, which was reduced with lithium aluminum hydride in ether to yield diols 115 and 116. Allylic oxidation of these diols with activated manganese dioxide gave aldehyde 117 and ketone 118, from which 117 was separated by column chromatography. The purified aldehyde (117) was converted into 98 in 95% yield by condensation with triethyl phosphonoacetate.

With hydroxy acid 110 in hand, a method was sought for its lactonization to vermiculine tetraketal 120. The procedure which Raphael had successfully used for the synthesis of pyrenophorin (66) (25) involved activation of a carboxylic acid (88) (see page 33) as its imidazolide 89. This was followed by base-catalyzed lactonization. The same approach in our hands using acid 110 gave no evidence of lactone formation. The ketal function at C-9 very probably makes

Scheme 12.


COOEt
OAc, H+
91
COOEt
OAc
111
+
3:1
COOEt
OAc
112
NaBH4
dioxane-H2O
COOEt
OH
113
+
7:3
COOEt
OH
114
LAH
CH2OH
OH
115
+
CH2OH
OH
116
MnO2
CHO
OH
117
+
CH2OH
O
118
COOEt
OH
98
(EtO)2P(O)CH2COOEt
NaH

esterification of the sterically-hindered imidazolide 119 unfavorable. The use of the 2-pyridyl thiolester as an activated carboxyl intermediate for lactonization has been demonstrated in an earlier synthesis of vermiculine (26). However, all attempts to produce thiolester 121 gave a polymer, which from the disappearance of vinyl protons in the NMR appeared to be the result of initial Michael attack by thiol on the double bond of 110. Carboxyl activation via dicyclohexylcarbodiimide, pivaloyl chloride, oxalyl chloride, or trifluoroacetic anhydride also produced no indication of a lactonized product.

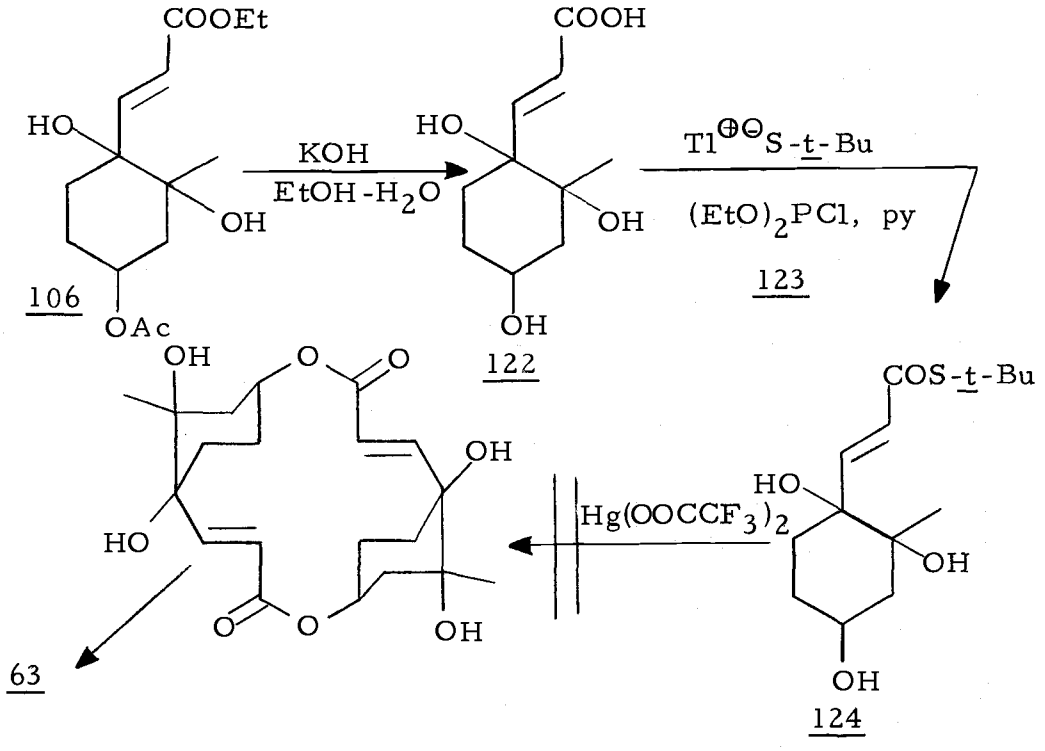


Since all attempts to bring about macrolide formation from 110 had been unsuccessful, attention was turned towards lactonization at an earlier stage in the sequence. Triol 122 appeared to be a suitable substrate for this purpose and was obtained in 87% yield by saponification of 106 with potassium hydroxide. However, attempts to initiate diolide formation from 122 via mixed anhydrides formed with pivaloyl chloride or diethyl chlorophosphate were unsuccessful.

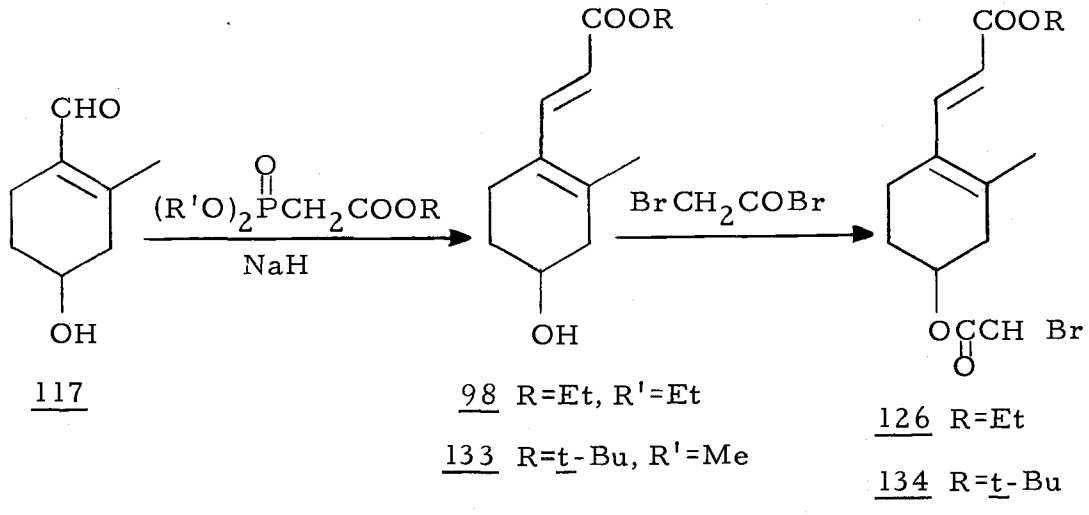
At this point, Masamune and co-workers (40) reported the use of t-butyl thiolesters as activating groups, including a lactonization to form the aglycone of methymycin (40). Thus, thiolesters of this type, upon treatment with mercuric trifluoroacetate in the presence of an alcohol are smoothly converted into the corresponding esters or lactones. Thiolester 124 was produced in 28% yield by sequential addition of diethyl chlorophosphate and the thallous salt of t-butylthiol (123) (40), to carboxylic acid 122. Treatment of 124 with mercuric trifluoroacetate in acetonitrile, however, failed to produce any trace of lactone.

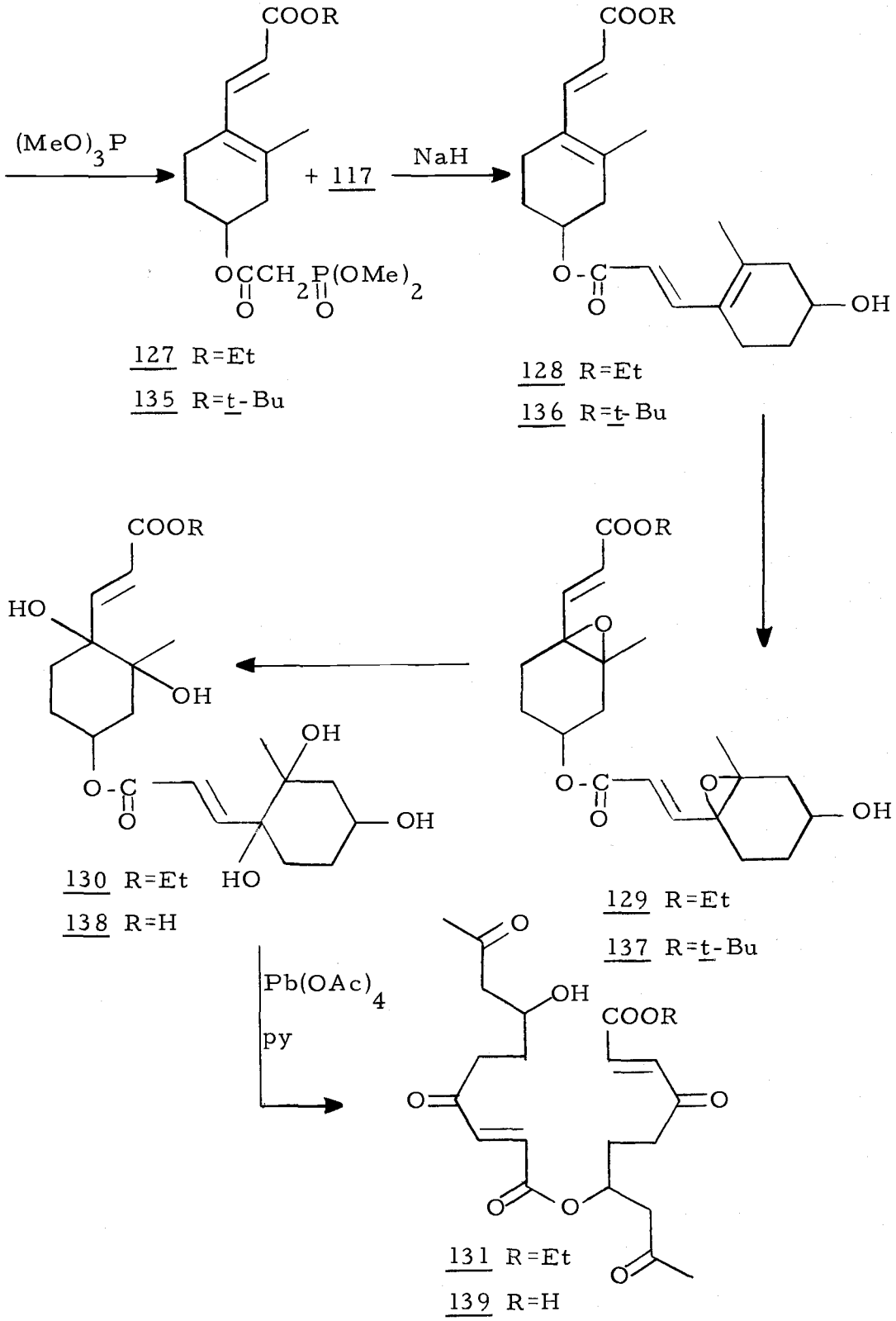
Since efforts to construct the skeleton of vermiculine by lactonization of a monomeric precursor had been unsuccessful, a route (Scheme 13) was sought which would lead to the synthesis of a dimeric, noncyclic precursor (139). This approach, in which lactone linkages are formed at separate stages, has the advantage that only

one coupling would be required at the final step to complete the macrolide.



Scheme 13.




COOR
(MeO)3P
+ 117
NaH
OCCH2P(OMe)2
O
O
127 R=Et
135 R=t-Bu
128 R=Et
136 R=t-Bu
OH
129 R=Et
137 R=t-Bu
HO
130 R=Et
138 R=H
Pb(OAc)4
py
131 R=Et
139 R=H

Bromoacetate 126 was prepared from 99 by the action of bromoacetyl bromide in methylene chloride. The Arbusov reaction of 126 with trimethylphosphite produced phosphonate 127 (41), which underwent condensation with 117 in the presence of sodium hydride in tetrahydrofuran to give the dimeric product 128 (63% from 99). Epoxidation of 128 with m-chloroperbenzoic acid gave diepoxide 129 in 96% yield, as a diastereomeric mixture. Acidic hydrolysis of 129 in aqueous tetrahydrofuran with 3% perchloric acid produced the pentahydroxy ester 130, again as a mixture of diastereomers. Treatment of 130 with lead tetraacetate in pyridine and ethyl acetate resulted in cleavage of the pair of 1,2-glycols to yield 131 in 85% yield. At this stage, the quantity of material remaining was considered to be too limited to permit a study of the selective ester hydrolysis required for 139. Consequently, a modification of this approach was investigated (Scheme 13), which began from t-butyl ester 133. The reaction of trimethylphosphite with t-butyl bromoacetate gave 132, which underwent condensation with 117 to afford 133 in 82% yield. In order to avoid acidic conditions, the formation of bromoacetate 134 was carried out by addition of 133 to a solution of bromoacetyl bromide and excess pyridine in ether. Conversion of 134 to phosphonate 135 proceeded in 88% yield with 1.2 equivalents of trimethylphosphite. Treatment of 135 with sodium hydride, followed by addition of aldehyde 117, gave a diastereomeric mixture of

diesters 136. This dimer was epoxidized to 137 in 91% yield by

$$BrCH_2COOt\text{-}Bu + (MeO)_3P \xrightarrow{\Delta} (MeO)_2\overset{\overset{O}{\|}}{P}CH_2COOt\text{-}Bu$$

132

m-chloroperbenzoic acid, with potassium hydrogen phosphate present as a buffer to avoid cleavage of the acid-sensitive t-butyl ester. Treatment of bisepoxide 137 with 3% perchloric acid in refluxing aqueous glyme for 30 minutes effected hydrolysis of the two epoxides and the t-butyl ester to produce the pentahydroxy carboxylic acid 138. Oxidative cleavage of 138, with lead tetraacetate was complicated by a reaction of the lead with the carboxyl group, affording only a low yield of what is thought to be 139. The work was stopped at this point in order to write this thesis.

In summary, it has been shown that the approaches described above lead to a number of potential precursors to vermiculine. Attempts to form the diolide structure by activation of the precursors as their imidazolide (25), 2-pyridyl thiolester (26), t-butyl thiolester (40), or mixed anhydrides have been unsuccessful. With the development of a route to dimeric intermediates, it is hoped that a cyclization will be forthcoming.

Further research directed toward cyclization of the precursors described in this work must, however, involve a search for methods

better than those currently available by which a carboxylic acid group can be suitably activated for macrolide formation, without undesirable reactions occurring at other functionality.

V. EXPERIMENTAL

General

Infrared spectra (ir) were obtained with a Perkin-Elmer 137 infrared spectrophotometer. Ultraviolet spectra (UV) were obtained with a Carey 15 spectrophotometer. Nuclear magnetic resonance spectra (nmr) were obtained with either a Varian HA-100 or a Varian EM-360 spectrometer and are reported in δ units with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) are given in Hertz; s = singlet, d = doublet, t = triplet, q = quartet and p = pentuplet. Elemental analysis were provided by Dr. Rottschaefer at the University of Oregon. Mass spectra were obtained by Dr. Rottschaefer or Dr. Wielesek at the University of Oregon using a Consolidated Electrodynamics Corporation model 21-110 double focus mass spectrometer equipped with a direct inlet system and using 70 ev ionization. Ozone was produced by a Welsbach Ozonator. Gas chromatographic results were obtained on a Varian aerograph model 700 gas chromatograph using a 5 ft x 0.25 in, SE-30 (25% on Chrom G) column. Thin layer chromatograms (tlc) were made on Em Reagents silica gel PF-254. Column chromatography was done with neutral aluminum oxide woelm or neutral silica gel woelm for column chromatography and was used as activity II. All boiling points (bp) and melting points (mp) are uncorrected.

Preparation of 2, 6-Dimethoxytoluene (34)

A 26.26 g (0.657 mole) sample of sodium hydroxide was dissolved in 100 ml of water. To this was added 20.55 g (0.165 mole) of 2-methylresorcinol. The solution was then chilled in an ice bath and 40.80 g (0.324 mole) of dimethyl sulfate was added over a 10 min period. The solution was heated at 100° for 4 hr then stirred overnight at room temperature. The solution was extracted with ether (4x100 ml), the extract was dried ($NaSO_4$), and the ether was removed under vacuum. The product was distilled at 120°/15 mm, to give 25.50 g (80%) of 34: ir (neat) 1235, 1030 cm^{-1}; nmr ($CDCl_3$) δ 2.15 (3H, s), 3.85 (6H, s), 6.5-7.1 (5H, m).

Preparation of 3-Methoxy-2-methylphenol (35)

A 12.4 g (0.10 mole) sample of 2, 6-dihydroxytoluene 33 was added to a solution of 50 ml of water and 4.00 g (0.10 mole) of sodium hydroxide. To this mixture, 12.8 g (0.10 mole) of dimethyl sulfate was added slowly. The solution was refluxed with stirring for 8 hr. After cooling, an additional 4.0 g (0.10 mole) of sodium hydroxide was added, and the solution was extracted with ether to remove all non-phenolic products. The aqueous portion was acidified with dilute hydrochloric acid and extracted with ether. The ether portion was washed with sodium bicarbonate solution, dried ($MgSO_4$), and the

solvent was remived *in vacuo*. The crude product was distilled at 58-68°C (0.04 mm), to yield 9.2 g (67%) of 35: ir (neat) 3400 (-OH), 1580, 770 cm^{-1}; nmr ($CDCl_3$) δ 2.05 (2H, s), 3.72 (3H, s), 5.02 (1H, s, -OH), 6.38 (1H, d, J=7), 6.42 (1H, d, J=7), 6.97 (1H, t, J=7).

Preparation of Potassium Nitrosodisulfonate (Fremy's Salt)

With stirring, 200 g of ice, 100 ml of 5N sodium nitrite, and 100 ml of 5N sodium bisulfite were mixed in a 3-liter flask. The solution was made acidic by the addition of 20 ml of glacial acetic acid, and stirring was continued for 15 min. An 18 ml sample of 28% ammonium hydroxide was then added (to make the solution basic), followed by a solution of 12.6 g of potassium permanganate in 400 ml of water. Manganese dioxide started forming immediately, and stirring was continued for 30 min. The solution was then vacuum filtered (aided by celite) to remove the manganese dioxide. To the deep violet filtrate, saturated potassium chloride was added (*ca* 1.5 ml/ml of filtrate). Stirring was continued for 1 hr at 0°C, by which time the orange Fremy's salt had completely precipitated. The product was collected by filtration (*ca* 28 g) and used immediately. Attempts to dry the product resulted in rapid decomposition!

Preparation of 2-Methoxy-3-methylbenzoquinone (29)

A. Oxidation of 34 with Sodium Dichromate. To a solution of 125.02 g (0.420 mole) of sodium dichromate in 220 ml of glacial acetic acid at 60°C was added 5.6 g (0.038 mole) of 2,6-dimethoxytoluene (34) in 25 ml of acetic acid. Upon heating to 90°C the reaction became very vigorous and was kept under control by cooling with an ice bath. After 7 min, the solution was extracted with ether (3x200 ml), and the ether was washed with water and then saturated aqueous sodium bicarbonate solution until neutral. The ether solution was then dried ($NaSO_4$), and the solvent was removed in vacuo. The product was distilled at 55-60°C (0.04 mm), to yield 1.01 g (18%) of 29: ir (neat) 1680, 1665, 1620, 840 cm^{-1}; nmr ($CDCl_3$) δ 2.02 (3H, s), 4.10 (3H, s), 6.65 (2H).

B. Oxidation of 35 with Fremy's Salt. A 43 g (0.21 mole) sample of potassium nitrosodisulfonate (Fremy's salt) was dissolved in 2.5 liters of water containing 16.2 g (0.20 mole) of sodium acetate (buffer). To this solution, 10 gm (0.072 mole) of 35 in 20 ml of ether was added. The solution was stirred for 2 hr and then extracted with ether (3x300 ml). The organic solution was dried ($MgSO_4$), and the ether was removed under vacuum, leaving a dark red oil. This was distilled at 55-60°C (0.04 mm) to give an orange oil, which solidified upon refrigeration; yield 4.2 g (42%).

Preparation of cis-5, 8, 9, 10-Tetrahydro-2-methoxy-3, 6, 7-trimethyl-1, 4-naphthoquinone (36)

A 3.28 g (0.022 mole) sample of quinone 29 was mixed with 1.9 g (0.023 mole) of 2, 3-dimethylbutadiene in 50 ml of petroleum ether (bp ~ 95°C) and heated for 8 hr at 65°C under a nitrogen atmosphere. The product crystallized after cooling the reaction solution to -78°C. It was collected by filtration and recrystallized from petroleum ether at -78°C to give 3.66 g (72%) of 36: ir (nujol) 1680, 1660, 1608 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (6H, s), 1.88 (3H, s), 2.0-2.6 (6H), 3.00-3.24 (2H, m), 3.96 (3H, s); m/e 234 (M^+).

Anal Calcd. for 36 $C_{14}H_{18}O_3$: C, 71.79; H, 7.70. Found: C, 71.53; H, 7.74.

Preparation of cis-1, 4, 5, 8-9, 10-Hexahydro-1, 4-dihydroxy-2-methoxy-3, 6, 7-trimethylnaphthalene (37)

A solution of 150 mg (0.64 mmole) of 36 in 15 ml of anhydrous ether was slowly added to 10 ml of ether containing 27 mg (0.70 mmole) of lithium aluminum hydride at -50°C. The solution was stirred for 0.5 hr, and then 40 ml of ethyl acetate was added, followed by careful addition of 1 ml of water. The solution was filtered and the filtrate was washed with 50 ml of ethyl acetate. The combined organic solutions were dried ($MgSO_4$), and the solvent was removed by evaporation, with the temperature maintained below 35°C. This

produced a yellow solid which was decolorized by washing with petroleum ether. The compound was further purified by dissolving it in ethyl acetate, removing the solvent in vacuo, and rewashing the solid with petroleum ether (mp 146-149°). Attempts to recrystallize 37 resulted in a new produce of undetermined structure; yield 126 mg (82%): ir (nujol) 3400 (-OH), 1660, 1310 (sharp) cm^{-1}; nmr (DMSO) δ 1.52 (9H, s), 1.55-1.83 (2H), 1.96-2.20 (4H), 2.48-2.58 (two peaks, 2H, disappeared on addition of D_2O), 3.50 (3H, s), 4.38 (2H, m).

Preparation of 5, 8-Dihydro-1, 4-dihydroxy-2-methoxy-3, 6, 7-trimethylnaphthalene (43)

A. Reduction of 36 with Sodium Borohydride. A 200 mg (0.86 mmole) sample of 36 was added to 34 mg (0.86 mmole) of sodium borohydride in 20 ml of t-butanol, and the solution was stirred at room temperature for 3 hr. Thirty ml of water was added and the solution was extracted with ether (4x30 ml). The organic layer was dried ($MgSO_4$), and the solvent was removed by evaporation, leaving 186 mg (93%) of 43 as an off-white solid: ir (nujol) 3400, 1100 cm^{-1}; nmr (DMSO) δ 1.74 (6H, s), 2.10 (3H, s), 3.12 (4H, s), 3.42 (2H, s), 3.64 (3H, s).

B. Meerwein-Poundorf-Verley Reduction of 36. A 200 mg (0.86 mmole) sample of Diels-Alder adduct 36 was dissolved in 50 ml of isopropanol containing 1.0 g of aluminum isopropoxide. The

mixture was slowly distilled (0.25 ml/min) until 50 ml of distillate had been collected (additional alcohol was added to maintain the flask volume at 50 ml). The mixture was added to 100 ml of 0.1N hydrochloric acid, the product was extracted with ether, washed with aqueous sodium bicarbonate, and dried ($MgSO_4$). The solvent was removed leaving a solid material which appeared to be 43 in ca 50% purity, based on its ir spectrum and thin-layer chromatography.

Preparation of 5, 8-Dihydro-2-methoxy-3, 6, 7-trimethylnaphthalene (38)

A 200 mg (0.84 mmole) sample of diol 37 was dissolved in 20 ml pyridine and cooled to -5°C. To this solution, 8.4 g (55.0 mmole) of phosphorus oxychloride was added slowly with stirring. The reaction was allowed to slowly warm to room temperature and was stirred for 24 hr. The excess phosphorus oxychloride was destroyed by slow addition of water at -5°C. The solution was added to 50 ml of water and extracted with ether. The ether layer was washed with dilute hydrochloric acid, saturated aqueous copper sulfate, and dried ($MgSO_4$). Upon removal of the ether, a solid residue was left which was recrystallized from methanol to yield 105 mg (65%) of 38: mp 112-114°C; ir (CCl_4) 1610, 1500, 1238 (sharp) cm^{-1}; nmr ($CDCl_3$) δ 1.76 (6H, s), 2.14 (3H, s), 3.22 (4H, s), 3.78 (3H, s), 6.55 (1H, s), 6.88 (1H, s); m/e 202 (M^+).

Preparation of 1, 4, 5, 8-Tetrahydro-2-methoxy 3, 6, 7-trimethylnaphthalene (39)

A 109 mg (0.54 mmole) sample of 38 in 20 ml of tetrahydrofuran was added to 80 ml of liquid ammonia and 20 ml of tetrahydrofuran. To this solution, 104 mg (14.9 mmole) of lithium wire (1% sodium) was added. The mixture was stirred for 0.5 hr and ethanol was added dropwise until the blue color disappeared. The reduction was repeated with a further 50 mg of lithium. After the final addition of ethanol, the ammonia was allowed to evaporate. One gram of ammonium chloride was then added, followed by the careful addition of 50 ml of water. The product was extracted with ether, dried ($MgSO_4$), and the ether was removed under vacuum. The solid residue was purified by recrystallization from methanol, giving 82 mg (74%) of 39: ir (CCl_4) 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.60 (9H, s), 2.48 (4H, s), 2.55 (4H, s), 3.54 (3H, s).

Preparation of 1, 2-Dimethylenecyclopentane (28)

A 5 g (0.027 mole) sample of 1, 2-bis(dimethylaminomethyl)-cyclopentane 52 (20) was treated with 20 ml of 30% hydrogen peroxide with stirring (cooling was required to maintain the solution at room temperature) for 48 hr. The unreacted peroxide was then decomposed by addition of a catalytic amount of platinum black with continued stirring for 3 hr. Water was removed from the mixture, first by

evaporation (40°) and then at high vacuum (.03 mm) for 6 hr. The amine oxide (53) remained as a viscous oil. To this material, 20 mg of hydroquinone was added, and the oxide was heated at 170-180°C (150 mm) in a continuous stream of nitrogen. The distillate was collected in two dry ice-acetone traps and was taken up in 15 ml of ether after completion of the reaction. The ether was washed with 0.1N hydrochloric acid until the washings were acidic, and then with saturated aqueous sodium bicarbonate. The ether solution of 28 was dried ($MgSO_4$) and used without further purification.

Preparation of cis-6,7-Cyclopenteno-5,8,9,10-tetrahydro-2-methoxy-3-methyl-1,4-naphthoquinone (30)

An ethereal solution of 28 was added to 2.50 g (16.4 mmole) of quinone 29 in 50 ml of petroleum ether, and the solution was stirred for 16 hr at room temperature under a nitrogen atmosphere. The product was obtained by cooling the solution to 78°C and collecting the yellowish-white crystals by filtration. These were recrystallized from petroleum ether at -78°C to give 1.2 gm (30%) of 30: mp 87-89°C; ir (nujol) 1690, 1655, 1600, 1280 cm^{-1}; nmr ($CDCl_3$) δ 1.88 (3H, s), 1.70-2.10 (2H, m), 2.10-2.60 (8H, m), 3.10-3.35 (2H, m), 3.96 (3H, s); m/e 246 (M^+).

Anal: Calcd for 30 $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.23; H, 7.41.

Preparation of cis-6,7-Cyclopenteno-1,4,5,8,9,10-hexahydro-1,4-dihydroxy-2-methoxy-3-methylnaphthalene (31)

A 150 mg (0.64 mmole) sample of 30 in 20 ml of anhydrous ether was slowly added to 28 mg (0.73 mmole) of lithium aluminum hydride in 25 ml of ether at -60° C with stirring. The solution was stirred for 1.5 hr after the completion of addition and then 40 ml of ethyl acetate was added, followed by 2 ml of water. The solution was allowed to warm to room temperature and was extracted with ethyl acetate, dried ($MgSO_4$), and the solvent was removed by evaporation at < 35° C. The product was further purified by redissolving it in ethyl acetate, removing the solvent again under vacuum, and rewashing with petroleum ether to yield 108 mg (68%) of 31: ir (nujol) 3500, 3000, 1680 (weak) 1630 (weak).

Preparation of 6,7-Cyclopenteno-5,8-dihydro-2-methoxy-3-methylnaphthalene (32)

To 928 mg (3.7 mmole) of diol 31 in 20 ml of pyridine at 0° C was slowly added 6.0 g (40 mmole) of phosphorus oxychloride. After completion of the addition, the solution was heated at 65° C for 18 hr. The excess phosphorus oxychloride was destroyed by careful addition of water at 0° C. The product was extracted with ether (3x50 ml), and the ether extract was washed with 1N hydrochloric acid until acidic, with aqueous sodium bicarbonate, and dried ($MgSO_4$). Removal of the

solvent *in vacuo* left an off-white solid, which was purified by chromatography on alumina (elution with hexane) to give 434 mg (55%) of *32*: ir (CCl_4) 1500, 1235, 1205, 1090 cm^{-1}; nmr ($CDCl_3$) δ 1.80-2.20 (2H, m), 2.19 (3H, s), 2.22-2.50 (4H, m), 3.31 (4H, s), 3.80 (3H, s), 6.60 (1H, 2), 6.91 (1H, s).

Preparation of 6,7-Cyclopenteno-1,4,5,8-tetrahydro-2-methoxy-3-methylnaphthalene (*26*)

A 198 mg (0.93 mmole) sample of *32* was dissolved in 100 ml of dry tetrahydrofuran and 80 ml of distilled liquid ammonia was added. A 100 mg (14.9 mmole) sample of lithium wire was added to the solution and 10 min later, 2 ml of 100% ethanol was added. After 15 min the solution became colorless, at which time the ammonia was allowed to evaporate. To the residue was added 50 ml of water and the product was extracted with ether (4x100 ml), dried ($MgSO_4$), and isolated by removing the solvent *in vacuo*. The residue was chromatographed on alumina, eluting with hexane, to give 172 mg (86%) of *26*: ir (CCl_4) 1135, 1165, 1200 cm^{-1}; nmr ($CDCl_3$) δ 1.65 (3H, s), 1.70-2.10 (2H, m), 2.10-2.40 (4H, m), 2.45-2.80 (8H, two broad singlets of 4H each), 3.52 (3H, s); m/e 216 (M^+).

Anal: Calcd for $C_{15}H_{20}O$: C, 83.33; H, 9.25. Found: C, 83.33; H, 9.36.

Ozonolysis of 6,7-Cyclopenteno-1,4,5,8-tetrahydro-2-methoxy-3-methylnaphthalene (26)

A 216 mg (1.0 mmole) sample of 26 was dissolved in 150 ml of methylene chloride at -78° C. A stream of ozone was passed through the solution until a light blue coloration indicated the presence of excess ozone. Nitrogen gas was then passed through the solution for one hour to remove excess ozone. The solution of ozonide was reduced with hydrogen and 10% palladium-on-charcoal at room temperature for 3 hr. The solution was filtered and the solvent was removed under vacuum, leaving a light yellow oil. Upon mixing 10 mg of the product with 0.5 ml of aqueous ferric chloride a red color was produced, indicating the presence of enol: ir (neat) 3500 (broad), 1730 (broad) cm^{-1}; nmr ($CDCl_3$) complex with discernable singlets at δ 3.67 and 3.80 (1:3); UV (EtOH) 273 nm (neutral), 298 nm and 358 nm (shoulder) (after addition of 1 drop 3N sodium hydroxide).

Preparation of 4,4-Ethylenedioxy-1-hydroxymethyl-2-methylcyclohexene (93)

A 17.73 g (78.5 mmole) sample of ester 92 (27) in 50 ml of ether was added to 2.9 g (76.3 mmole) of lithium aluminum hydride in 400 ml of ether at 0° C by dropwise addition. Stirring was continued at room temperature for 4 hr after addition was complete. The excess hydride was decomposed by careful addition of water. The

solution was filtered to remove aluminum salts, which were washed with ether. The combined ether extract was evaporated in vacuo and the residue was distilled at 108-112°C (.07 mm) to yield 12.13 g (84%) of 93: ir (neat) 3500, 2900, 1650 (weak), 1085 cm^{-1}; nmr ($CDCl_3$) δ 1.75 (2H), 1.70 (3H, s), 2.24 (4H, s), 3.15 (1H, disappears upon addition of D_2O), 4.00 (4H, s), 4.15 (2H, s); mass spectrum m/e 184.108 (M^+, calc for $C_{10}H_{16}O_3$ 184.110).

Preparation of 4,4-Ethylenedioxy-1-formyl-2-methylcyclohexene (94)

A 5.02 g (27.3 mmole) sample of alcohol 93 was dissolved in 15 ml of chloroform and 250 ml of low-boiling petroleum ether. Activated manganese dioxide (50 g) was added and the solution was stirred for 24 hours under a nitrogen atmosphere. The solution was filtered and the manganese dioxide was extracted, first with ether (200 ml), and then with ethanol. The solvent was removed in vacuo, leaving a light yellow oil. Distillation at 95-105° (0.06 mm) gave 3.49 g (69%) of 94: ir (neat) 2950, 2780 (weak) 1665, 1640 cm^{-1}; nmr (CCl_4) 1.64 (2H, t, J=6), 2.13 (3H, s), 2.36 (2H), 2.39 (2H, s), 3.90 (4H, s), 10.04 (1H, s); mass spectrum m/e 182.094 (M^+, calc for $C_{10}H_{14}O_3$ 182.094).

Preparation of Ethyl 3-(4,4-Ethylenedioxy-2-methylcyclohex-1-enyl)acrylate (95)

To a solution of 268 mg (1.20 mmole) of triethyl phosphonoacetate in 5 ml of dry tetrahydrofuran at 0°C, 60 mg (1.20 mmole) of sodium hydride (50% mineral oil suspension) was added with stirring. After 20 min, 184 mg (1.00 mmole) of aldehyde 94 was added, and the solution was allowed to warm to room temperature during a 30-min period. Wet ether was added to destroy excess sodium hydride, and the solution was poured into 10 ml of water. The product was extracted with ether (3x40 ml), the ether solution was dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed on silica gel, eluting with ether-hexane (1:1), to give 217 mg (86%) of 95: ir (neat) 3000, 1720, 1640, 1620, 1360, 1180 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (3H, t, J=7), 1.79 (2H), 1.90 (3H, s), 2.40 (4H, s, broad), 4.00 (4H, s), 4.22 (2H, q, J=7), 5.81 (1H, d, J=16), 7.81 (1H, d, J=16); mass spectrum m/e 252.134 (M^+, calc for $C_{14}H_{20}O_4$ 252.136).

Preparation of 3-Methyl-4-(1-carboethoxyethylid-2-en)-cyclohex-2-enone (96)

Ketal 95 (452 mg, 1.79 mole) in 50 ml of acetone containing 100 mg of p-toluenesulfonic acid was heated under reflux overnight. The solution was washed with sodium bicarbonate solution and

extracted with ether. The ether extract was dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was purified by bulb-to-bulb distillation at 125°C/.05 mm, yielding 354 mg (95%) of 96: ir (neat) 3000, 1745, 1670, 1640, 1590 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (3H, q, J=7), 2.12 (3H, s), 2.88-2.28 (4H, m), 3.32 (2H, d, J=7), 4.20 (2H, q, J=7), 5.89 (1H, s), 6.15 (1H, t, J=7); mass spectrum m/e 208.111 (M^+, calc for $C_{12}H_{16}O_3$ 208.110).

Preparation of Ethyl 3-(4-Acetoxy-2-methylcyclohexa-1,3-dienyl)acrylate (97)

A 100 mg (0.481 mmole) sample of ketone 96 was stirred with 0.5 g of acetic anhydride and 1 ml of pyridine for 24 hr. The solution was then washed with saturated, aqueous sodium bicarbonate until the excess acetic anhydride had completely decomposed. The solution was extracted with ether (3x25 ml) and washed with copper sulfate solution. After drying ($MgSO_4$) the solution, ether was removed under vacuum. Thin-layer chromatography on silica gel (ether-hexane, 85:15) showed two principal spots in a 1:1 ratio. The nmr spectrum of the reaction mixture showed a doublet (J=7) at 3.32 and additional olefinic protons at 5.60-6.30, which indicated the presence of 102. The mixture was converted to 98 and 104 without further purification. A sample of 97 was purified by column chromatography on silica gel (ether-hexane, 6:4): ir (neat) 1760, 1710, 1660, 1600, 1560 cm^{-1};

nmr ($CDCl_3$) δ 1.25 (3H, t, J=7), 2.02 (3H, s), 2.10 (3H, s), 2.42 (4H, s, broad), 4.15 (2H, q, J=7), 5.67 (1H, s), 5.70 (1H, d, J=16), 7.67 (1H, d, J=16).

Reduction of Enol Acetates 97 and 102

A mixture of 97 and 102 (87 mg, 0.35 mmole) was dissolved in 4 ml of dioxane and 1 ml of water, to which was added 200 mg of sodium borohydride. The solution was heated at 100° C for 1.5 hr. The reaction was then cooled and 10 ml of water was added. The product was extracted with ether (3x50 ml) and the ether extract was washed with 25 ml of water, dried ($MgSO_4$), and the solvent was removed in vacuo. Chromatography of the residue on silica gel yielded the two isomeric products 98 and 104 in 61% combined yield.

Compound 104, 29.1 mg (29%): ir (neat) 3500, 2960, 1745, 1620 (weak) cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3H, t, J=7), 1.84 (3H, s), 2.22-1.42 (2H, m), 2.60-1.90 (2H, m), 3.17 (2H, d, J=7), 4.18 (2H, q, J=7), 4.44-4.02 (1H, m), 5.80-5.42 (2H, m).

Compound 98, 32.1 mg (32%): ir (neat) 3400, 1710, 1625, 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.41 (3H, t, J=7), 1.50-2.22 (2H, m), 1.92 (3H, s), 2.45 (1H, s, exchangeable), 2.10-2.60 (4H, m), 3.95 (1H, m), 4.22 (2H, q, J=7), 5.80 (1H, d, J=16), 7.80 (1H, d, J=16); mass spectrum m/e 210.129 (M^+, calc for $C_{12}H_{18}O_3$ 210.126).

Preparation of Ethyl 4-Acetoxy-2-methylenclohexa-1,3-dienylcarboxylate (111)

A mixture of 45.54 g (0.250 mole) of Hagemanns' ester (commercial material, distilled), 65 ml of isopropenyl acetate, and 0.5 g of p-toluenesulfonic acid, was refluxed under nitrogen for 12 hr. The mixture was then stirred overnight at room temperature, after which 1.5 g of sodium acetate was added, and the mixtured stirred for a further 20 min. The reaction mixture was poured into 100 ml of water and extracted with ether (2x200 ml). The extract was dried ($MgSO_4$) and the solvent was removed under vacuum, leaving a reddish-yellow oil, which was used without further purification. Gas chromatographic analysis (5 ft x 0.25 in, SE-30 column, 180°C) revealed two products in a ratio of 3:1. The minor product was assigned structure 112 based on nmr peaks at 5.99 and 5.00 (olefinic), and 3.35 (methine). The major product was 111: ir (neat) 1760, 1706, 1580, 1362 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (3H, t, J=7), 2.17 (3H, s), 2.20-2.50 (2H, m), 2.55-2.86 (2H, m), 4.24 (2H, q, J=7), 5.72 (1H, s); m/e 222 (M^+-2, loss of H_2 to form an aromatic fragment).

Ethyl 4-Hydroxy-2-methylcyclohex-1-enylcarboxylate (113)

The crude enol acetate 111 was added to 50 ml of dioxane containing 50 ml of water and 25 g of sodium borohydride at 40°C.

The solution was then heated at 95°C for 2 hr. After the mixture had cooled, 200 ml of water was added, the product was extracted with ether (4x300 ml), and the extract was washed with 100 ml of water. The ether layer was dried ($MgSO_4$) and the solvent was removed under vacuum, leaving 43.4 g (95% from 91) of a red oil which gas chromatographic analysis (5 ft x 0.25 in SE-30 column, 150°C) revealed was a mixture of the two isomers 113 and 114 in a 7:3 ratio.

Compound 113: ir (neat) 3500, 1710, 1640 (weak) cm^{-1}; nmr ($CDCl_3$) δ 1.32 (3H, t, J=7), 1.45-2.10 (2H, m), 2.02 (3H, s), 2.14-2.70 (4H, m), 2.26 (1H, s, -OH), 3.98 (1H, m), 2.21 (2H, q, J=7); mass spectrum m/e 184.112 (M^+, calc for $C_{10}H_{16}O_3$ 184.110).

Compound 114: ir (neat) 3500, 1740 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3H, t, J=7), 1.72 (3H, s), 1.50-2.20 (4H, m), 1.92 (1H, s, -OH), 2.95 (1H, m), 4.20 (2H, q, J=7), 5.71 (1H, m).

Preparation of 4-(Hydroxymethyl)-3-methylcyclohex-3-en-1-ol (115)

A 43.0 g (0.22 mole) sample of the 7:3 isomeric mixture of 113 and 114 was dissolved in 100 ml of ether and added to 10.0 g (0.26 mole) of lithium aluminum hydride in one liter of anhydrous ether at 0°C. After 6 hr the excess lithium aluminum hydride was decomposed, first by addition of wet ether, and then by the dropwise addition of water. The aluminum salts were collected by filtration and washed

twice with ether (100 ml per wash). The ether was removed from the combined organic fractions under vacuum, leaving a colorless oil which was purified by distillation (108-114°C, 0.05 mm) to yield 27.2 g (82%) of a 7:3 mixture of 115 and 116. Separation by gas chromatography (5 ft x 0.25 in, SE-30 column, 150°C) gave a pure sample of 115: ir (neat) 3450 (strong), 1650 (weak), 1065 cm^{-1}; nmr ($CDCl_3$) δ 1.56-2.10 (2H, m), 1.71 (3H, s), 2.00-2.60 (4H, m), 3.99 (1H, m), 4.14 (2H, d), 2.30 (2H, s, -OH); mass spectrum m/e 142.100 (M^+, calc for $C_8H_{14}O_2$ 142.099).

Preparation of 4-Formyl-3-methylcyclohex-3-en-1-ol (117)

A 3.20 g sample of the isomeric mixture (7:3) of diols 115 and 116 was stirred with 32 g of activated manganese dioxide in 25 ml of methylene chloride for 20 hr. The solution was filtered and the manganese dioxide was extracted in a Soxhlet extractor with ether overnight. The organic portions were combined and the solvent was removed under vacuum. The residue was chromatographed on silica gel (ether-hexane, 6:4) to give 1.85 g (83% based on a 1:3 ratio in the starting material) of a light-yellow, low-melting solid (partially solid at room temperature): ir (neat) 1700, 1670, 1370, 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.45-1.95 (2H, m), 2.15 (3H, s), 2.00-2.52 (4H, m), 3.70-4.20 (1H, m), 3.99 (1H, s, -OH), 10.16 (1H, s); mass spectrum m/e 140.086 (M^+, calc for $C_8H_{12}O_2$ 140.084).

Preparation of Ethyl 3-(4-Hydroxy-2-methylcyclohex-1-enyl)acrylate (98)

A 240 mg (1.07 mmole) sample of triethyl phosphonoacetate in 3 ml of tetrahydrofuran was stirred at 0°C and 70 mg (1.45 mmole) of sodium hydride (50% mineral oil suspension) was added. Stirring was continued for 15 min, at which time evolution of hydrogen had stopped. The aldehyde (117) (100 mg, 0.714 mmole) in 1 ml of tetrahydrofuran was added and the solution was stirred for 30 min at room temperature. Wet ether was added to destroy excess sodium hydride. The solution was poured into 10 ml of water, extracted with ether (4x30 ml), and the extract dried ($MgSO_4$). Removal of the solvent under vacuum, followed by chromatography of the residue on silica gel (ether-hexane, 6:4) gave 142 mg (95%) of 98: ir (neat) 3450, 1705, 1625, 1615, 1280 cm^{-1}; nmr ($CDCl_3$) δ 1.41 (3H, t, J=7), 1.50-2.22 (2H, m), 1.92 (3H, s), 2.45 (1H, s, disappears upon addition of D_2O), 2.10-2.60 (4H, m), 3.95 (1H, m), 4.22 (2H, q, J=7), 5.80 (1H, d, J=16), 7.80 (1H, d, J=16).

Preparation of Ethyl 3-(4-Acetoxy-2-methylcyclohex-1-enyl)acrylate (99)

A 278 mg (1.32 mmole) sample of 98 was added to a solution of 4 ml of pyridine and 2 ml of acetic anhydride. The solution was stirred overnight at room temperature and was poured into 30 ml of

saturated, aqueous sodium bicarbonate. When the excess anhydride had decomposed, the product was extracted with ether (3x30 ml). The ether solution was washed with saturated, aqueous copper sulfate and then with water. After drying ($MgSO_4$) the extract, solvent was removed in vacuo. The product (319 mg, 96%) which remained showed a single spot on thin-layer chromatography and was not purified further: ir (neat) 1740, 1710, 1630, 1610 cm^{-1}; nmr (CCl_4) δ 1.30 (3H, t, J=7), 1.60-2.20 (2H, m), 1.92 (3H, s), 2.05 (3H, s), 2.26 (4H, m), 4.20 (2H, q, J=7), 4.98 (1H, m), 5.80 (1H, d, J=16), 7.80 (1H, d, J=16).

Preparation of Ethyl 3-(4-Acetoxy-2-methyl-1,2-oxiranylcyclohexyl)acrylate (105)

A 319 mg (1.27 mmole) sample of 99 was stirred for 24 hr at room temperature with 300 mg (1.48 mmole) of m-chloroperbenzoic acid (85%) in 15 ml of methylene chloride. The solution was washed with 10 ml of aqueous sodium bisulfite followed by 10 ml of aqueous sodium bicarbonate. The wash solutions were extracted with 50 ml of methylene chloride, and the organic solutions were combined and dried ($MgSO_4$). Removal of the solvent in vacuo, followed by chromatography on silica gel (elution with ether-hexane, 1:1) produced 336 mg (99%) of 105 as a 2:1 mixture of diastereomers 105a and 105b (based on nmr analysis): ir (neat) 1745, 1710, 1655, 1360, 1240 cm^{-1}; nmr

(CCl_4) δ 1.23 (3H, s), 1.27 (3H, t, J=7), 1.32-1.90 (2H, m), 2.00 (3H, s), 1.75-2.30 (4H, m), 4.15 (2H, q, J=7), 4.80 (1H, m), 5.88 (1H, d, J=16), 6.88 (d, J=16) and 6.90 (d, J=16) (1H total); mass spectrum m/e 268.132 (M^+, calc for $C_{14}H_{20}O_5$ 268.131).

Preparation of Ethyl 3-(4-Acetoxy-1,2-dihydroxy-2-methylcyclohexyl)acrylate (106)

A 1.00 g (3.73 mmole) sample of epoxide 105 with 20 ml of tetrahydrofuran and 10 ml of water was brought to reflux and 5 ml of 3% perchloric acid was added. The reaction was heated under reflux for 40 min and was then cooled and poured into a solution consisting of 20 ml of saturated sodium bicarbonate and 10 ml of saturated brine. The product was extracted with ether (4x100 ml), dried ($MgSO_4$), and the solvent was removed in vacuo. Thin-layer chromatography of the residue on silica gel (ether-hexane, 88:15) showed two principal spots in a 3:2 ratio (based on nmr) at R_f 0.45 and R_f 0.35. The two diols (843 mg total, 70%) were separated by column chromatography on silica gel (elution with ether-hexane, 6:4) and assigned structures 106b (R_f 0.45) and 106a (R_f 0.35). Compound 106b: ir (neat) 3450 (broad), 1710 (broad) 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (3H, s), 1.25 (3H, t, J=7), 1.30-2.10 (6H, m), 2.00 (3H, s), 2.20 (1H, s, disappears on addition of D_2O), 2.40 (1H, s, disappears on addition of D_2O), 4.20 (2H, q, J=7), 5.10 (1H, m), 6.10 (1H, d, J=16), 7.25 (1H, d, J=16); mass

spectrum m/e 286.143 (M^+, calc for $C_{14}H_{22}O_6$ 286.142). Compound 106a: 3450 (broad), 1710 (broad), 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (3H, s), 1.25 (3H, t, J=7), 1.50-2.30 (6H, m), 2.10 (3H, s), 2.42 (1H, s, disappears on addition of D_2O), 3.22 (1H, s, disappears on addition of D_2O), 4.20 (2H, q, J=7), 5.18 (1H, m), 6.10 (1H, d, J=16), 7.42 (1H, d, J=16); mass spectrum m/e 286.143 (M^+, calc for $C_{14}H_{22}O_6$ 286.142).

Preparation of Ethyl trans-7-Acetoxy-4,9-diketo-2-decenoate (107)

A 505 mg (1.76 mmole) sample of diol 106 was dissolved in 30 ml of dry ethyl acetate and 0.5 ml of pyridine at room temperature. Lead tetraacetate (2.35 g, 5.30 mmole) was added and the solution was stirred for 20 min. The excess lead tetraacetate was decomposed by the addition of 1 g of oxalic acid, followed by the careful addition of water (5 ml total). When the lead salts had completely turned white, the product was extracted with ether (4x40 ml). The ether extract was washed with 40 ml of water and then with sodium bicarbonate until basic. The ether solution was dried ($MgSO_4$) and the product (107) (486 mg, 97%) was isolated by removal of the solvent under vacuum: ir (neat) 1700-1750 (broad C=O), 1630 (weak), 1360, 1235 cm^{-1}; nmr ($CDCl_3$) δ 2.30 (3H, t, J=7), 1.72-2.28 (2H, m), 2.00 (3H, s), 2.18 (3H, s), 2.59-2.90 (4H, m), 4.26 (2H, q, J=7), 5.25 (1H, m), 6.62 (1H, d, J=16), 7.10 (1H, d, J=16); mass spectrum m/e 284 (M^+, calc for $C_{14}H_{20}O_6$ 284.126).

Preparation of Ethyl trans-7-Acetoxy-4,4,9,9-bisethylenedioxy-2-decenoate (108)

A 130 mg (0.457 mmole) sample of diketone 107 was stirred at room temperature with 2 ml of dry ethylene glycol and 50 mg of p-toluenesulfonic acid for 24 hr. To this was added 10 ml of saturated aqueous sodium bicarbonate and the solution was extracted with ether (4x25 ml). The ether solution was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was chromatographed on silica gel (ether-hexane, 6:4) to give diketal 108 (106 mg, 62%), along with about 20% of monoketalized products. Compound 108: ir (neat) 1725, 1362, 1035 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (3H, t, J=7), 1.30 (3H, s), 1.82 (6H, m), 2.02 (3H, s), 3.90 (4H, s), 3.92 (4H, s), 4.24 (2H, q, J=7), 5.18 (1H, m), 6.08 (1H, d, J=16), 6.75 (1H, d, J=16); mass spectrum m/e 372.175 (M^+, calc for $C_{18}H_{28}O_8$ 372.178).

Preparation of 4,4,9,9-Bisethylenedioxy-7-hydroxy-2-decenoic Acid (110)

A 531 mg (1.43 mmole) sample of diester 108 was stirred at room temperature for 24 hr in 5 ml of ethanol and 5 ml of 1N potassium hydroxide. The solution was extracted with ether to remove any non-acidic components. The mixture was chilled by the addition of a small amount of ice, was quickly made acidic by the addition of 1N hydrochloric acid, and then rapidly extracted with ethyl acetate and

dried ($MgSO_4$). Upon removal of the solvent under vacuum, 359 mg of residue remained. This appeared by nmr to be 110 in about 80% purity: ir (neat) 3500-2550 (-OH), 1710, 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (3H, s), 2.00-1.50 (6H, m), 4.10-3.60 (1H, m), 3.96 (4H, s), 4.00 (4H, s), 6.02 (1H, d, J=16), 6.81 (1H, d, J=16), 7.10 (2H, s, broad, disappears on addition of D_2O); mass spectrum m/e 302.139 (M^+, calc for $C_{14}H_{22}O_7$ 302.137).

Preparation of 3-(1,2,4-Trihydroxy-2-methylcyclohexyl)-acrylic Acid (122)

A 493 mg (1.72 mmole) sample of diester 106 was stirred in a solution of 5 ml of ethanol and 5 ml 1N potassium hydroxide for 24 hr. The solution was extracted with ether to remove non-acidic material, acidified with 1N hydrochloric acid, and extracted with ethyl acetate (4x20 ml). The extract was dried ($MgSO_4$) and the solvent was removed under vacuum, leaving 325 mg (87%) of 122 as a glass: ir (neat) 3550 (broad, OH), 1710, 1360 cm^{-1}; nmr (d_6-acetone) δ 1.10 (3H, s), 2.20-1.50 (6H, m), 4.22 (1H, m), 5.95 (4H, broad, OH), 6.12 (1H, d, J=16), 7.30 (d, J=16) and 7.45 (1H total, d, J=16).

Preparation of S-t-Butyl 3-(1,2,4-Trihydroxy-2-methycyclohexyl)acrylthioate (124)

A 104 mg (0.48 mmole) sample of 122 was dissolved in 3 ml of dry tetrahydrofuran and 300 mg of pyridine and 91 mg (0.53 mmole) of

diethyl chlorophosphate was added. After stirring the mixture for 3 hr, 155 mg (0.53 mmole) of thallous t-butylthioate 123 was added and the mixture was stirred overnight. The mixture was taken up into 60 ml of ether and was washed with saturated, aqueous copper sulfate, followed by saturated, aqueous sodium bicarbonate. The ether layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (ether-hexane, 6:4), yielding 38.8 mg (28%) of 124: nmr (d_6-acetone) δ 1.00 (3H, s), 1.50 (9H, s), 2.10-1.50 (6H, m), 3.08 (3H, s, OH), 4.20-3.90 (1H, m), 6.27 (1H, d, J=16), 7.28 (d, J=16), 7.32 (d, J=16) (1H total).

Preparation of Ethyl 3-(4-Bromoacetoxy-2-methylcyclohex-1-enyl)acrylate (126)

A 112 mg (0.533 mmole) sample of 98 was cooled to -78° C in 4 ml of methylene chloride and 0.5 g of anhydrous potassium carbonate was added, followed by 322 mg (1.60 mmole) of bromoacetyl bromide. The solution was allowed to warm slowly to room temperature over a period of 2 hr and poured into 10 ml of sodium bicarbonate solution. The product was extracted with ether (3x30 ml) and dried ($MgSO_4$). Upon removal of the solvent in vacuo, 240 mg of a light-yellow oil was recovered, which was used without further purification. Nmr analysis indicated the presence of the desired product 126: nmr ($CDCl_3$) δ 1.28 (3H, t, J=7), 1.93 (3H, s), 1.65-2.10 (2H, m), 2.10-2.62 (4H, m), 3.88

(2H, s), 4.26 (2H, q, J=7), 5.11 (1H, p), 5.83 (1H, d, J=16), 7.83 (1H, d, J=16). In addition, ethyl bromoacetate was present as an impurity.

Preparation of Ethyl 3-(4-Dimethylphosphonoacetoxy-2-methylcyclohex-1-enyl)acrylate (127)

The crude mixture containing 126 was heated with trimethylphosphite at 90° for 1.5 hr. The excess trimethylphosphite was removed *in vacuo*, and the product was chromatographed on silica gel, eluting with ether. There was obtained 223 mg of a mixture of ethyl dimethylphosphonoacetate and 127. The latter showed the following spectral data: ir (neat) 1740, 1710, 1640, 1620, 1280 (broad), 1050 (broad) cm^{-1}; nmr ($CDCl_3$) δ 1.30 (3H, t, J=7), 1.91 (3H, s), 2.10-1.50 (2H, m), 2.60-2.10 (4H, m), 3.00 (2H, d, J=24), 3.73 (3H, s), 3.92 (3H, s), 4.22 (2H, q, J=7), 5.10 (1H, p, J=5), 5.82 (1H, d, J=16), 7.82 (1H, d, J=16); mass spectrum m/e 360.131 (M^+, calc for $C_{16}H_{25}O_7P$ 360.134).

Preparation of Ethyl 3-(4-(3'-(4'-Hydroxy-2'-methylcyclohex-1'-enyl)acryloyloxy)-2-methylcyclohex-1-enyl)acrylate (128)

A 223 mg sample of the mixture containing 127 was stirred in 5 ml of tetrahydrofuran at 0°C and 40 mg of sodium hydride (50% mineral oil suspension) was added. After 20 min, 100 mg (0.71 mmole) of aldehyde 117 was added. Stirring was continued for 30 min, after which excess sodium hydride was destroyed by addition of wet

ether. The solution was poured into 20 ml of water and extracted with ether (3x30 ml). The extract was dried ($MgSO_4$) and the solvent was removed under vacuum. Chromatography on silica gel (ether-hexane, 6:4) gave 157 mg (63% from 98) of a mixture of diasteromers 128: ir (neat) 3500, 1705, 1630, 1620, 1280, 1175 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (3H, s), 2.12-1.60 (4H, m), 2.62-2.10 (8H, m), 2.98 (1H, s, OH), 4.20-3.80 (1H, m), 4.26 (2H, q, J=7), 5.12 (1H, m), 5.84 (d, J=16) and 5.86 (2H total, d, J=16), 7.91 (2H, d, J=16); mass spectrum m/e 374.211 (M^+, calc for $C_{22}H_{30}O_5$ 374.209).

Preparation of Ethyl 3-(4-(3'-(1',2'-Oxiranyl-4'-hydroxy-2'-methylcyclohexyl)acryloyloxy)-1,2-oxiranyl-2-methylcyclohexyl)acrylate (129)

A 15.7 mg (0.420 mmole) sample of 128 was stirred in 5 ml of methylene chloride with 207 mg (1.02 mmole) of m-chloroperbenzoic acid (85%) for 24 hr. The solution was washed with aqueous sodium bicarbonate and extracted with methylene chloride (3x40 ml). The organic extract was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The colorless residue was purified by chromatography on silica gel (ether-hexane, 6:4) to give 164 mg (96%) of diastereomers 129: ir (neat) 3500, 1728, 1655, 1300 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (6H, s), 1.29 (3H, t, J=7), 1.66 (4H, m), 2.18 (8H, m), 3.23 (1H, broad singlet), 3.78 (1H, m), 4.22 (2H, q, J=7), 5.00 (1H, m), 5.97 (d, J=16),

5.99 (d, J=16), and 6.02 (2H total, d, J=16), 6.97 (d, J=16), and 7.02 (2H total, d, J=16); mass spectrum m/e 406.195 (M^+, calc for $C_{22}H_{30}O_7$ 406.199).

Preparation of 3-(4-(3'-(1', 2', 4'-Trihydroxy-2-methylcyclohexyl)acryloyloxy)-1, 2-dihydroxy-2-methylcyclohexyl)acrylate (130)

The dimer 129 (164 mg, 0.40 mmole) was heated to reflux in 5 ml of tetrahydrofuran and 1 ml of water, and 1 ml of 3% perchloric acid was added. Refluxing was continued for 20 min, after which the solution was cooled and poured into 5 ml of saturated, aqueous sodium bicarbonate. The product was extracted with ethyl acetate (3x30 ml) and dried ($MgSO_4$). After removal of the solvent under vacuum, the crude residue was chromatographed on silica gel (ether-hexane, 95:5) to give 62 mg (35%) of a mixture of diastereomes, 130: nmr (d_6-acetone) δ 1.00 (s), and 1.10 (s) (6H total), 1.22 (3H, t, J=7), 2.40-1.60 (12H, m), 3.78 (6H, broad singlet), 4.16 (2H, q, J=7), 5.14 (1H, m), 6.04 (d, J=16), and 6.13 (d, J=16) (2H total), 7.28 (d, J=16), 7.38 (d, J=16), 7.42 (d, J=16) (2H total).

Oxidation of 130

A 62 mg (0.14 mmole) sample of 130 was dissolved in 5 ml of ethyl acetate and 200 mg of pyridine. To this, 372 mg (0.84 mmole) of lead tetraacetate was added, and the mixture was stirred at room

temperature for 20 min. Oxalic acid (250 mg) was added along with 2 ml of water. The suspension was stirred until the precipitate was completely white (ca 2 min) and the product was extracted with ether (3x20 ml). The ether extract was washed with aqueous solutions of copper sulfate and sodium bicarbonate. After drying ($MgSO_4$), the solvent was removed in vacuo to leave 52 mg (85%) of 131: nmr ($CDCl_3$) δ 1.30 (3H, t, J=7), 2.41-1.60 (4H, m), 2.18 (6H, s), 3.10-2.50 (8H, m), 2.86 (1H, s, OH), 4.12 (1H, m), 4.28 (2H, q, J=7), 5.40 (1H, m), 6.59 (2H total, d, J=16), 7.08 (d, J=16), and 7.11 (2H total, d, J=16).

Preparation of t-Butyl Bromoacetate

To a well-stirred solution of 7.66 g (0.103 mole) of t-butanol and 15 g (0.124 mole) of N,N-dimethylaniline in 50 ml of anhydrous ether at 0°C, was added dropwise 24.84 g (0.123 mole) of bromoacetyl bromide. After addition was complete, the solution was stirred for 30 min, and then taken up in 200 ml of ether (ethanol free) and rapidly washed with 1N sulfuric acid and aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and the ether was removed by distillation through a 12-inch vigreaux column at atmospheric pressure. The residue was distilled at 56-64°C/20 mm to yield 14.79 g (74%) of t-butyl bromoacetate: ir (neat) 1740, 1360, 1290, 950 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9H, s), 3.79 (2H, s).

Preparation of t-Butyl Dimethylphosphonoacetate (132)

A sample (11.0 g, 0.056 mole) of t-butyl bromoacetate was heated at 110°C for 20 min with 7.02 g (0.057 mole) of trimethylphosphite. The mixture was distilled under vacuum, giving 8.9 g (70%) of phosphonate 132, bp 75-80 (0.1 mm): ir (neat) 1740, 1362, 1270 (broad), 1035 (broad) cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9H, s), 2.92 (2H, d, J=22), 3.78 (3H, s), 3.95 (3H, s).

Preparation of t-Butyl 3-(4-Hydroxy-2-methylcyclohex-1-enyl)acrylate (133)

A 1.16 g (5.20 mmole) sample of phosphonate 132 was stirred at 0°C in 10 ml of dry tetrahydrofuran and 300 mg (6.20 mmole) of sodium hydride (50% mineral oil suspension) was carefully added. The mixture was stirred for 20 min, after which 484 mg (3.50 mmole) of aldehyde 117 in 2 ml of tetrahydrofuran was added. The solution was allowed to warm to room temperature with stirring during 30 min. Wet ether was added to destroy excess sodium hydride and the solution was poured into 30 ml of water. The solution was extracted with ether (3x50 ml), and solvent was removed *in vacuo* after drying ($MgSO_4$). The yellow oil which remained was purified by chromatography on silica gel (ether-hexane, 6:4) to yield 674 mg (82%) of 133: ir (neat) 3500, 1705, 1630, 1610, 1363 cm^{-1}; nmr ($CDCl_3$) δ 1.52 (9H, s), 2.10-1.66 (2H, m), 2.88 (3H, s), 2.50-2.00 (4H, m), 2.85

(1H, s, OH), 3.92 (1H, m), 5.70 (2H, d, J=16), 7.75 (1H, d, J=16); mass spectrum m/e 238.155 (M^+, calc for $C_{14}H_{22}O_3$ 238.157).

Preparation of t-Butyl 3-(4-Bromoacetoxy-2-methylcyclohex-1-enyl)acrylate (134)

Bromoacetyl bromide (232 mg, 1.15 mmole) was added to 300 mg of pyridine in 10 ml of dry ether at 0°C. A white precipitate formed immediately. To this mixture was added 85 mg (0.36 mmole) of t-butyl ester 133 with stirring. After 1 hr the solution was poured into 10 ml of saturated, aqueous sodium bicarbonate and the product was extracted with ether (3x40 ml). The extract was washed with saturated, aqueous copper sulfate (2x25 ml) and dried ($MgSO_4$). The solvent was removed under vacuum and the remaining oil was chromatographed on silica gel (ether-hexane, 6:4) to give 106 mg (83%) of bromoacetate 134: ir (neat) 1740, 1710, 1638, 1615, 1365 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9H, s), 1.92 (3H, s), 2.15-1.60 (2H, m), 2.60-2.10 (4H, m), 3.82 (2H, s), 5.06 (1H, p, J=5), 5.72 (1H, d, J=16), 7.82 (1H, d, J=16).

Preparation of t-Butyl 3-(4-Dimethylphosphonoacetoxy-2-methylcyclohex-1-enyl)acrylate (135)

Bromoacetate 134 (577 mg, 1.61 mmole) was heated at 110°C for 1 hr with 219 mg (1.74 mmole) of trimethyl phosphite. The reaction was cooled and chromatographed on silica gel (ether) to give

549 mg (88%) of phosphonate 135: ir (neat) 1740, 1710, 1635, 1610, 1365, 1040 (broad) cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9H, s), 2.20-1.65 (2H, m), 1.90 (3H, s), 2.60-2.10 (4H, m), 3.01 (2H, d, J=21), 3.72 (3H, s), 3.91 (3H, s), 5.08 (1H, m), 5.78 (1H, d, J=16), 7.74 (1H, d, J=16); mass spectrum m/e 388.159 (M^+, calc for $C_{18}H_{29}O_7P$ 388.165).

Preparation of t-Butyl 3-(4-(3'-(4'-Hydroxy-2'-methylcyclohex-1'-enyl)acryloyloxy-2-methylcyclohex-1-enyl)acrylate (136)

Sodium hydride (90 mg, 1.88 mmole, 50% mineral oil suspension) was carefully added to 549 mg (1.41 mmole) of phosphonate 135 in 5 ml of tetrahydrofuran at 0°C. After stirring for 20 min the evolution of hydrogen had stopped and 218 mg (1.56 mmole) of aldehyde 117 was added. Stirring was continued for 30 min, after which wet ether was added to destroy excess sodium hydride. The solution was poured into 15 ml of water, which was extracted with ether (3x30 ml). The ether solution was dried ($MgSO_4$) and the solvent was removed in vacuo. Purification of the remaining oil by chromatography on silica gel (ether-hexane, 6:4) gave 425 mg (74%) of the dimer 136 as a mixture of diastereomers: ir (neat) 3550 (OH), 1710, 1635, 1620, 1155 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9H, s), 2.10-1.60 (4H, m), 1.92 (6H, s), 2.60-2.00 (8H, m), 3.12 (1H, s, OH), 3.92 (1H, m), 5.10 (1H, m), 5.75 (2H, d, J=16), 7.76 (d, J=16), and 7.81 (2H total, d, J=16).

Preparation of t-Butyl 3-(4-(3'-(1',2'-Oxiranyl-4'-hydroxy-2'-methylcyclohexyl)acryloyloxy)-1,2-oxyranyl-2-methylcyclohexyl)acrylate (137)

A 425 mg (1.06 mmole) sample of 136 was stirred with 516 mg (2.54 mmole) of m-chloroperbenzoic acid and 1 g of potassium hydrogen phosphate (buffer) in 10 ml of methylene chloride for 24 hr. The solution was poured into 25 ml of saturated, aqueous sodium bicarbonate and the product was extracted with methylene chloride (3x30 ml). The organic solution was dried ($MgSO_4$) and the solvent was removed under vacuum. The crude product was purified by chromatography on silica gel (ether-hexane, 6:4) and gave 416 mg (91%) of diepoxide 137 as a mixture of diastereomers: ir (neat) 3500, 1715, 1655, 1155 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (6H, s), 1.50 (9H, s), 1.90-1.50 (4H, m), 2.35-1.88 (8H, m), 3.35 (1H, s, OH), 3.81 (1H, p), 5.00 (1H, m), 5.90 (d, J=16), and 5.95 (2H total, d, J=16), 6.81 (d, J=16), 6.85 (d, J=16), 6.92 (d, J=16), and 6.95 (2H total, d, J=16); mass spectrum m/e 434.229 (M^+, calc for $C_{24}H_{34}O_7$ 434.230).

Preparation of t-Butyl 3-(4-(3'-(1',2',4'-Trihydroxy-2'-methylcyclohexyl)acryloyloxy)-1,2-dihydroxy-2-methylcyclohexyl)acrylate (138)

The diepoxide 137 (60 mg, 0.14 mmole) was heated to reflux in 5 ml of glyme and 1 ml of water, and 1 ml of 3% perchloric acid was added. Refluxing was continued for 30 min, after which the solution

was cooled and 10 ml of saturated, aqueous sodium chloride was added. The product was extracted with ethyl acetate (4x30 ml) and the extract was dried ($MgSO_4$). Removal of the solvent under vacuum left 85 mg of a brown "glass" which retained solvent even after prolonged exposure to high vacuum. Nmr analysis indicated a mixture of diastereomers 138: ir (neat) 3550-2700 (strong, OH), 1710, 1655 cm^{-1}; nmr (d_6-acetone) δ 1.16 (6H, s), 2.20-1.50 (12H, m), 4.02 (1H, m), 5.10 (6H, broad singlet, OH), 5.15 (1H, m), 6.10 (d, J=16), and 6.13 (2H total, d, J=16), 7.30 (d, J=16), and 7.40 (2H total, d, J=16).

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