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Title: Approaches to the Total Synthesis of Verrucarol

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Dr. James D. White

Verrucarol is the sesquiterpene portion of a number of macrocyclic di- and triesters of potential medicinal importance. In this study, a novel approach to the synthesis of this fungal metabolite is presented.

An A-B-C route was investigated in which C-3 and C-4 of the C-ring were emplaced using a [2+2] photocycloaddition reaction between acetylene or ketene dimethyl acetal and an A-B ring synthon such as *cis*-3-Acetoxy-4a-carbomethoxy-4-methyl-7,7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin (121). The photoaddition reactions were not successful in cases where the A-B ring synthon was substituted at the 3-position but otherwise proceeded in approximately 70% yield to give single stereoisomers of the desired cyclobutenes or cyclobutanes.

Ring expansion of these photoadducts to afford the trichothecene skeleton was attempted using several methodologies. In one attempt, *cis-anti-cis*-6,6,- Dimethoxy-7-methyl-8-carbomethoxy-11,11-ethylenedioxy-2-oxatricyclo[6.4.0.$0^{4,7}$]dodec-3-one (133) was subjected to potassium pyrosulfate in refluxing xylene in a variation of the Cargill reaction. This reaction proceeded by an alternative mechanism to yield bicyclobutane 137. Other attempted ring expansions on similar lactones or lactol derivatives also failed to afford the desired ring skeleton.

Approaches to the Total Synthesis of Verrucarol

by

David E. Hill

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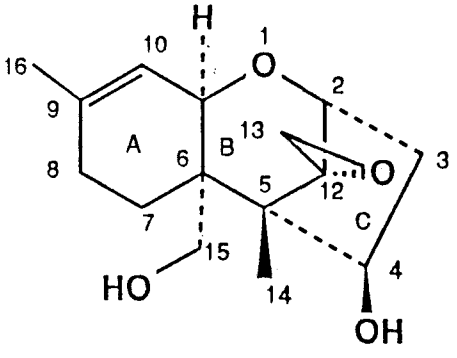
APPROACHES TO THE TOTAL SYNTHESIS OF VERRUCAROL

INTRODUCTION

Verrucarol (1) is the sesquiterpene nucleus of a number of macrocyclic fungal metabolites possessing biological activity. These compounds display cytotoxic, dermatological, phytotoxic, insecticidal, and hematological effects.[1] The first compound containing this ring system, 2, was named trichothecin after the fungus (Trichothecium roseum) from which it was isolated. Other sesquiterpenes with this skeleton, including verrucarol, are now called trichothecenes.



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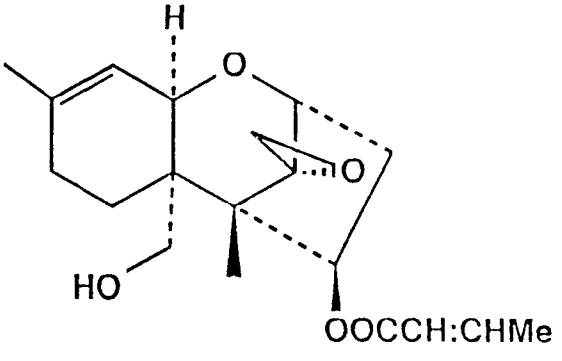

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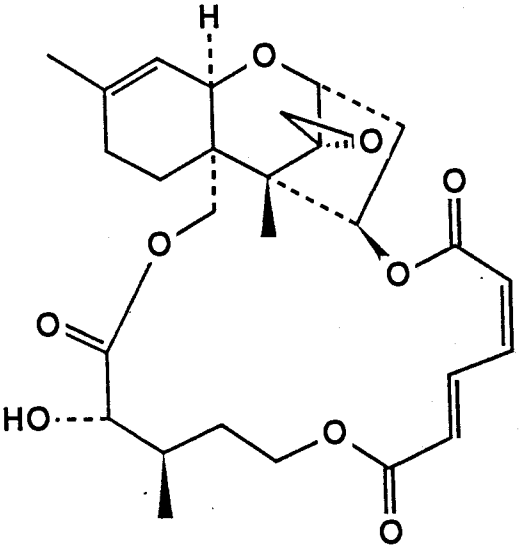

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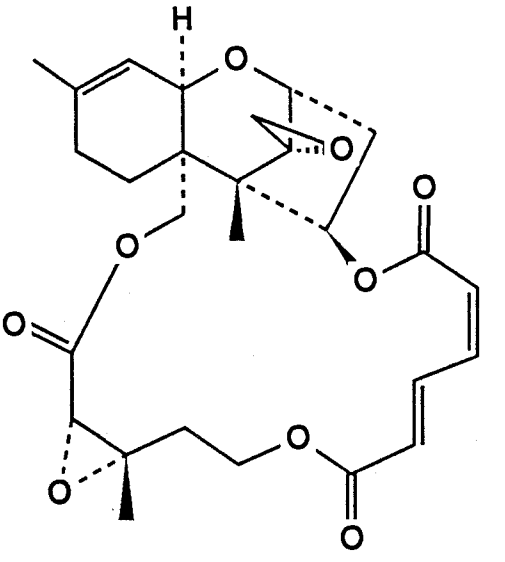

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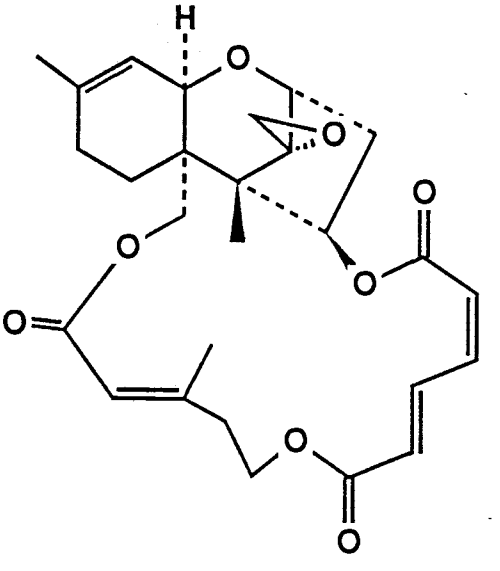

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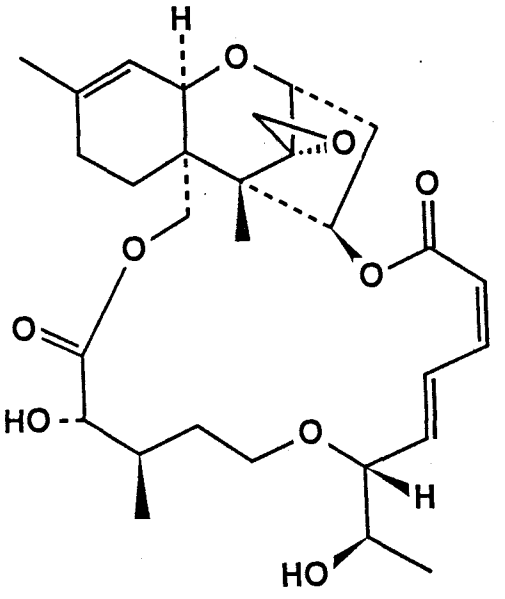
Representative members of the group of macrocyclic structures based on the trichothecenes include verrucarin A (3), B (4), and J (5), produced by the soil fungus Myrothecium verrucaria, and roridins A (6), C (7), D (8), and E (9), produced by

Myrothecium roridum. These substances are of intense medicinal interest due to their



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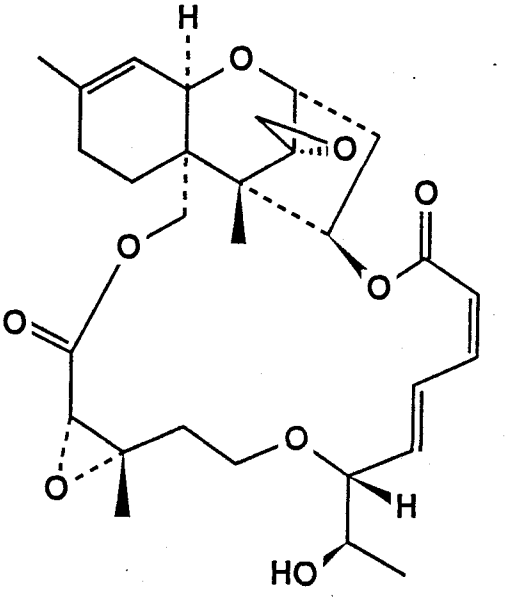

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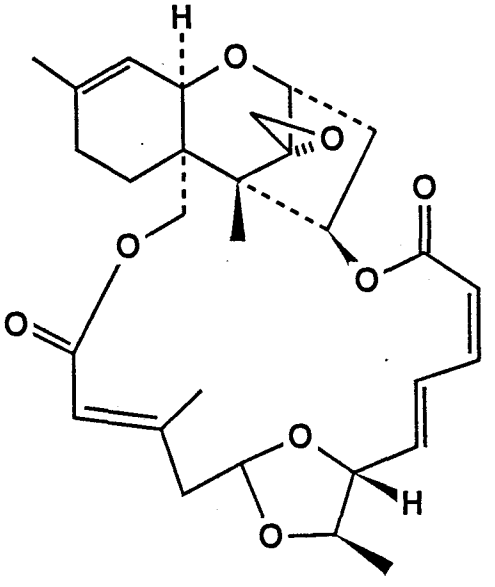

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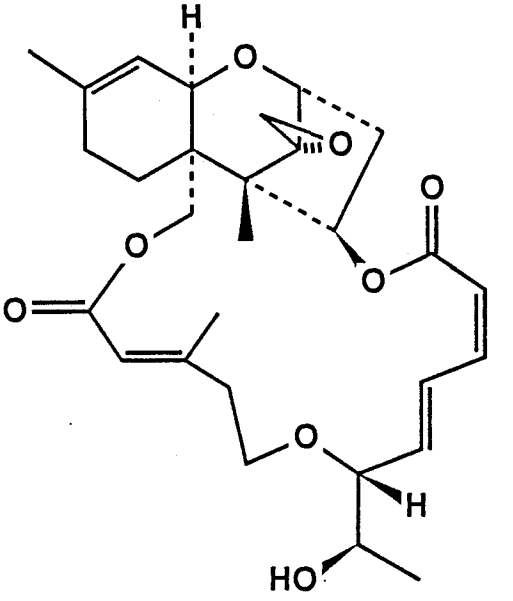
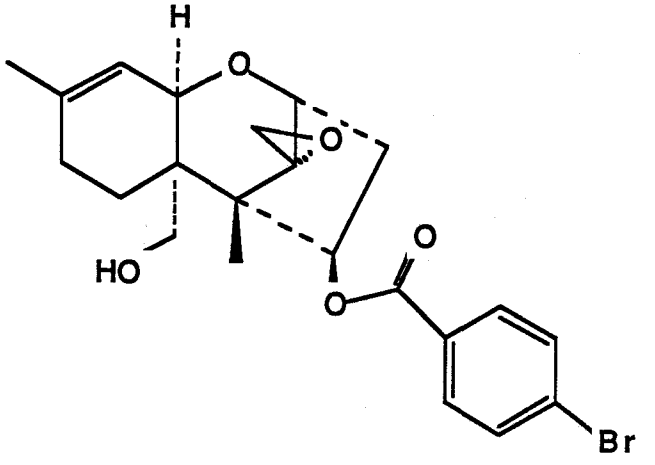


9

cytotoxicity. In particular, verrucarin A causes 50% inhibition of P815 tumor cells at a concentration of 0.6 ng/mL.[2]

The molecular basis for the cytotoxicity of these compounds is their inhibitory effect on protein synthesis.[3] All three phases of protein synthesis-translation, elongation, and termination- may be inhibited, depending on concentration of toxin and the nature of the translation system.[3] The 12,13-epoxide of the trichothecene structure is required for activity since reduction of the epoxide with lithium aluminum hydride leads to a complete loss of effectiveness.[4]

Early degradative work on trichothecenes led to erroneous conclusions. However, an x-ray crystallographic analysis of the p-bromobenzoate derivative of trichodermol (10) by Abrahamsson and Nillson,[5] together with successful correlation

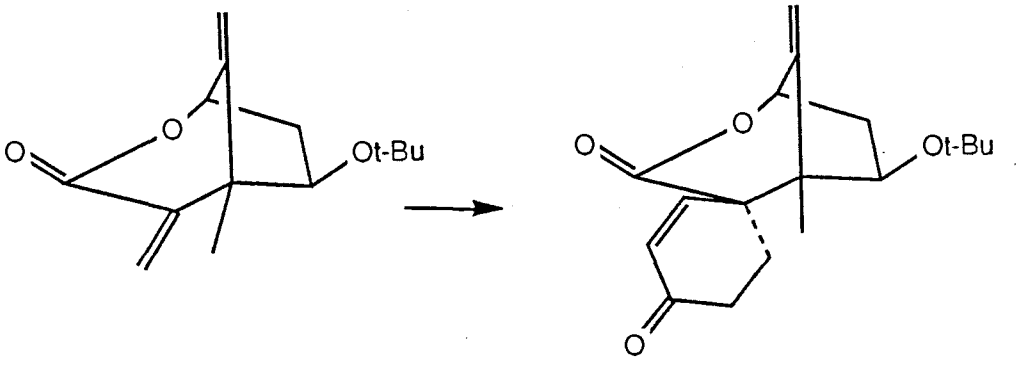


10

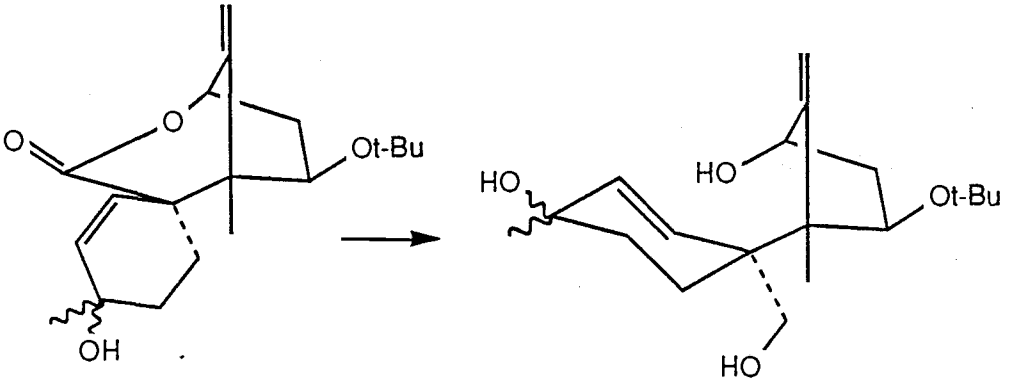
of verrucarol with trichodermol by Gutzwiller,[6] left no doubt as to the structure of 1.

Three successful syntheses of verrucarol have been reported,[7,8,9] all of which start with a highly functionalized C ring precursor and add the A and B rings via

Diels-Alder reactions. The first synthesis,[7] reported by Schlessinger, used as a key step the Diels-Alder reaction between C-ring synthon 11 and 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene to furnish, after hydrolysis and



11 12



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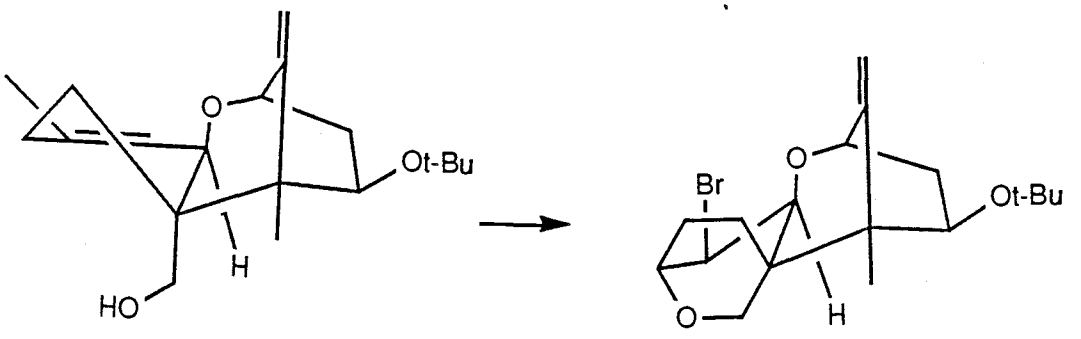
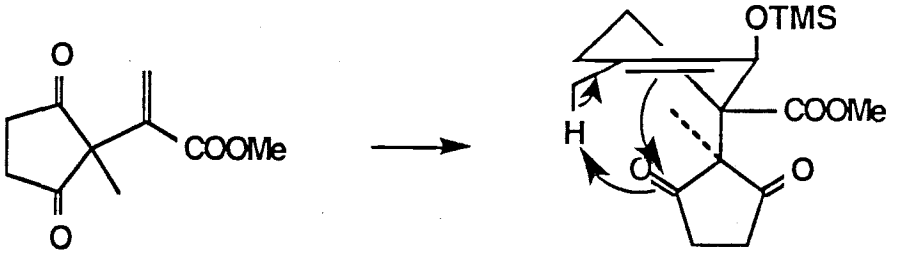


15 16

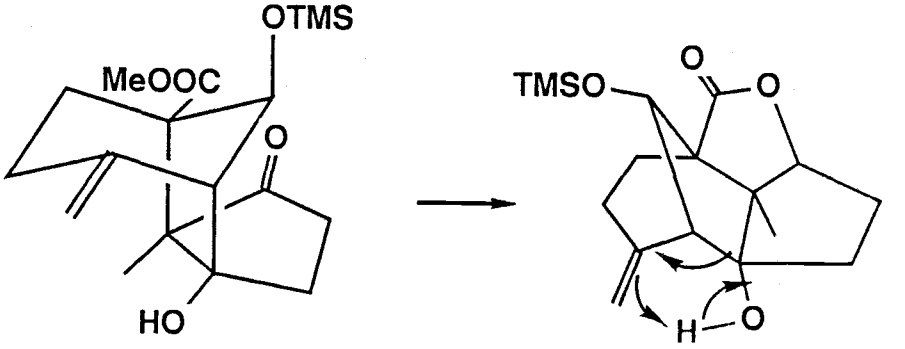
elimination, the enone 12. Selective reaction of 12 with methyllithium afforded 13. Reduction of 13 with lithium aluminum hydride yielded 14 which was cyclized under acidic catalysis to give 15. This ring closure was first applied to the trichothecene series by Kamikawa, who observed only cis fused product.[10] The final steps in the reaction sequence involved bromoetherification to protect the A ring double bond, epoxidation of the exomethylene functionality of 16, and, finally, regeneration of the A-ring double bond with sodium in ethylamine.

Trost's synthesis of verrucarol differs markedly from the others.[8] The symmetrical C ring synthon 17 was reacted with 1-(trimethylsilyloxy)-3-methyl-1,3-butadiene to furnish Diels-Alder adduct 18, which

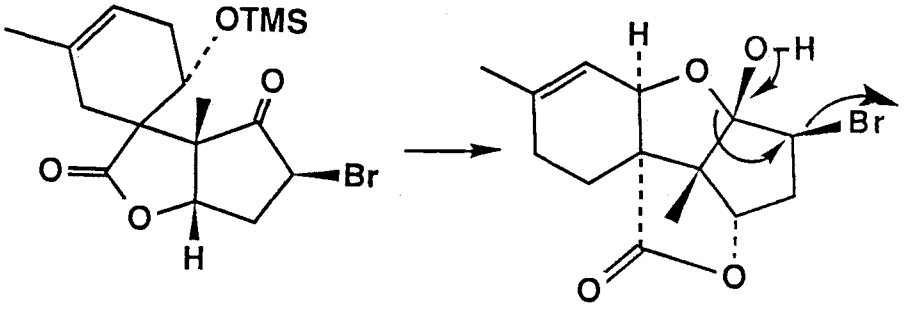


17 18

however was not isolated. Rather, at a reaction temperature of 155 °C 18 underwent a remarkable ene reaction involving the methyl group and double bond of the incipient A ring and one of the carbonyl groups of the cyclopentanedione ring to yield 19. This unforeseen rearrangement served to differentiate the two diastereotopic carbonyl groups by protecting one and allowing the other to be reduced to yield lactone 20. A retro-ene reaction and bromination of the resulting ketone provided 21 which, upon treatment with trifluoroacetic acid, formed hemiketal 22. Fluoride ion-catalyzed ring expansion

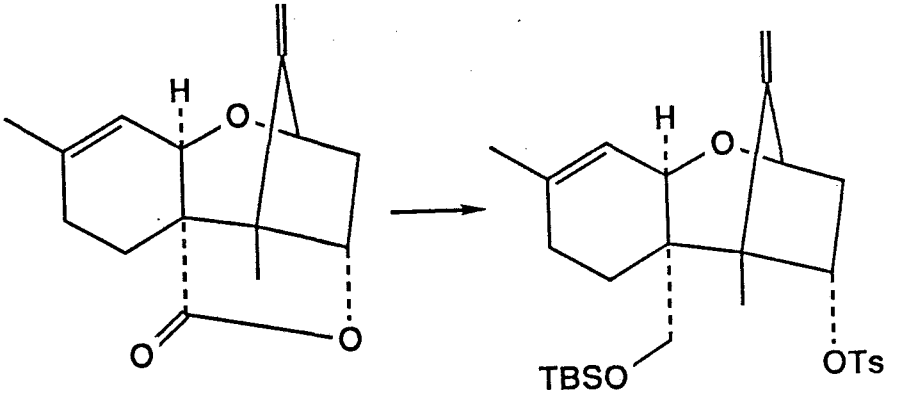


19 20



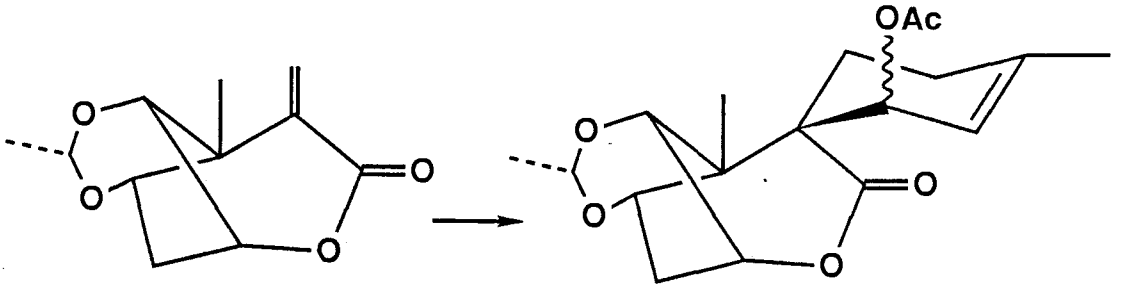
21 22

of 22, followed by a Wittig reaction with methylenetriphenylphosphorane at the C12 carbonyl gave 23. The lactone functionality of 23 was reduced with diisobutylaluminum hydride to give a diol which could be selectively silylated at the primary hydroxyl group. Tosylation of the remaining hydroxyl function provided 24. Inversion of configuration at C4 was accomplished using cesium propionate to displace the tosyl group, followed by potassium carbonate to saponify the resulting propionate ester. The olefin 24 was selectively epoxidized at the C12-C13 double bond using molybdenum hexacarbonyl and tertiary butyl hydroperoxide.[11] Desilylation then completed this synthesis of verrucarol.



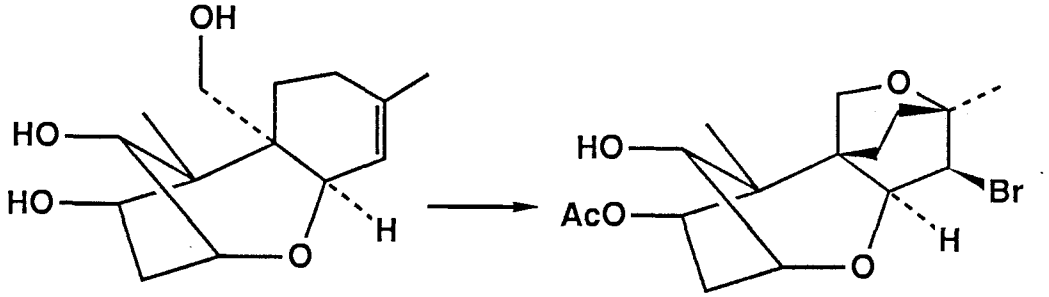
23 24

The third synthesis of verrucarol to be reported is due to Roush[9] and closely parallels the work of Schlessinger[7] described earlier. The intermediate 25, available in ten steps from 1-(trimethylsilyloxy)-3-methylcyclopentadiene, was reacted with 1-acetoxy-1,3-butadiene to give 26 as a mixture of diastereomers. Reduction of 26 with

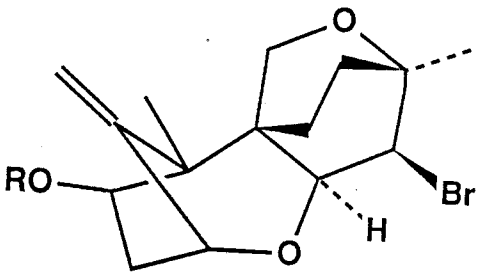


25 26

lithium aluminum hydride, followed by an acid-catalyzed cyclization, afforded 27. Internal bromoether formation and acetylation produced 28. Oxidation of the free hydroxyl group of 28 to a ketone and then treatment with methylenetriphenylphosphorane gave 29. This substance was epoxidized and deprotected to afford verrucarol.



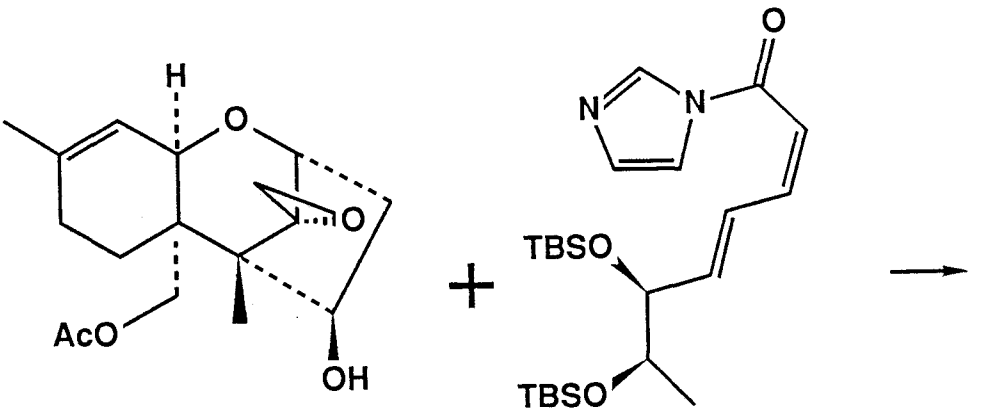
27 28



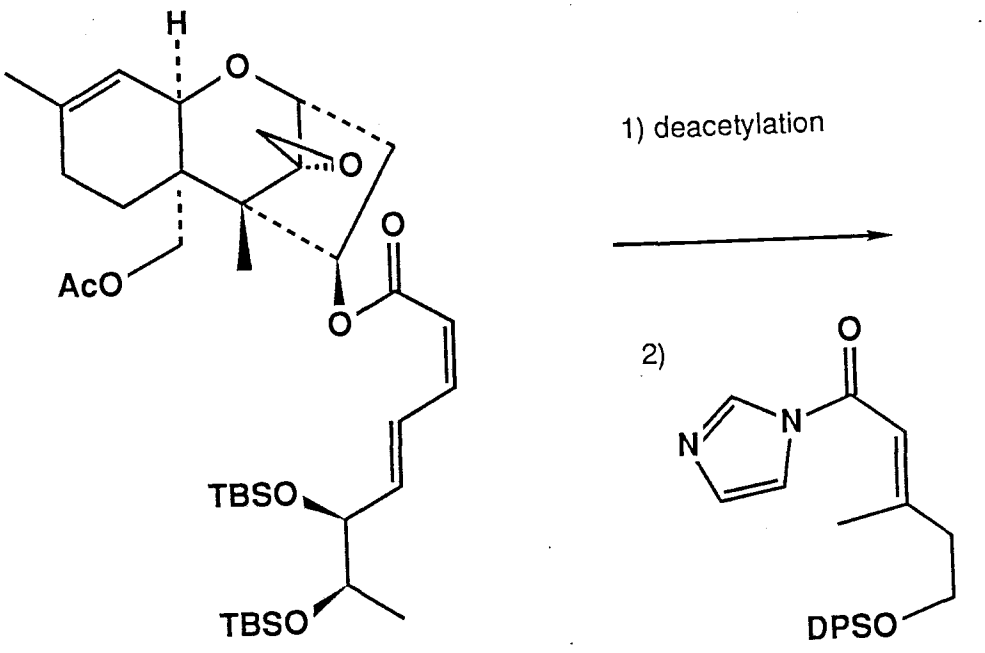
29

Several syntheses of complete trichothecene macrocycles have been reported.[12,13,14,15,16] Those using verrucarol as the sesquiterpene portion are described below.

Verrucarin J (5) was synthesized by Fraser-Reid[12] in a convergent manner through coupling of acetoxyverrucarol (30) with carbohydrate-derived 31 to afford 32. The primary hydroxyl group of 32 was then deacetylated and coupled with 33. After desilylation and diol cleavage of coupling product 34 with sodium periodate, an oxidative lactonization was carried out. Pyridinium dichromate in dimethylformamide afforded a 50% yield of verrucarin J (5).


H
O
O
AcO
OH
O
N
N
TBSO
TBSO

30 31


H
O
O
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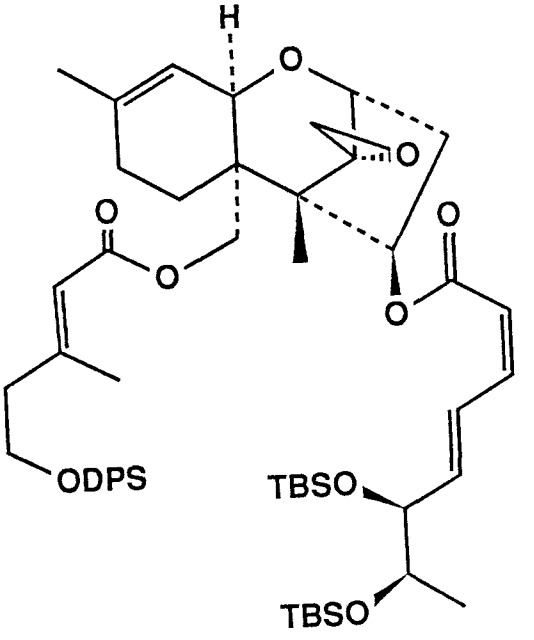
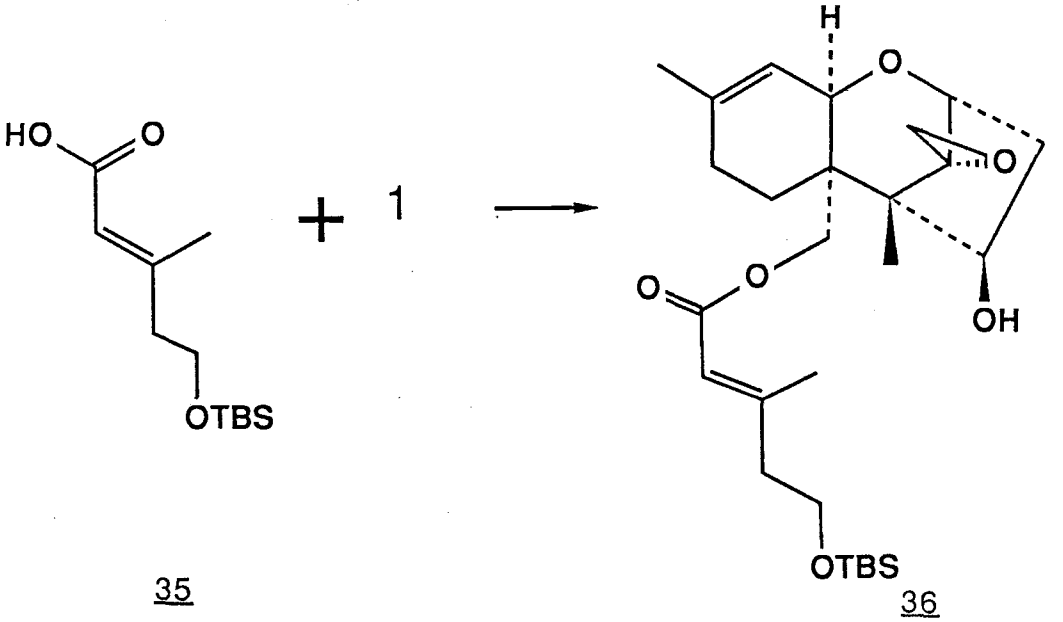
TBSO
TBSO
1) deacetylation
2)
O
N
N
DPSO

32 33

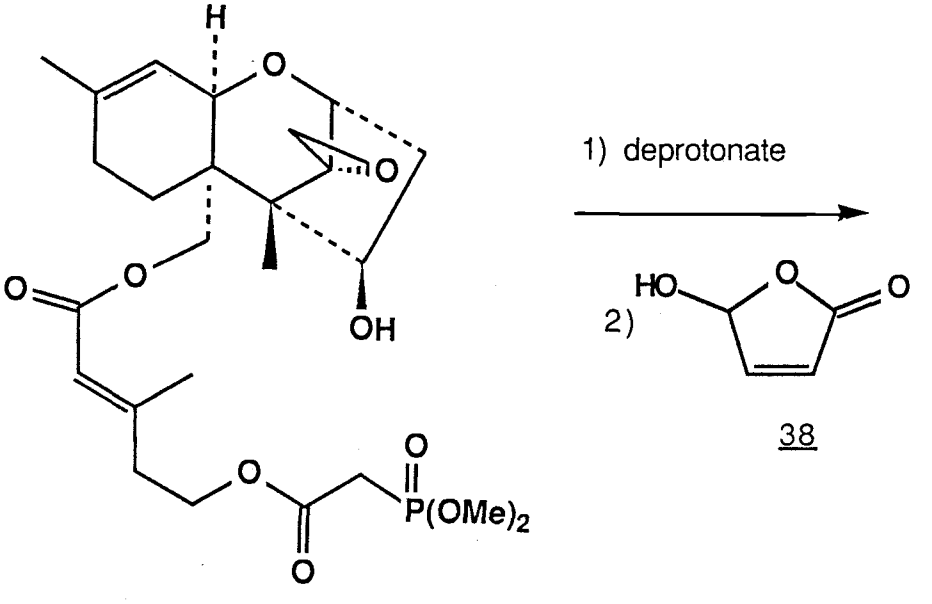


34

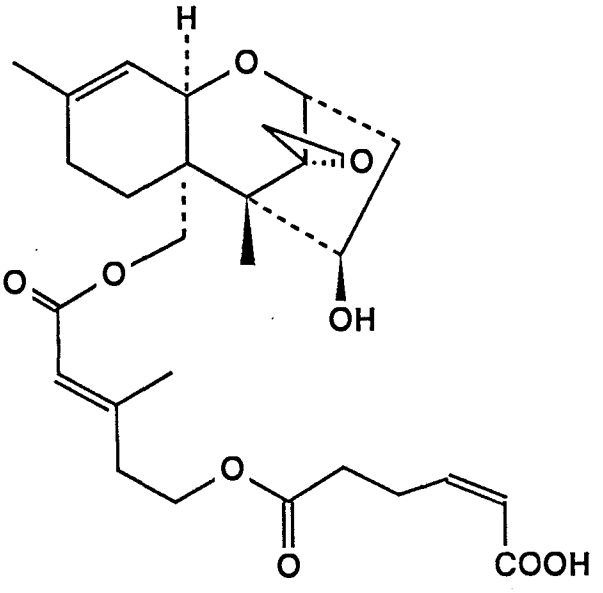
The verrucarin J synthesis of Roush[13] used an alternative, possibly more general, strategy in which a macro chain precursor was first attached to C15 of verrucarol. The ester was elaborated and closed via lactonization at C4. Thus, acid 35 (derived from 3-butyn-1-ol) was used to esterify the C15 hydroxyl of 1 in the presence of dicyclohexylcarbodiimide. After desilylation, 36 was esterified with (dimethoxyphosphinyl)acetic acid and dicyclohexylcarbodiimide to afford 37, the enolate of which reacted with 38 to provide 39. Finally, 39 was treated with pivaloyl chloride to give a mixed anhydride which, in the presence of 4-pyrrolidinopyridine, closed at the C4 hydroxyl group to give verrucarin J.



35 36



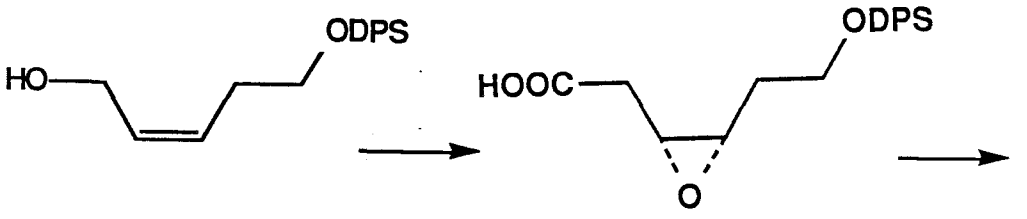
37 38



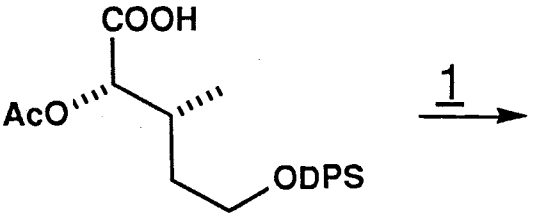
39

Two syntheses of verrucarin A have been reported. The first, due to Still,[14] entailed esterification of a protected verrucarinic acid segment 42 by the C15 hydroxyl group of verrucarol to afford 43, and of (E,Z)-muconic acid segment 46 by the C4 hydroxyl group of 43. This was followed by deprotection and macrolactonization.

The acid 42 was synthesized from propargyl alcohol. First, the hydroxyl group was protected as the ethoxyethyl ether and the resulting ketal was deprotonated to afford an acetylide which was quenched with ethylene oxide. After a protection-deprotection sequence and semihydrogenation over Lindlar catalyst, 40 was obtained. A Sharpless asymmetric epoxidation with diethyl D-tartrate, tertiary butyl hydroperoxide, and titanium tetraisopropoxide,[17] followed by oxidation of the free hydroxyl group with ruthenium trichloride and sodium periodate,[18] gave the chiral epoxy acid 41. Finally, 41 was converted to 42 using a regioselective methylation of the epoxyacid with trimethylaluminum, followed by acetylation of the resulting



40 41



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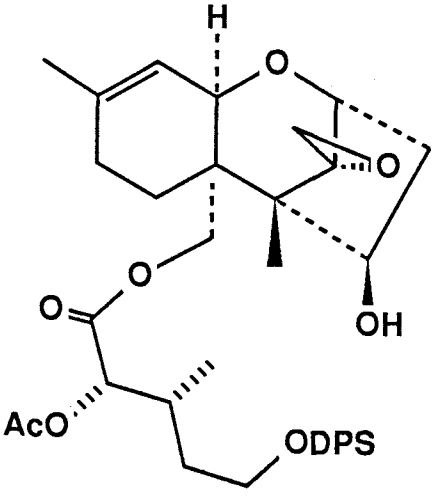
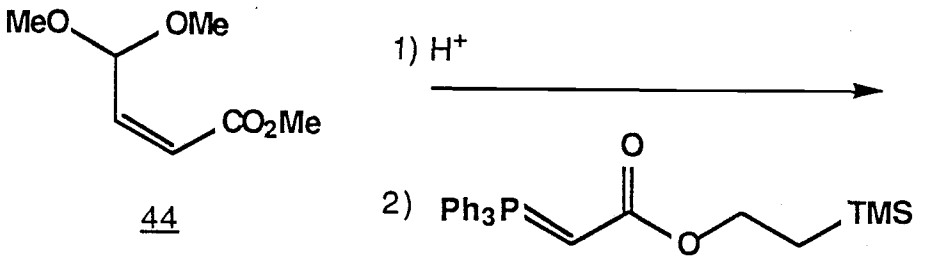


43

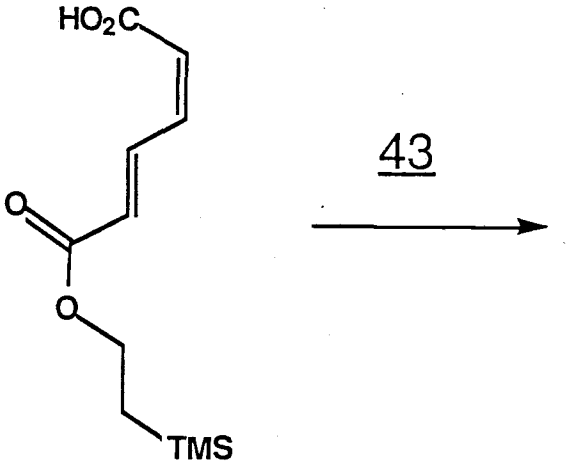
secondary alcohol. The protected (E,Z)-muconic acid segment 46 was prepared by hydrolysis of 44 (obtained by electrochemical oxidation of furfural) and



44

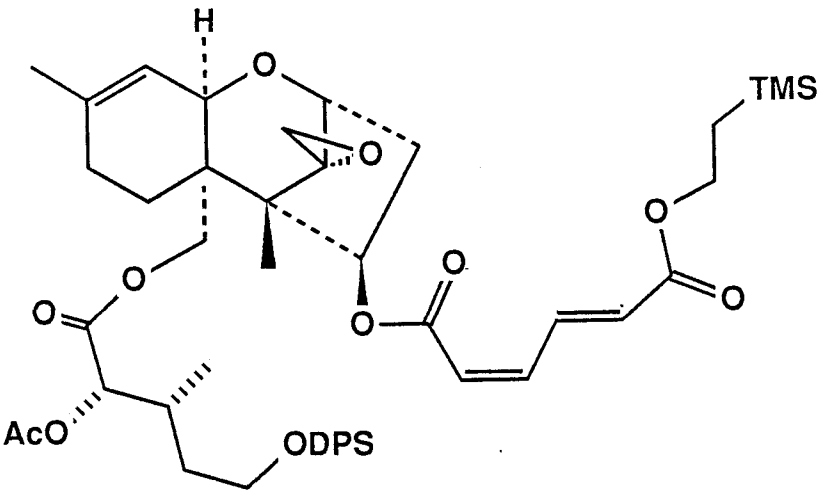
45

3) OH^-



46

treatment of the resulting aldehyde with Wittig reagent 45 . The macro ring segments were attached using two dicyclohexylcarbodiimide-promoted esterifications, first of 42 to C15 of verrucarol, and then of 46 to C4 of 43. After deprotection of the resulting 47, the macro ring was closed using triphenylphosphine and diethyl azodicarboxylate.[19] Finally, deacetylation with sodium methoxide gave verrucarin A.



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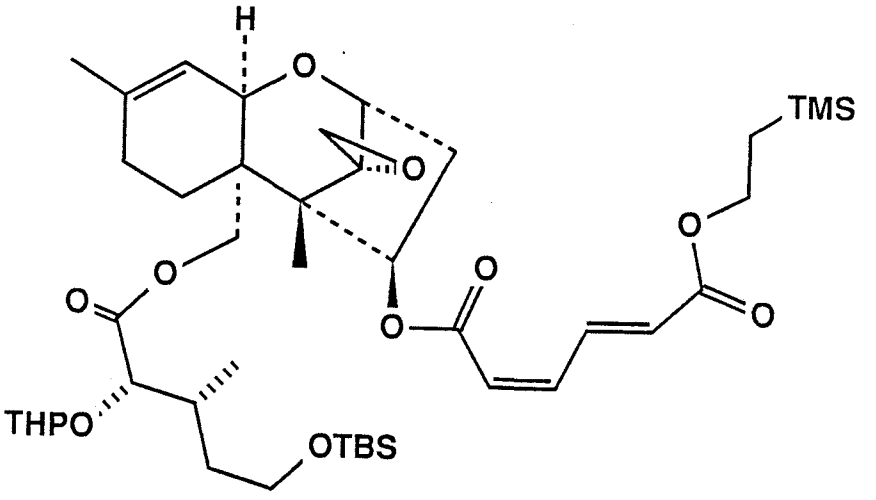
The verrucarin A synthesis reported by Tamm[15] uses the same general concept found in the Still approach. Thus, the verrucarinic acid segment 48 was linked to C15 of verrucarol and a subsequent condensation of muconic acid derivative 46 at C4

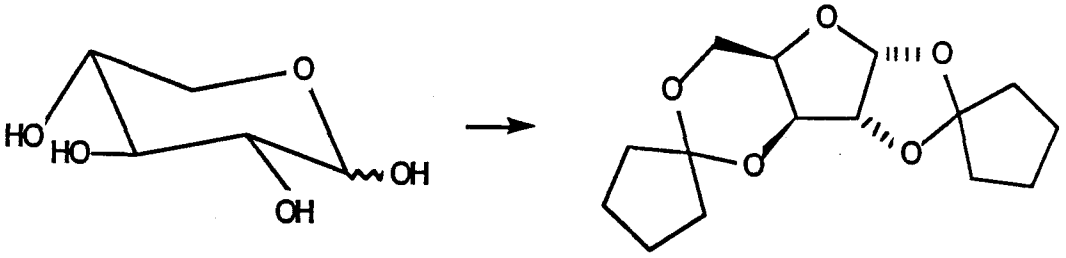
48



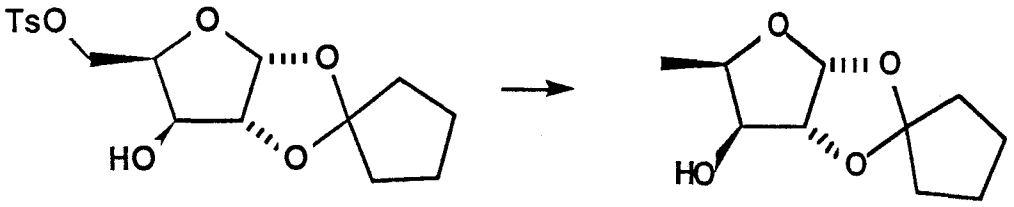
49

afforded 49. Deprotection of 49 and macrolactonization using Yamaguchi's mixed anhydride technique (2,4,6-trichlorobenzoyl chloride and triethylamine, followed by 4-dimethylaminopyridine at 110° C)[20] afforded verrucarin A. Varying degrees of isomerization of the (E,Z)-muconic acid fragment are observed in both of the verrucarin A syntheses described above during the course of the esterification at C4 of verrucarol. The ester of unwanted (E,E) configuration was obtained in about 33% yield in the Tamm synthesis.[15] Tamm reported chromatographic separation of this unnatural isomer prior to cyclization, while Still[14] reported that, upon macrolactonization with the Mukaiyama[19] reagent system, only the correct, (E,Z) configuration was obtained in the final product regardless of the configuration of the starting material.

One other verrucarol-containing macrocycle, roridin E (8) has been synthesized by Still.[20] Roridin E contains two chiral centers in the macro ring which were derived from D-xylose (50) in this synthetic scheme. D-xylose was converted to a diketal 51 with cyclopentanone, copper sulfate, and a trace of sulfuric acid. This compound was selectively deketalized and monotosylated to afford 52, which was

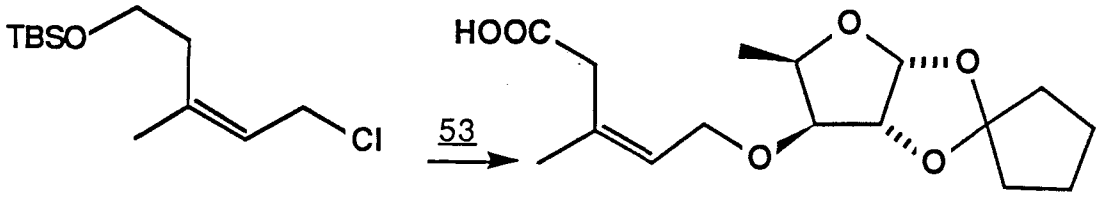


50 51



52 53

reduced to 53 with lithium aluminum hydride. The sodium salt of 53 was coupled with chloride 54 (derived from 3-butyn-1-ol), and the resulting ether was desilylated and oxidized with Jones' reagent to furnish 55. In analogy with previous syntheses of these macrolides, 55 selectively esterified the C15 hydroxyl group of verrucarol using dicyclohexylcarbodiimide and 4-pyrrolidinopyridine, and the resulting product 56 was then esterified with (dimethoxyphosphinyl)acetic acid to yield 57. Deketalization of 57,



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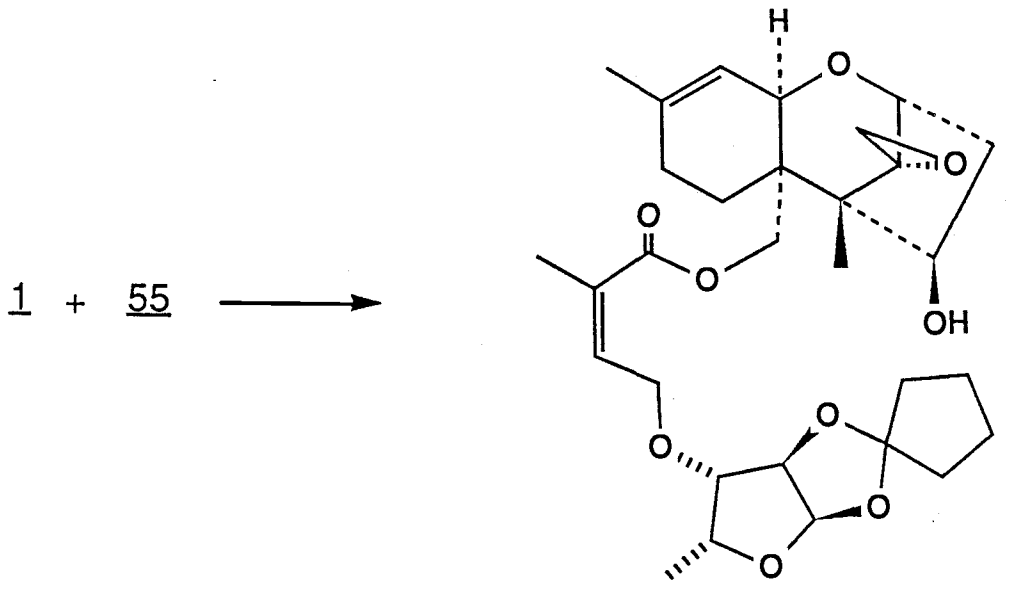

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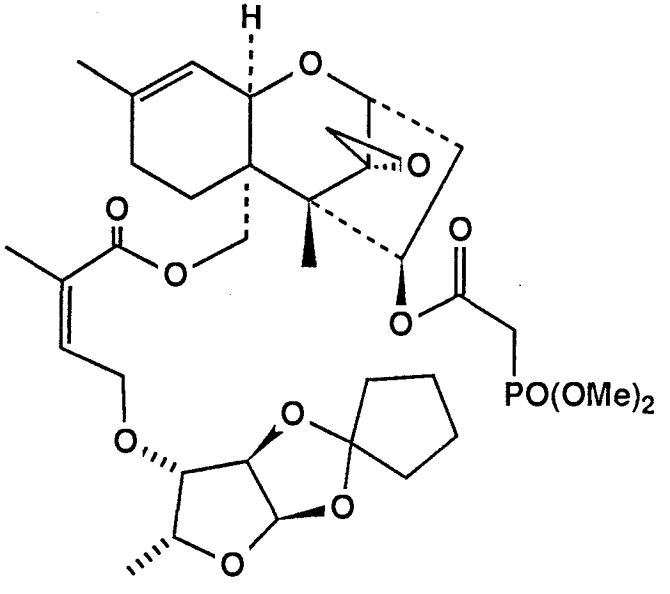

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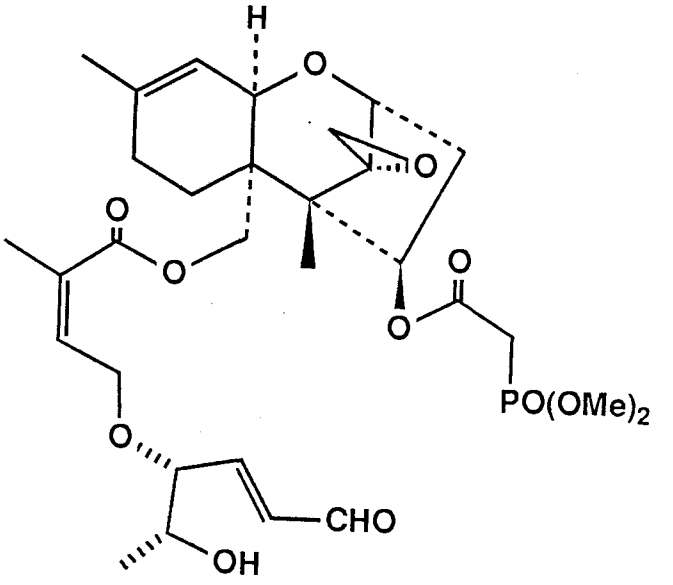
followed by periodate oxidation and deformylation with triethyamine in methanol,

yielded an aldehyde which could be treated with excess (formylmethylene)triphenyl-



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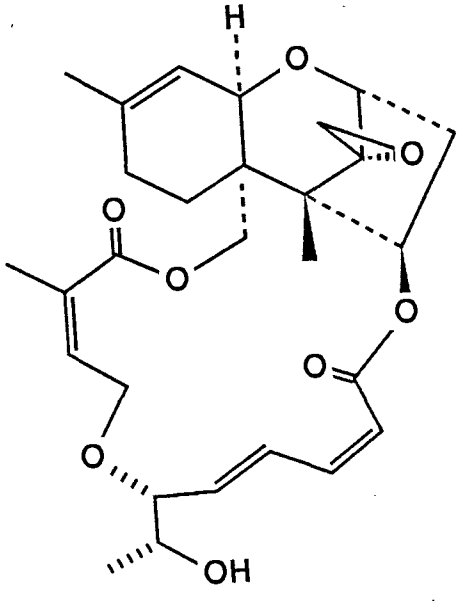

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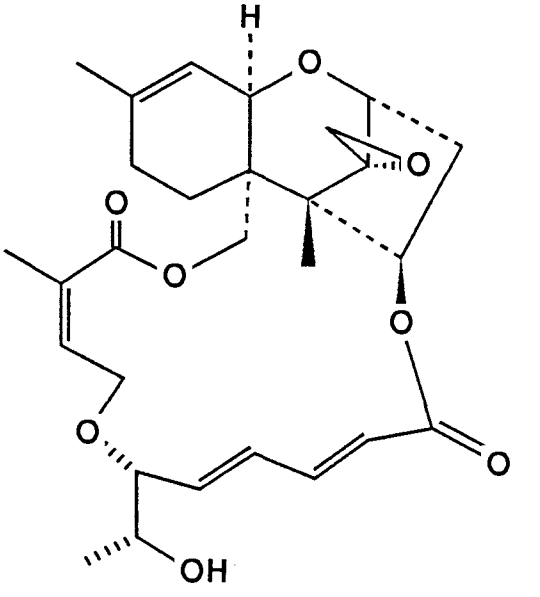
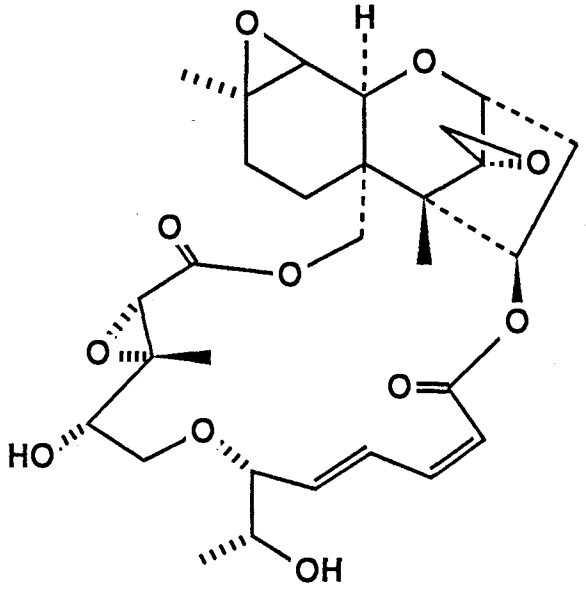


60

phosphorane to afford 58 as a 4:1 E:Z mixture. Macrolactonization of the correct isomer of 58 was carried out using potassium carbonate in the presence of 18-crown-6 to give a 1.5:1 mixture of 59 and 60. The former was separated by flash chromatography and isomerized to roridin E with potassium t-butoxide in isopropyl alcohol. Still was able to use the conformational properties of the macro ring of 59 for a synthesis of baccharin B5 (61), a potent antileukemic currently being evaluated by NIH.[16]



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With this substantial background of accomplishment, the goal of our research project was to develop methodology for the synthesis of verrucarol (1) that was significantly different from any of the foregoing routes. It was envisioned that the route chosen would be amenable to modifications leading to other, more highly functionalized members of this class of sesquiterpenes.

DISCUSSION

Our projected route to the target compound verrucarol (1) is shown in retrosynthetic form in figure 1. It can be described as a "B-A-C" approach in which the

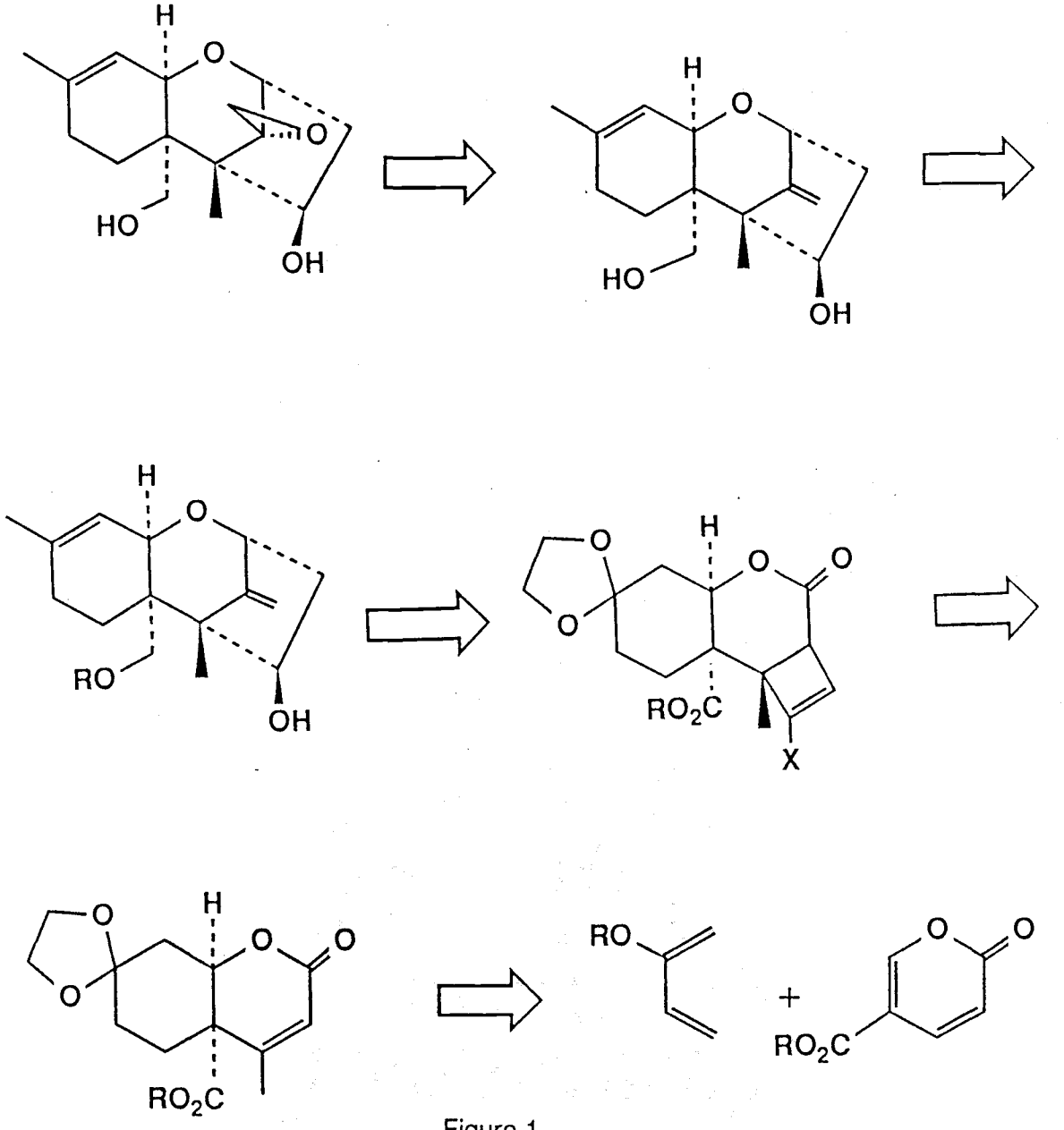


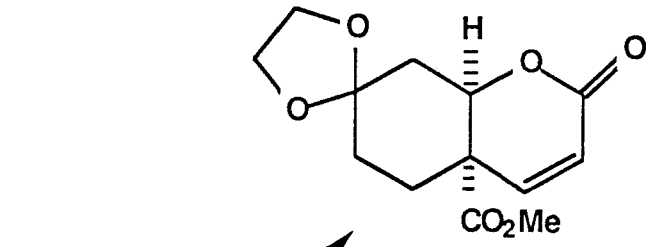
Figure 1

Retrosynthetic Analysis

A-B ring system is formed via a Diels-Alder reaction. The C ring would then be constructed via a [2+2] photoaddition and ring enlargement. The key cyclobutene-to-cyclopentene ring expansion was expected to proceed via ionization of the lactone carbonyl carbon and subsequent 1,2- shift of a cyclobutenyl bond.[21] The A ring methyl group and double bond are added via addition of methylmagnesium bromide to the C9 carbonyl (trichothecene numbering) followed by elimination of the resulting tertiary alcohol. Finally, the oxirane is to be emplaced via the highly stereo- and regioselective methodology used by Trost in his successful synthesis of verrucarol.[8]

The starting point for our synthetic effort was the known Diels-Alder reaction between 62 and 63 to yield 64.[22] The regiochemistry of the [4+2] cycloaddition reaction is governed by the directing-activating groups present in the diene and the dienophile. In the case of 2-substituted dienes like 63, the regiochemistry of addition to olefins activated by an electron-withdrawing group (EWG) is known to be predominantly "para", in which the diene substituent and EWG are in a 1,4 relationship in the product cyclohexene ring. This regiochemistry can be explained using molecular orbital considerations.[23] In an aromatic, Hueckel transition state like that shown in Figure 2, mutual conjugation can occur between the electron-withdrawing and electron-donating substituents when they are "para". Thus, 64 and not 65 is the expected product from the reaction of 62 with 63. An x-ray crystal structure of 66, a derivative of 64, was obtained and showed the compound to posess the expected regiochemistry.[24] An ORTEP plot of 58 is shown in Figure 3.

The bicyclic lactone 64 appeared to be a versatile precursor to the AB ring system of verrucarol. The latent A ring ketone would allow introduction of the necessary double bond and methyl group at a suitable point in the synthesis. Also, epoxidation of this enol ether functionality would permit introduction of an α–hydroxyl group at C-8 needed for synthesis of T-2 toxin 67 and related trichothecenes.



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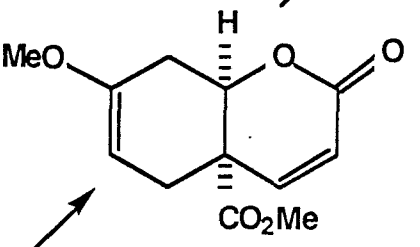

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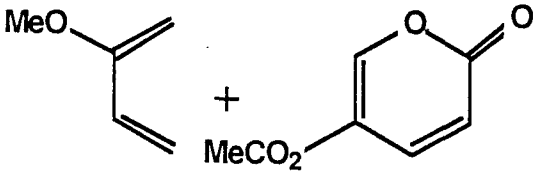
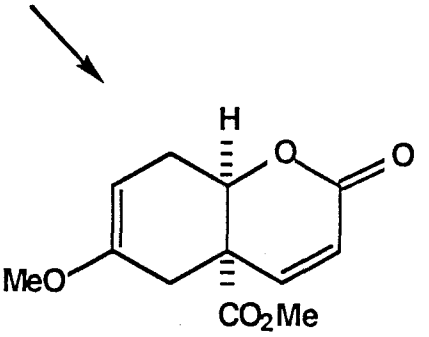


62 63



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The B ring of 64 also had what seemed to be suitable functionality for a facile trichothecene synthesis. The requisite methyl group could be attached at C-5 via a

cuprate addition to the α,β-unsaturated lactone. After reintroduction of the double bond, a [2+2] photoaddition would be possible.

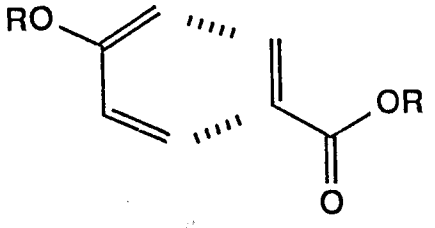
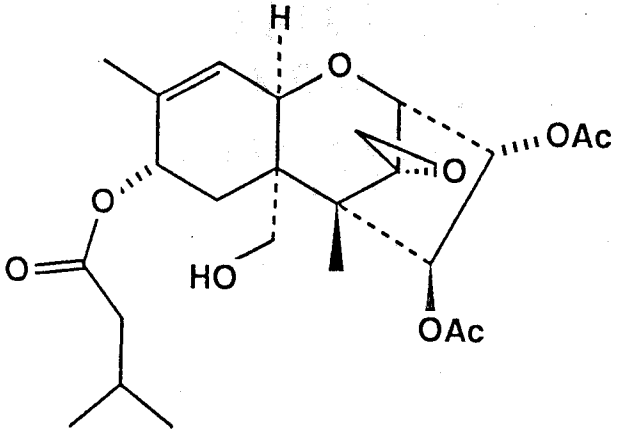


Figure 2
Regiochemistry of the Diels-Alder Reaction



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Addition of a photopartner to the A-B framework was anticipated to occur from the α or exo face.[21,25] Lactone reduction and the key acid-catalyzed ring expansion would then furnish the tricyclic nucleus of verrucarol.

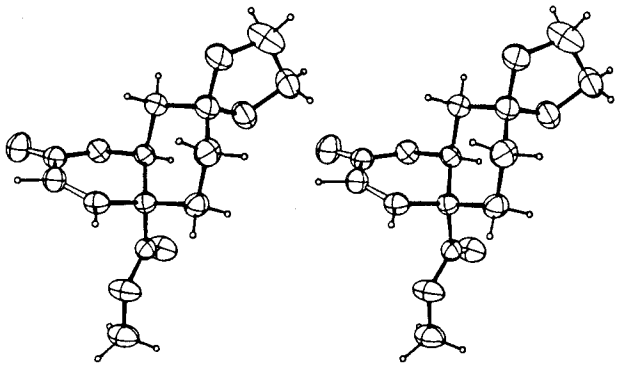


Figure 3
X-ray of a Diels-Alder Adduct Derivative

Cuprates are versatile yet selective organometallic reagents.[26] They replace halide in alkyl, acyl, and aryl halides with alkyl substituents and they add to several functional groups including epoxides, vinyl epoxides, and α,β -unsaturated ketones, esters, and nitriles. These conjugate addition reactions are believed to take place as shown in Figure 4.[27] Single electron transfer from the cuprate to the α,β-unsaturated system initiates the reaction if the oxidation potential of the acceptor molecule is suitable. Electron transfer is followed by bonding of the copper atom of the cuprate complex to the β-carbon of the acceptor system. These steps constitute an oxidative addition of the cuprate to the substrate, and the formal oxidation state of copper changes from +1 to +3. The final step is a reductive elimination in which an R group is transferred from copper to the β-carbon of an acceptor while the copper-carbon bond is being broken. The immediate product is an enolate system which may be simply protonated in an aqueous workup or trapped at the α-carbon with an alkylating agent RX. In cases where the double bond of the acceptor system is fixed in a ring, the

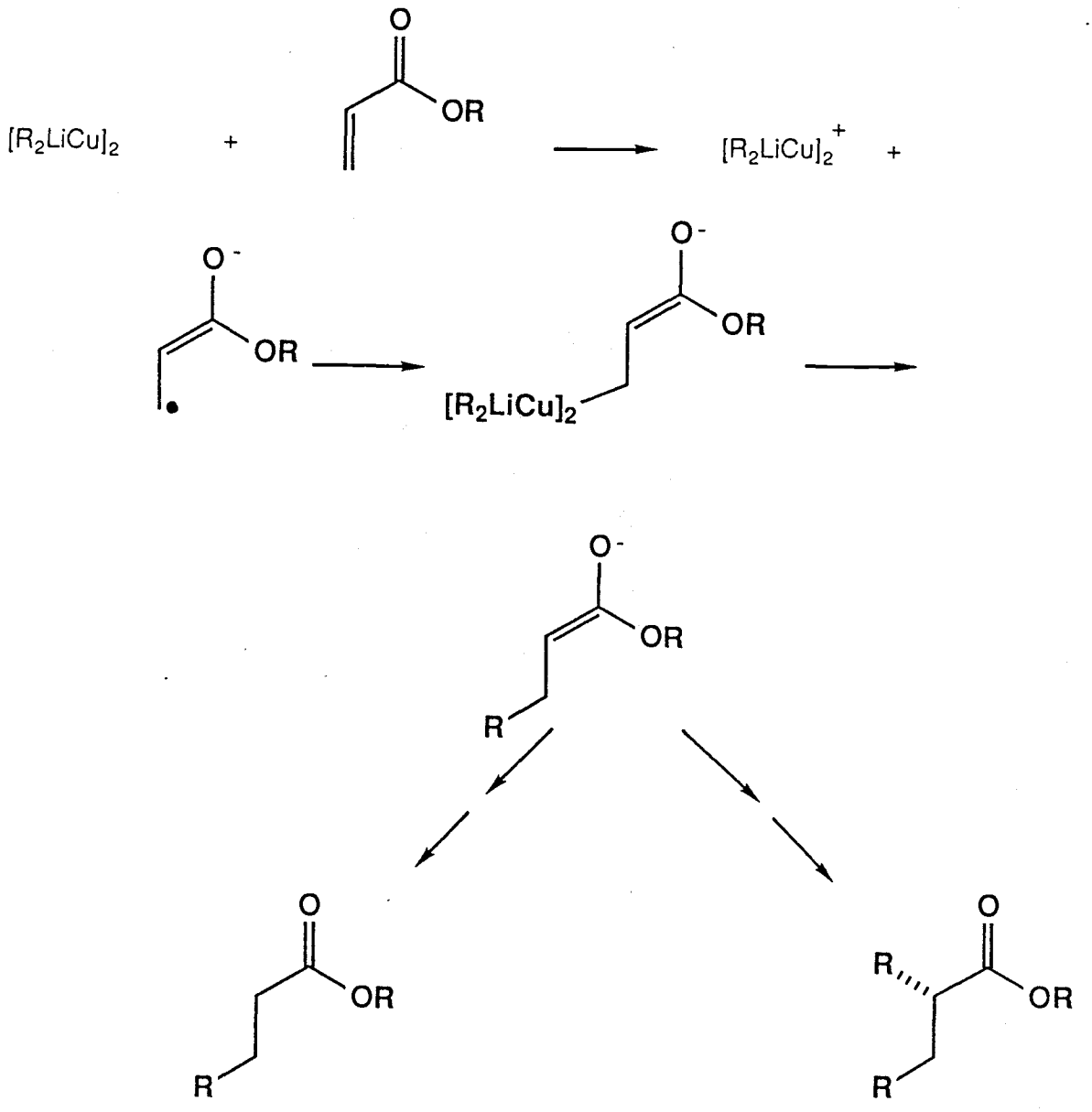


Figure 4
Mechanism of Cuprate Addition Reaction

alkylating agent is usually added stereospecifically *trans* to the cuprate-derived β-substituent. The solvents dimethoxyethane and HMPA are often used in these reactions to increase enolate reactivity.[28]

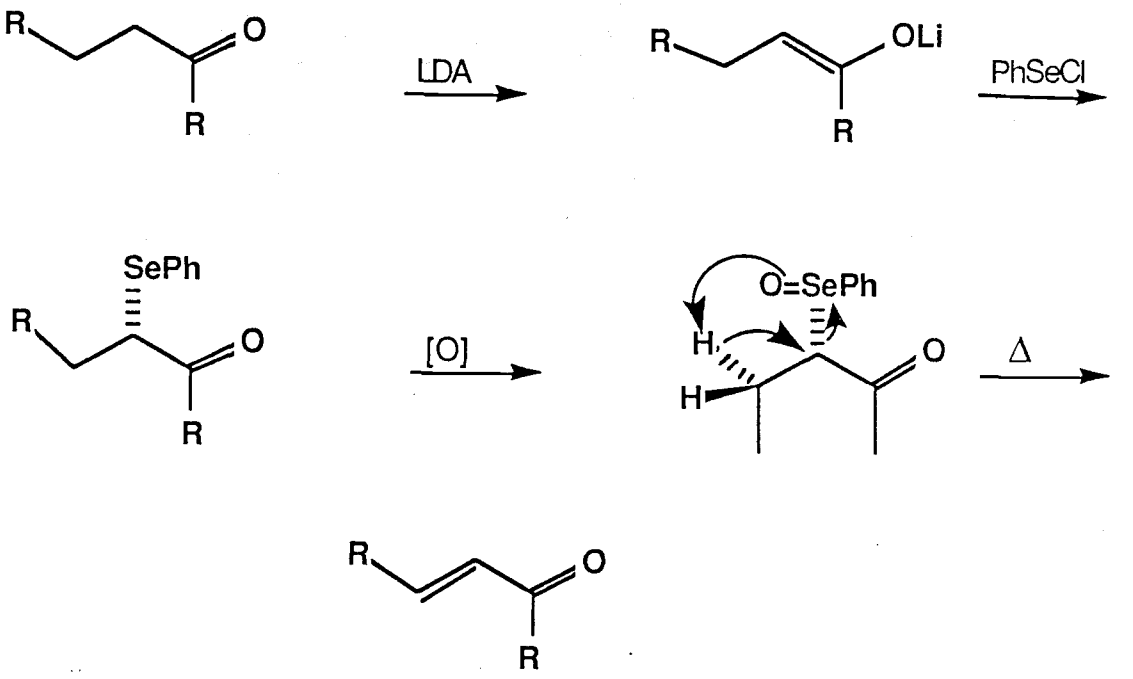


Figure 5
Phenylselenide Route to Enones

An elimination step is necessary after cuprate addition in order to regenerate an α,β-unsaturated lactone system. Three methods of introducing this unsaturation suggested themselves. The first is the phenylselenation-oxidation-elimination approach outlined in Figure 5. Deprotonation of the lactone substrate with lithium diisopropylamide followed by trapping of the enolate with phenylselenyl chloride would give the α-phenylselenyl lactone. Oxidation with hydrogen peroxide gives the selenoxide, which undergoes a *syn* elimination at room temperature to furnish the desired α,β-unsaturated lactone. A potentially higher-yielding but more costly approach is shown in Figure 6 where an enolate resulting from cuprate addition is

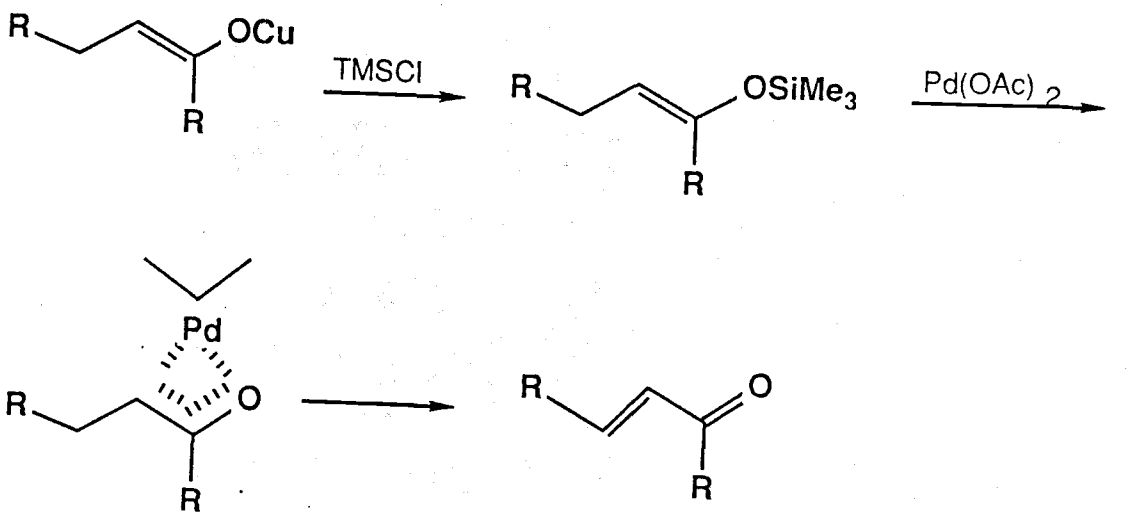


Figure 6
Palladium Acetate Route to Enones

trapped as its trimethylsilyl enol ether. This in turn could be oxidized with palladium acetate to afford the α,β-unsaturated lactone.[30] A drawback here is the need to use the the palladium oxidant in stoichiometric amounts. A third approach, shown in Figure 7, is to introduce ketone functionality α to the lactone carbonyl.[31] The method of Wasserman is shown in the figure. Tris(dimethylamino)methane dissociates to an appreciable extent, affording dimethylamide anion and bis(dimethylamino)methyl cation. The former deprotonates the lactone and the latter traps the lactone enolate at its α- carbon. Elimination of dimethylamide ion leads to formation of an enaminone. This may be oxidized with singlet oxygen to afford the desired α-ketolactone, which would be expected to exist very largely in its enol form. This could be alkylated or acylated. Although no examples of a photoaddition to an enolized α-ketolactone could be found, α-diketones and β-diketones and their derivatives are known to undergo this reaction.[32]

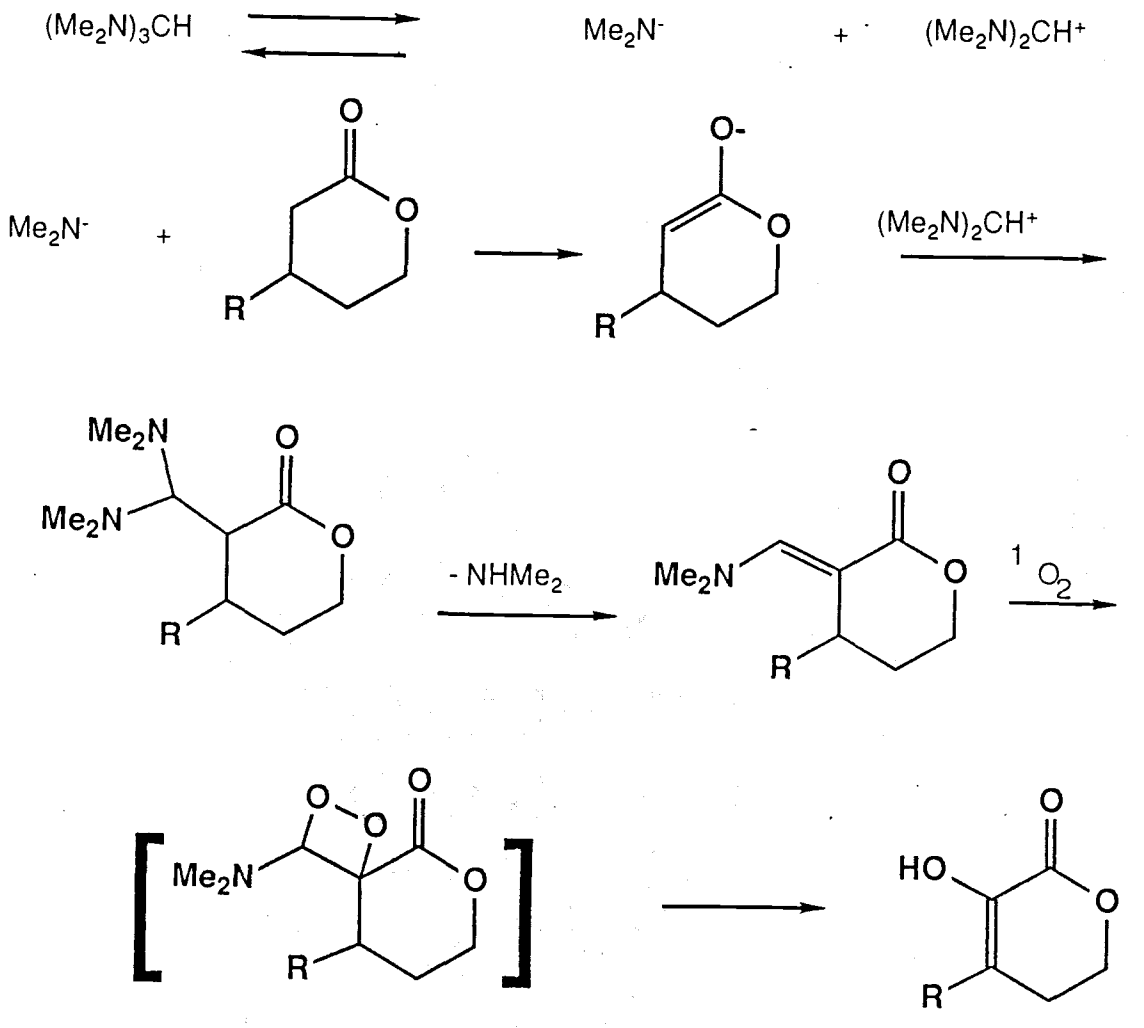
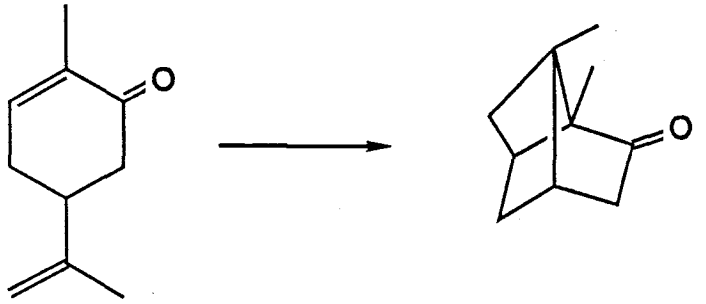


Figure 7
Enaminone Route to α-Ketolactones

The [2+2] photoaddition reaction of α,β-unsaturated ketones to olefins and acetylenes has been known since 1908 when Ciamician reported conversion of carvone (68) to carvone camphor (69) upon exposure to Italian sunlight.[33] More recent work on the reaction has led to partial elucidation of the mechanism and to a fair ability to predict the stereochemistry and regiochemistry of addition. The generally accepted mechanism is outlined in Figure 8.[34] In brief, the α,β-unsaturated ketone moiety E absorbs a quantum of light and is excited to an $n \rightarrow \pi^*$ singlet state S_1, which undergoes



68 69

rapid intersystem crossing to the triplet state T_1. T_1 may be either $n\rightarrow\pi^*$ or $\pi\rightarrow\pi^*$ in nature. The triplet of E then interacts reversibly with a molecule of alkene A to give an exciplex which can lead to [2+2] product EA via either a concerted or a diradical pathway. The regiochemistry of addition is controlled largely by dipolar interactions in the exciplex, although solvent polarity is known to play a role. For example, an exciplex of cyclohexenone and ketene dimethyl acetal would have the molecular orientations shown in Figure 8. Note that the polarity of the ketone in the excited state is the opposite of its ground state polarization. This exciplex would be expected to give the "head to tail" product via either a concerted addition or, more likely, a stepwise addition involving a diradical. Initial bond formation is believed usually to be at the α-carbon of E. The stereochemistry of these photoadditions is influenced by the polarity of the alkene and by the presence or absence of a substituent on the β-carbon of the enone. Thus, while electron-rich olefins like ketene dimethyl acetal yield a

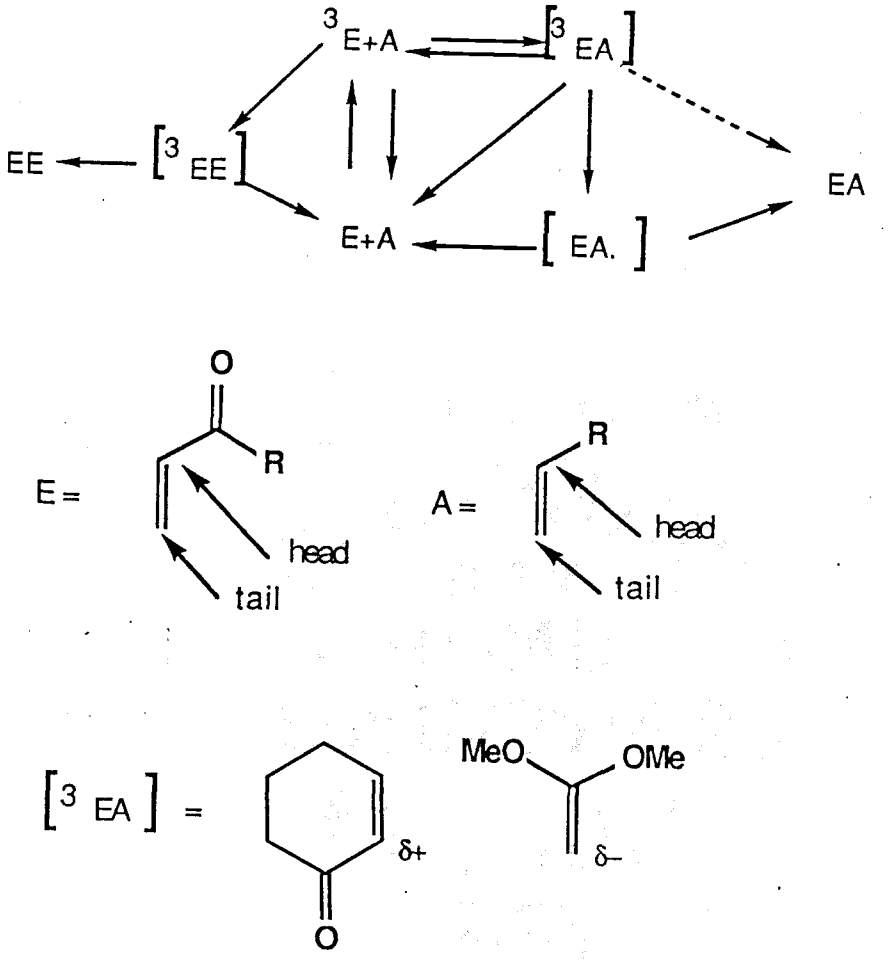
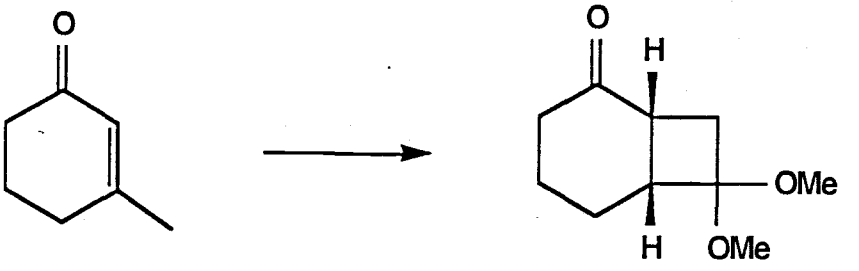


Figure 8
Mechanism of [2+2] Photoaddition reactions

preponderance of trans-fused product upon addition to unsubstituted enones, the presence of a β-methyl group in 3-methylcyclohexenone (70) leads exclusively to cis-fused product upon reaction with ketene dimethyl acetal.[35] Use of alkynes such as acetylene leads to exclusive formation of cis-fused systems.[36] Addition of alkene photopartners to cis-fused bicyclic enones gives tricyclic products possessing the cis-anti-cis configuration. For example, addition of ketene dimethyl acetal to 72



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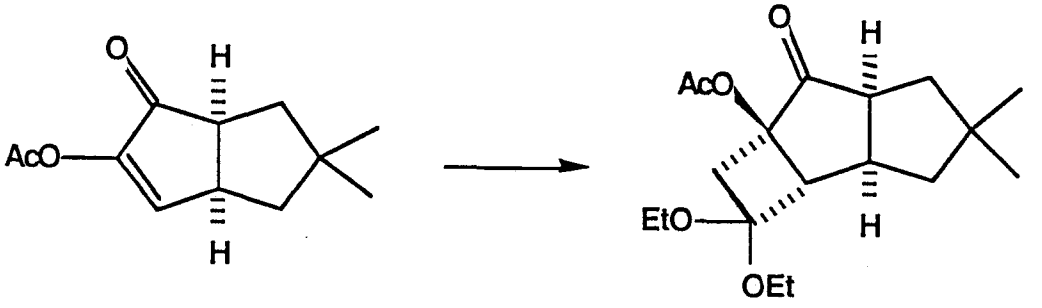
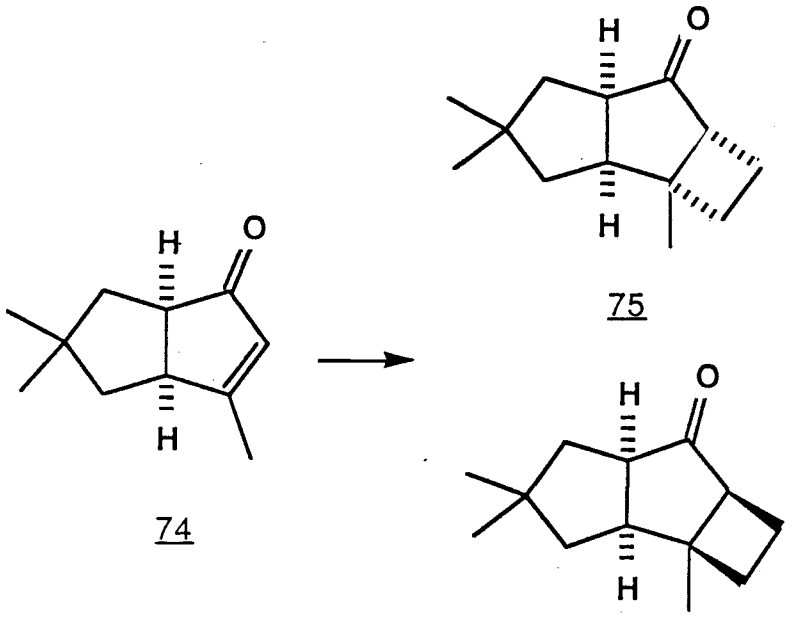
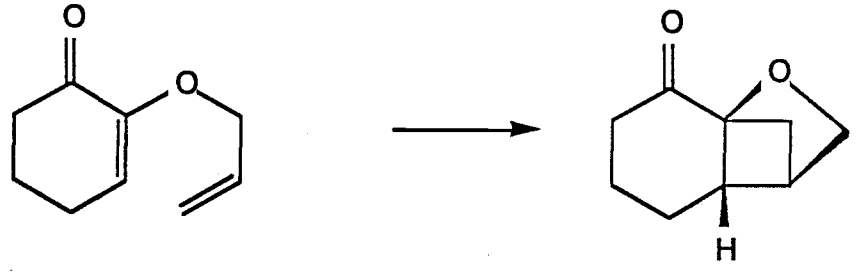


72 73



yielded only 73 while addition of ethylene to 74 led to a 75:8 ratio of 75 to 76.[25,37] Substituents at the α-carbon of enone systems have little effect in photoadditions to cyclopentenone systems, but prevent or dramatically retard photoadditions to cyclohexenones.[38] This has been attributed to a facile mode of conversion of the triplet cyclohexenone to a twisted ground state. Such a process is much less feasible in the corresponding cyclopentenone systems. This difficulty with 2-substituted cyclohexenones has been overcome by running the reactions



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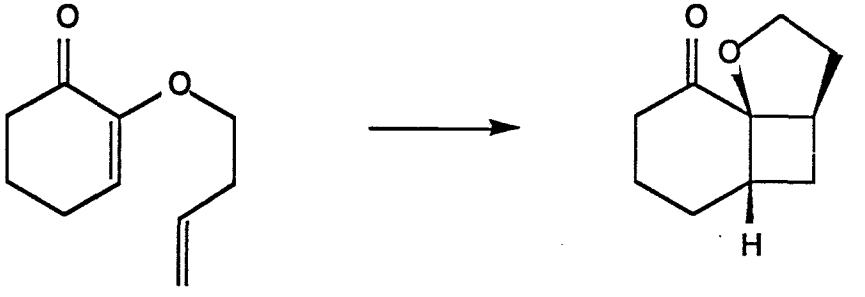
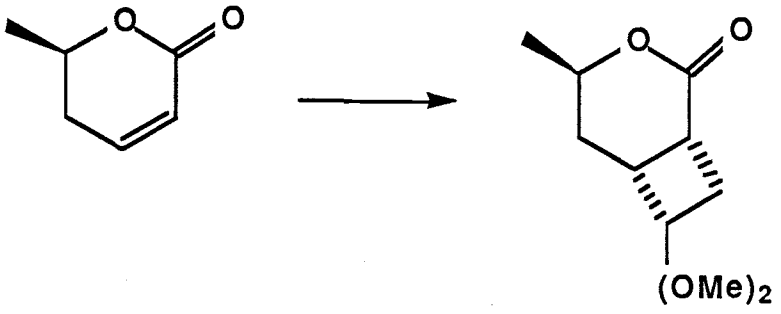


79 80

intramolecularly. Irradiation of 1,2-cyclohexanedione derivative 77 in acetone led to formation of 78, while irradiation of 79 led to 80.[39] The regiochemistry observed here and in other intramolecular additions can be predicted if not explained by the "rule of five". In 1,5-diene systems the preferred orientation is head-to-tail, while in 1,6-systems head-to-head addition is favored. In each case, the product would arise

from an initial five-membered-ring biradical.[40]

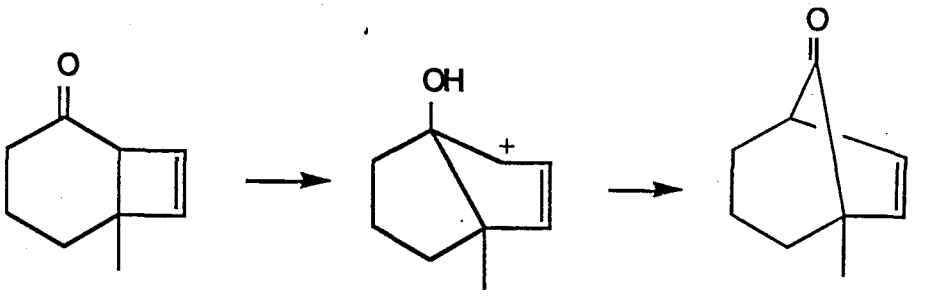
In contrast to the extensive literature on the photochemistry of α,β-unsaturated ketones, reports of additions to the corresponding lactones have been few.[41,42, 43,22] The work that has been done indicates that γ– and δ–lactones readily undergo the reaction with photopartners such as acetylene, ethylene, and ketene dimethyl acetal. The regiochemistry in the case of ketene dimethyl acetal addition is as predicted based on the exciplex dipole argument. For example, parasorbic acid (81)



81 82

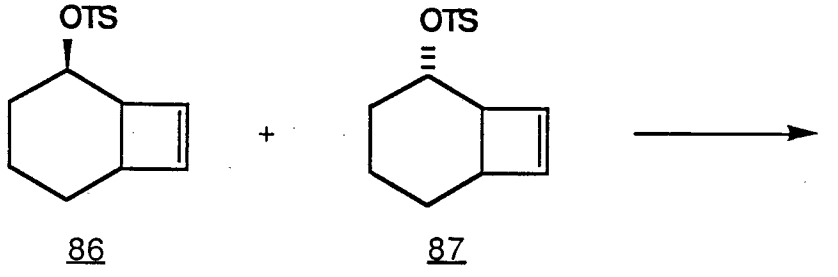
reacted with ketene dimethyl acetal to give 82 , the "head to tail" product.[41]

A key step in the synthetic scheme outlined in Figure 1 is the rearrangement of a bicyclo[4.2.0] system to a bicyclo[3.2.1]framework. Reactions of this sort have been investigated in several bicyclo[4.2.0] and bicyclo[3.2.0] structures derived from photoadditions to enones. For example, Cargill found that ketone 83 could be converted exclusively to 85 upon warming in benzene containing p-toluenesulfonic acid.[44] The mechanism of this reaction involves a shift of the 1,6 bond to give intermediate 84. This intermediate in turn rearranges to 85 via another 1,2 alkyl shift. Ring expansions of this type have been carried out more comonly on reduced derivatives of these bicyclic systems. Hess found that an 80:20 mixture of tosylates 86

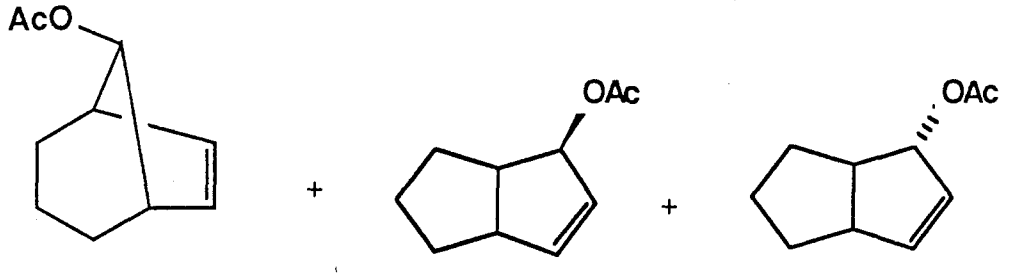


83 84 85

and 87 rearranged to give an 80:4:16 mixture of 88, 89, and 90 upon reflux for 18 h in acetic acid.[45] Although 86 and 87 were not solvolyzed separately, a plausible



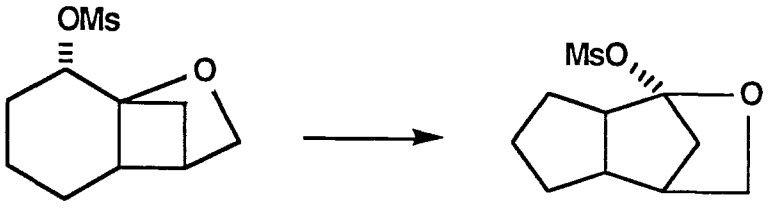
86 87



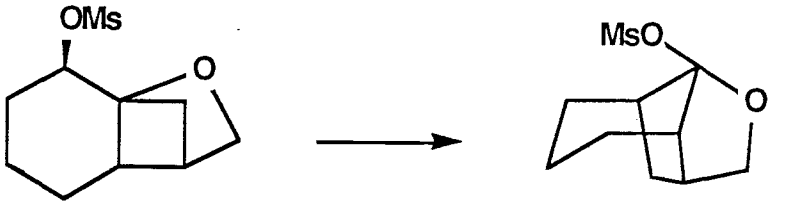
88 89 90

assumption is that 88 arises from 86 via synchronous shift of the 1,8 bond and displacement of tosylate. The resulting carbonium ion is acetylated only from the endo side because of a stereoelectronic effect-the positive charge is partially delocalized into the pi system of the ethylene bridge.[46] Correspondingly, 89 and 90 arise from the synchronous shift of the 1,6 bond of 87 and displacement of tosylate followed by

trapping of acetate by the resulting carbonium ion. This assumption follows from results obtained upon solvolysis of pure isomers in saturated bicyclo[4.2.0] systems. For example, solvolysis of 91 gave only 92 while solvolysis of 93 furnished only 94.[47]



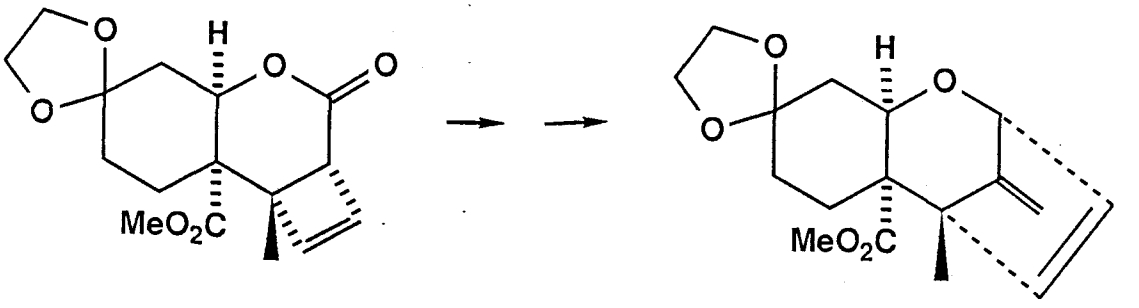
91 92



93 94

A Cargill rearrangment is obviously to be preferred to a solvolytic approach in our synthetic scheme. In principle, Cargill rearrangement of 95 yields the trichothecene nucleus complete with a ketone precursor to the oxirane functionality of verrucarol in one step from the [2+2] photoadduct. On the other hand solvolysis requires reduction of the carbonyl functionality, activation of the resulting hydroxyl group, saponification of the ester product from solvolysis, and re-oxidation to the carbonyl oxidation state.

Stereospecific introduction of a hydroxyl group at C4 (trichothecene numbering) was planned for a step subsequent to the ring expansion reaction. In the case of 96, derived hypothetically from acetylene photoadduct 95,[21] saponification of



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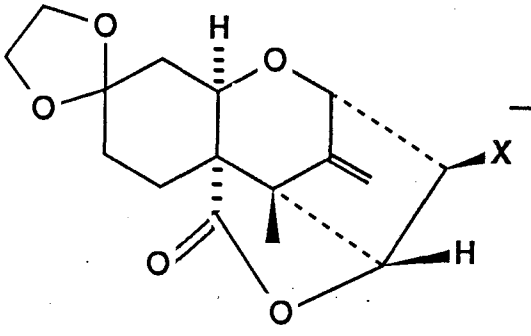
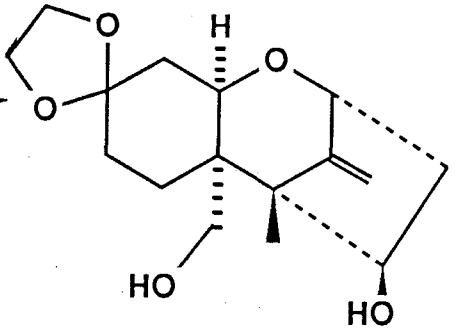
96



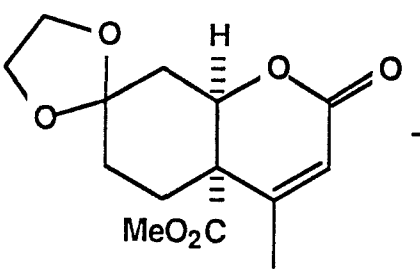
97 X = H or I



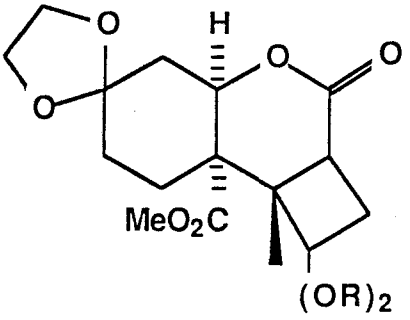
98

the angular carbomethoxy group followed by either acid- or iodine-catalyzed lactonization of the resulting carboxyl group to the cyclopentene ring would furnish 97. Methodology developed by Trost in his synthesis of verrucarol would then afford 98.[8] Alternatively, 101, potentially derived from photoaddition of 99 to a ketene acetal followed by ring expansion and Wittig olefination, could be hydrolyzed and reduced to yield 98.

The A ring functionality could be introduced at several points in our proposed synthetic scheme. Hydrolysis of ketal 98 followed by treatment of the resulting ketone with methylmagnesium bromide to give 102 and acid-catalyzed elimination to 103 is one of several possible approaches.



99



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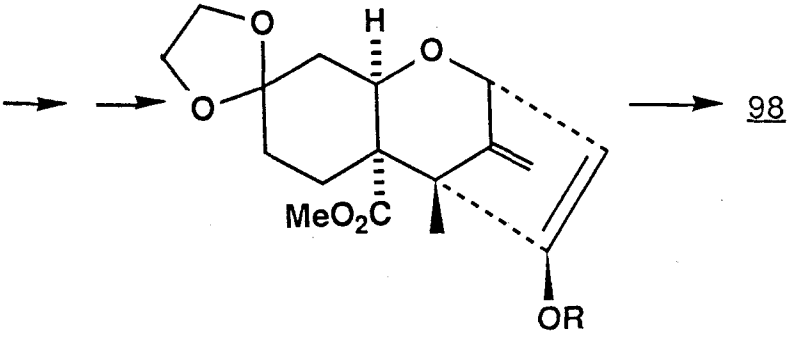
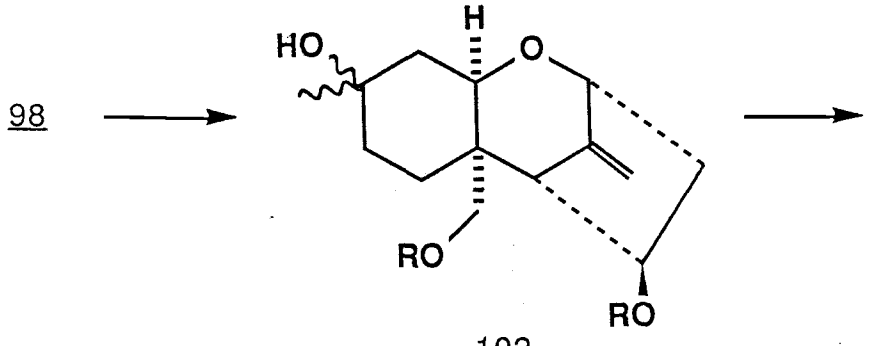
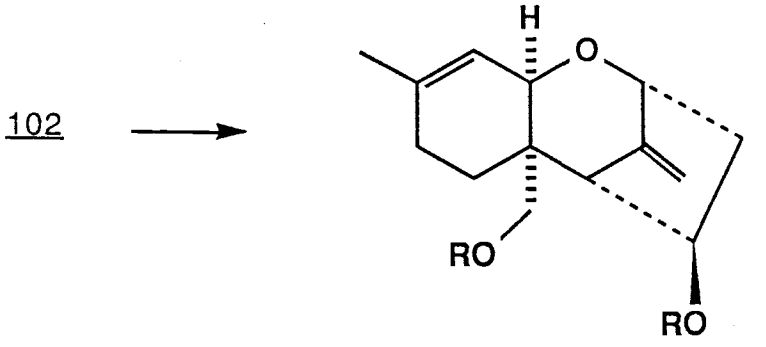


101

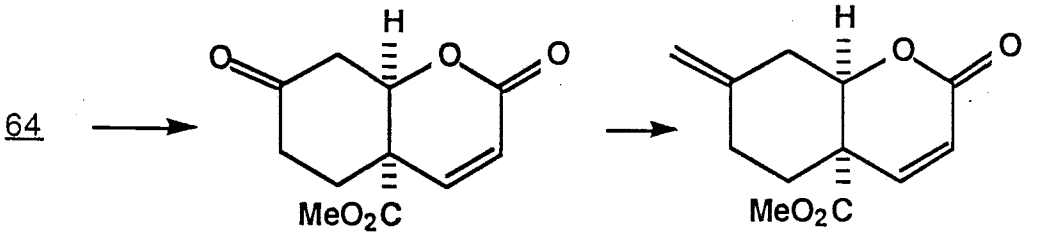


102

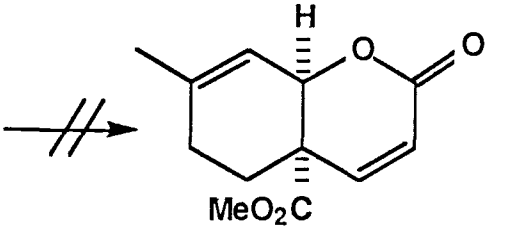


103

In an attempt to install the A ring functionality of verrucarol early in the sequence, Diels-Alder adduct 64 [22] was hydrolyzed with dilute hydrochloric acid to



104 105

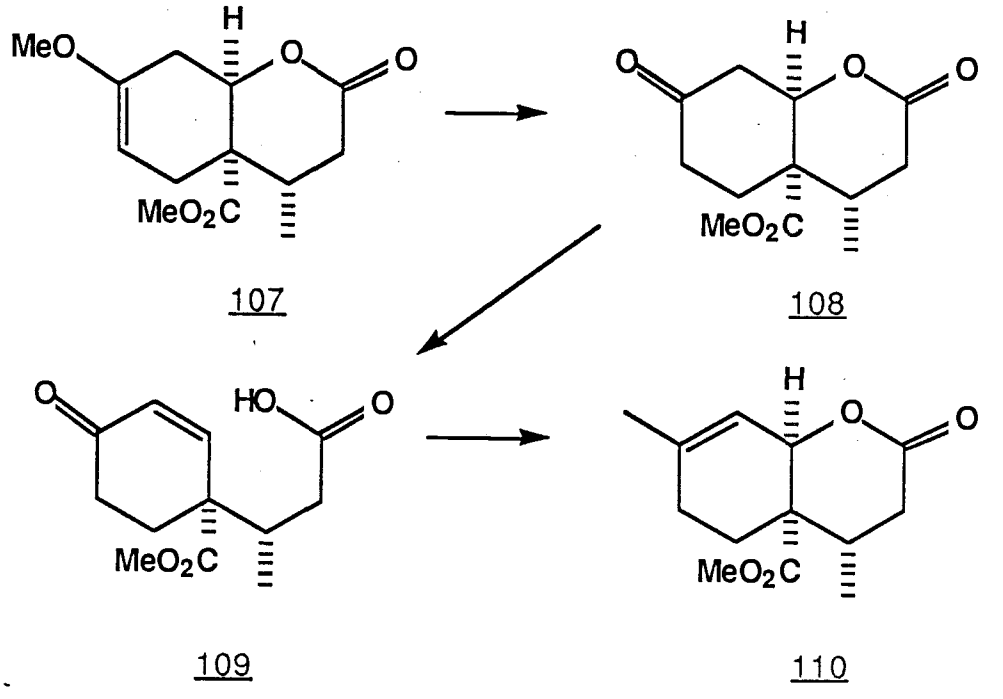


106

give an excellent yield of 104 after recrystallization. It was anticipated that Wittig olefination of 104, followed by acid- or ruthenium (III)-catalyzed isomerization, would yield predominantly 106, known to be the more thermodynamically stable olefin of the

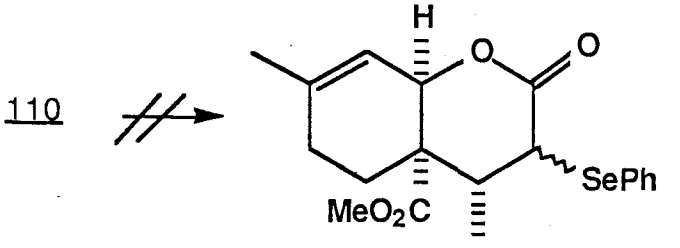
three posssible isomers.[48] Unfortunately, treatment of 104 with methylenetriphenylphosphorane under a variety of conditions gave only low yields of 105. Best results were obtained using a Scandinavian procedure involving addition of 1.1 equivalent of ylide at 0° C followed by water quench of remaining ketone enolate and then renewed treatment with ylide.[49] A total of three cycles resulted in a 20% yield of the desired exo-methylene compound 105. Rather surprisingly, neither rhodium trichloride trihydrate[50] nor hydrochloric acid induced isomerization of 105 to 106.

Subsequently, a much superior method was found for introducing the A-ring double bond and methyl group. Treatment of 107 [21] with dilute hydrochloric acid



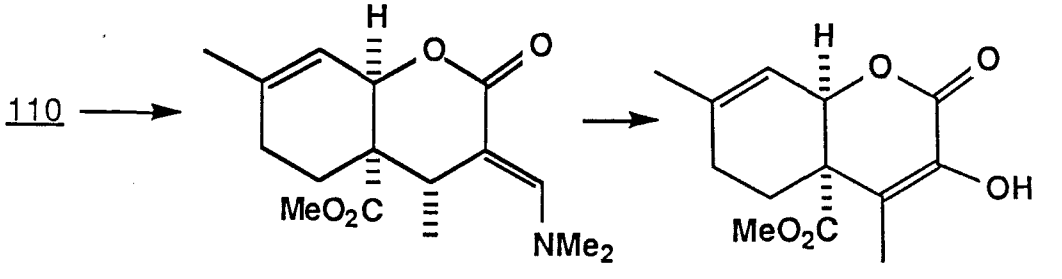
in acetone yielded ketone 108 which was stirred with potassium carbonate in acetone to give a quantitative yield of 109. Upon methylation of the ketone functionality of 109 with methylmagnesium bromide, followed by p-toluenesulfonic acid- catalyzed ring closure, the olefin 110 was obtained. Compound 110 was assumed to possess the *cis*

ring geometry indicated based on Kamikawa's precedent.[10] The next task in the reaction sequence was conversion of 110 to an α,β-unsaturated lactone. While treatment of 110 with lithium diisopropylamide followed by phenylselenyl chloride returned only starting material and none of the desired 111, sequential treatment of



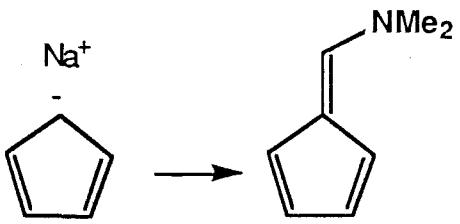
111

110 with lithium diisopropylamide and dimethylformamide-dimethylsulfate 1:1 complex afforded enaminone 112. Although no precedent for trapping of lactone



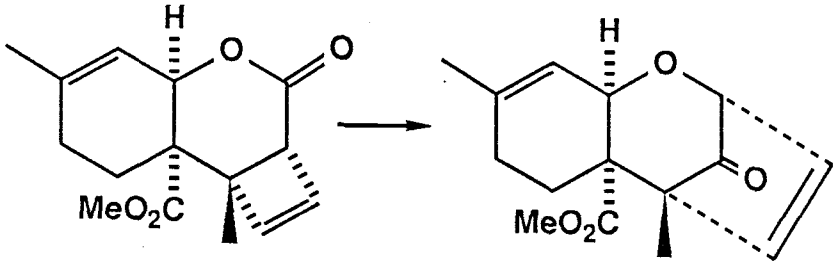
112 113

enolates by dimethylformamide-dimethyl sulfate complex was found, an Organic Syntheses procedure describes a similar reaction in which sodium cyclopentadienide (114) reacts with the complex to afford 6-(dimethylamino)fulvene (115).[51] A more conventional synthesis of enaminolactones involving treatment with tris(dimethylamino) methane[31] gave a very poor conversion of 110 to 112.



114 115

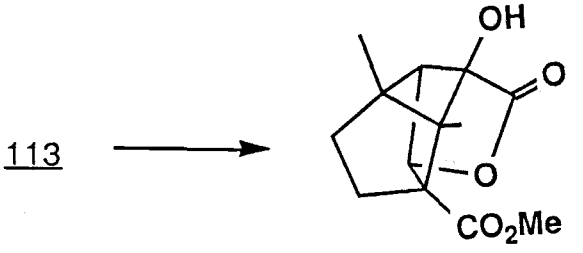
Enaminone 112 was oxidized to ketolactone 113 with singlet oxygen. This reaction was effected by irradiation of a solution containing 112 and a trace of the sensitizer Rose Bengal with a 400 Watt sodium lamp while bubbling oxygen through the solution. The ketolactone 113 exists almost entirely in its enolic form as indicated by the chemical shift (1.85) and multiplicity (singlet) of the β-methyl group in the proton NMR. Some literature precedent exists for intramolecular [2+2] photoadditions to five-membered α-diketone derivatives,[32] and a photoadduct of type 116 would be an



116 117

ideal substrate for a ring expansion to afford 117 via a pinacol-type reaction. Therefore, 113 was irradiated with a Vycor-filtered mercury lamp in acetonitrile

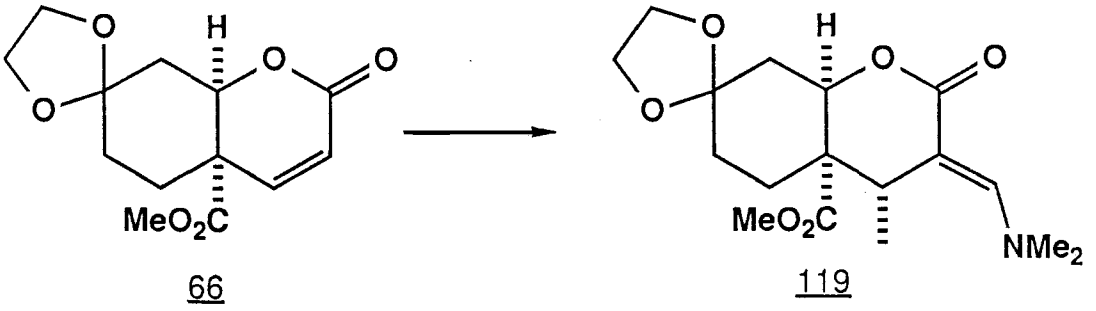
saturated with acetylene with the expectation of producing 116. However, though 113 was consumed during the course of the reaction, no 116 was formed. Rather, 113 underwent an internal [2+2] photoaddition to give 118. The structure shown for 118



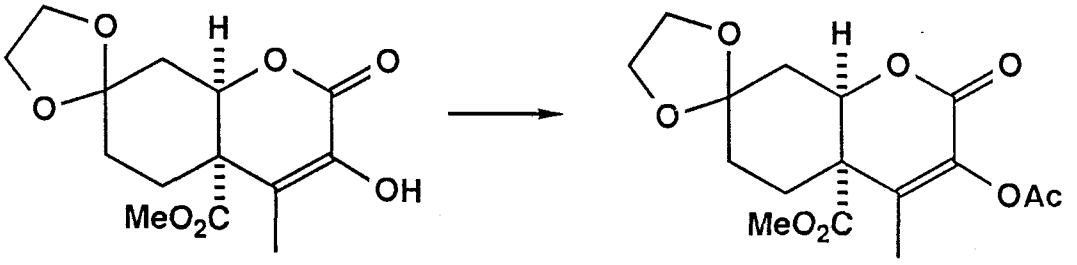
118

was deduced by analysis of several types of spectral data. The photoadduct 118 shows a molecular ion in its' mass spectrum at m/e 252, identical to that of the starting material. The proton NMR spectrum of 118 contained no resonances in the olefinic region, and showed shifts for the C14 and C16 methyl groups (trichothecene numbering), indicating that they are no longer bonded to vinyl carbons. Finally, the IR spectrum showed a carbonyl stretch at 1790 cm^{-1}, consistent with the gamma lactone moiety of 118.

It was clear from this result that the A ring double bond was incompatible with a successful photoaddition to the B-ring unsaturation. We therefore returned to enol ether 64 in order to avoid this impasse. Ketal 66 was prepared by refluxing a benzene solution of 64 with ethylene glycol and catalytic p-toluenesulfonic acid through a column packed with 4A molecular sieves,[21] and was sequentially treated with lithium dimethylcuprate and dimethylformamide-dimethylsulfate 1:1 complex to furnish



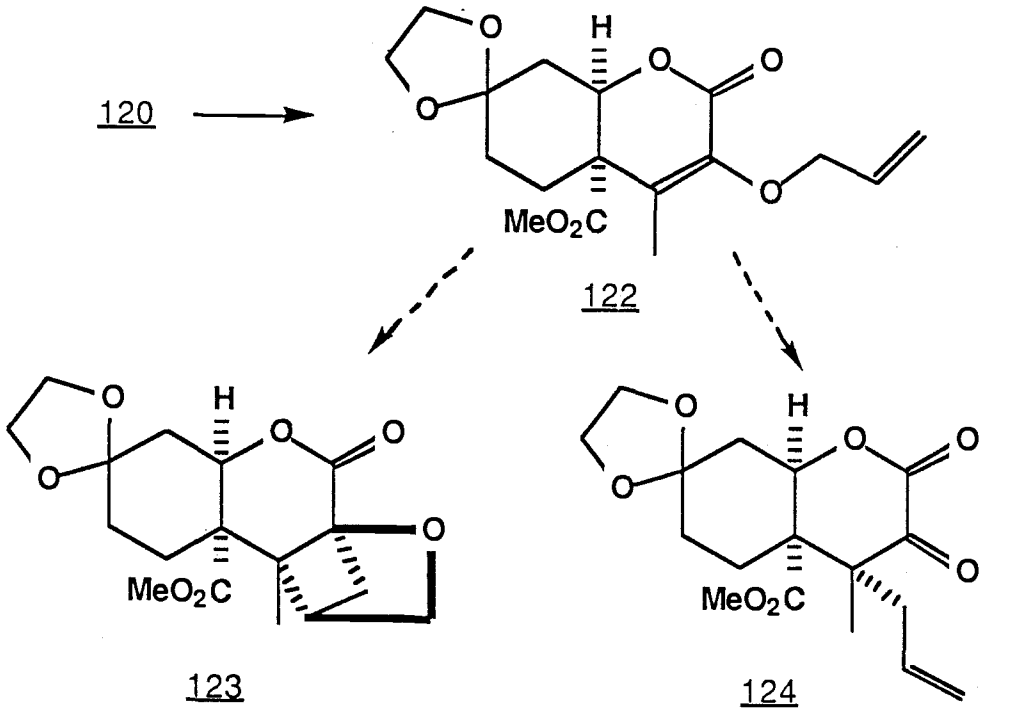
66 119



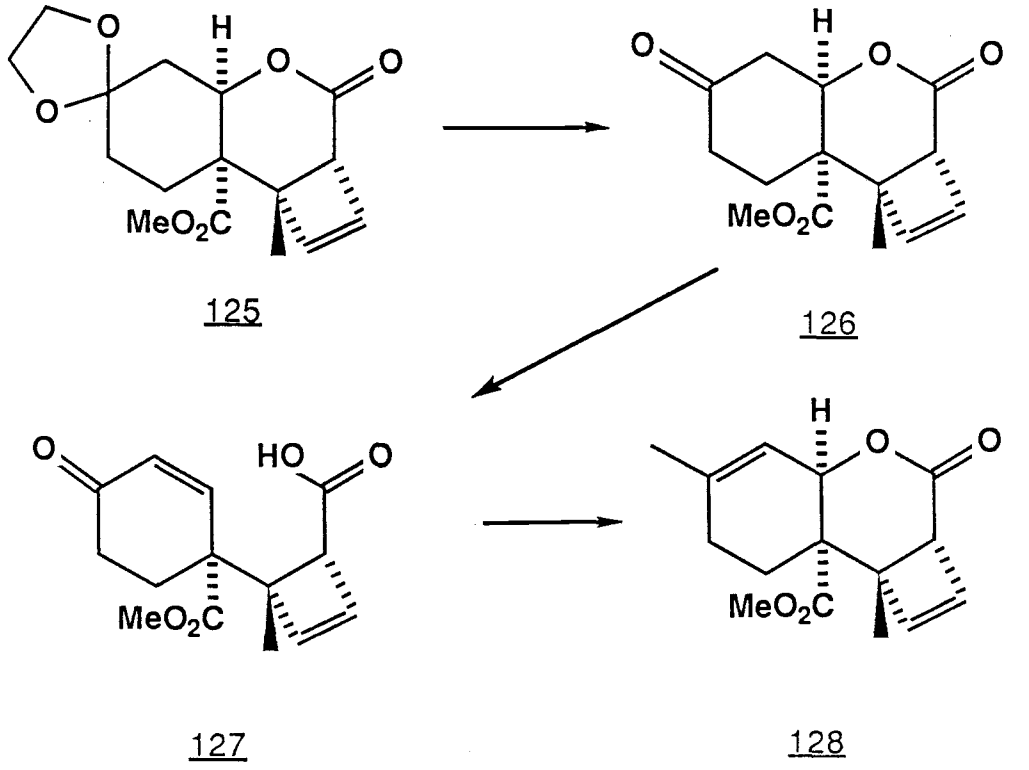
120 121

enaminone 119. This substance was oxidized with singlet oxygen as before to afford 120 which was acetylated to give 121. Unfortunately, when 121 was irradiated in the presence of a variety of photopartners, including ketene dimethyl acetal, acetylene, 1,2-dichloroethylene, and vinyl acetate, it failed to react with any of them under conditions that did not lead to complete destruction of 121. In a final attempt at a photoaddition to an α-ketolactone derivative, 120 was treated with allyl bromide and tetra-n-butylammonium fluoride to give 122. Based on literature precedent, 122 should have reacted to give 123. However, this compound was unreactive photochemically and it also failed to undergo a Claisen rearrangement to 124 upon reflux in dichlorobenzene.

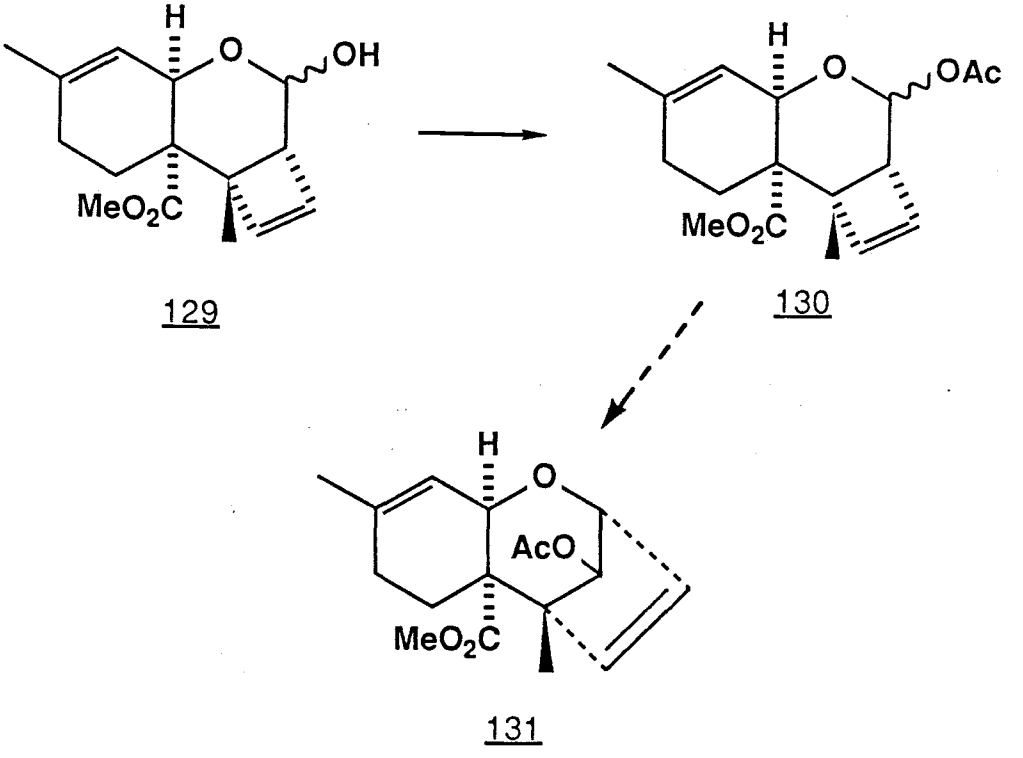
At this stage, a variation on an earlier theme was explored. It was envisioned that 125, obtained from the [2+2] photoreaction of 87 and acetylene,[21] could be transformed into 128 via the elimination-addition sequence described earlier and that



128 would be a suitable precursor for ring expansion to 130. In practice, 125 was first deketalized to afford 126 using acetone and p-toluenesulfonic acid as catalyst.



After some experimentation it was found that potassium carbonate in refluxing methanol brought about the elimination of 126 to 127, although in modest yield. A grignard reaction of 127 with methylmagnesium bromide, followed by camphorsulfonic acid-catalyzed ring closure, gave 128. Reduction of 128 with diisobutylaluminum

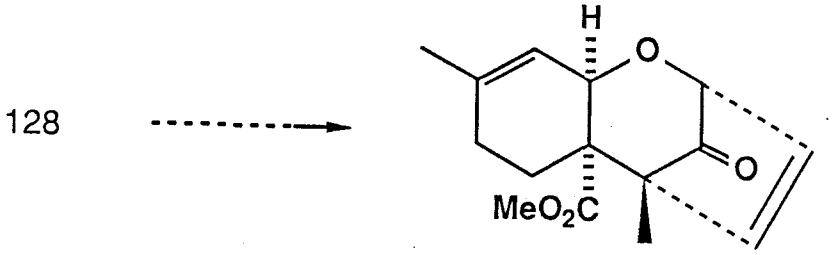


129 130 131

hydride in tetrahydrofuran afforded an excellent yield of hemiacetal 129 with no contamination from reduction of the ester. Based on proton NMR peak intensities, 129 consisted of a roughly 1:1 mixture of anomers.

It had been our hope that acid-catalyzed rearrangement of 129 or a derivative such as 130 would lead to the ring-expanded product 131. However, exposure of 129 and 130 to acetic acid, formic acid, or boron trifluoride etherate did not lead to a compound clearly characterizable as 131. The upfield shift of the olefinic proton signal

in the proton NMR spectrum expected upon enlargement of a cyclobutene to a cyclopentene system was observed upon examination of the crude mixture obtained by treatment of 129 with 98% formic acid. However, this mixture was not investigated further since the low overall yield in the transformation of 125 to 129 made this route impractical. In an alternative approach, a Cargill rearrangment was attempted on 128 with the hope of obtaining 132. However, no reaction was observed upon heating 128 in benzene containing p-toluenesulfonic acid.



132

Another attempt at synthesis of the trichothecene nucleus was made using a close variant of the Cargill reaction developed by a Japanese group.[52] Their innovation, shown in Figure 9, involved generating a cyclobutene system by elimination of a mole of methanol from a dimethyl ketal precursor and rearranging this to a cyclopentene on an acidic gas chromatography column at 200 °C. Their substrate varies in two respects from the one in the present study. The compound is volatile enough to pass through a gas chromatograph, and it is a ketone, not a lactone. Nevertheless, based on this intriguing precedent, 133 was synthesized from ketene dimethyl acetal and 99 in a photoaddition reaction using a Vycor-filtered 450 Watt mercury lamp with acetonitrile

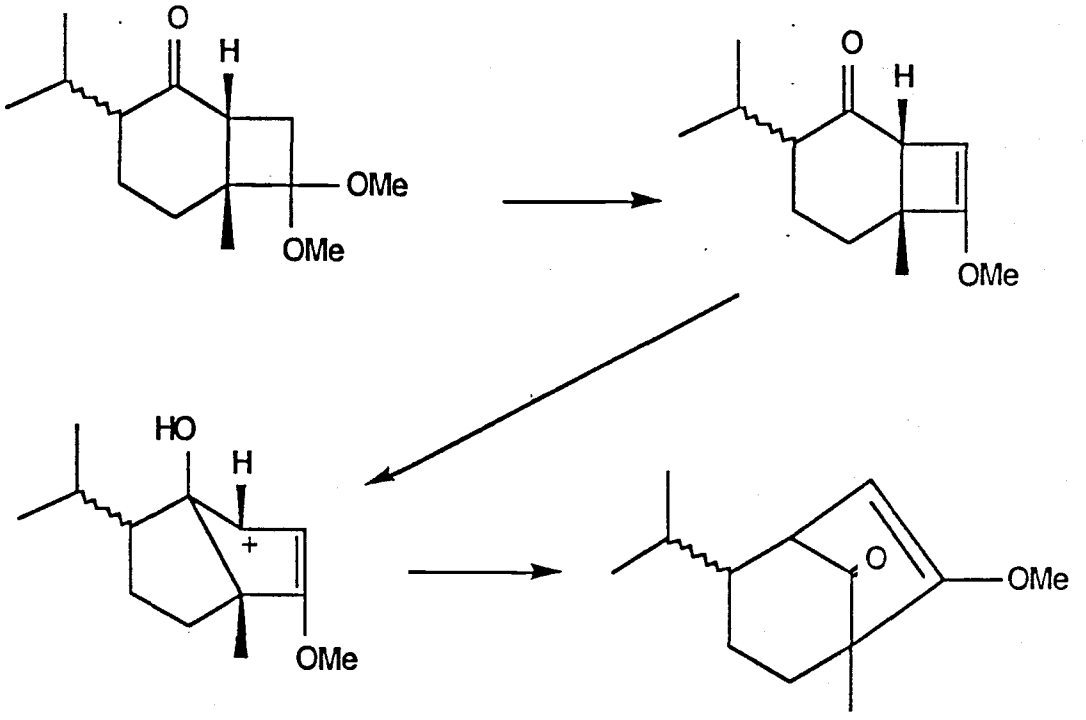
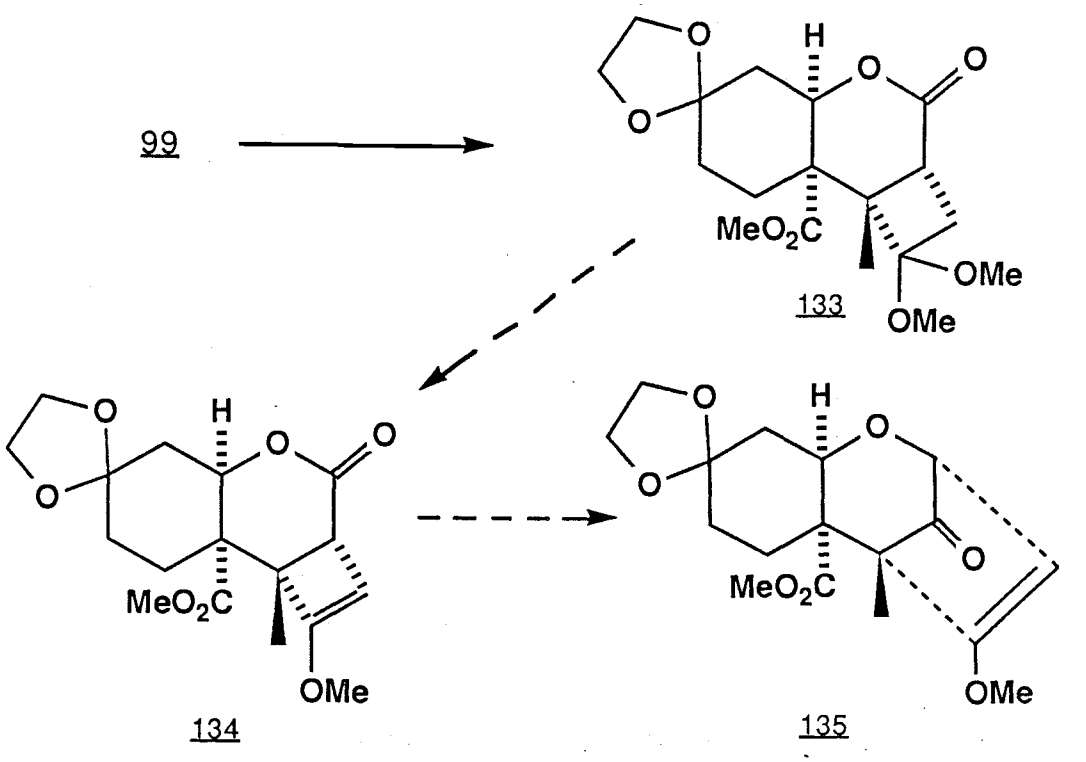
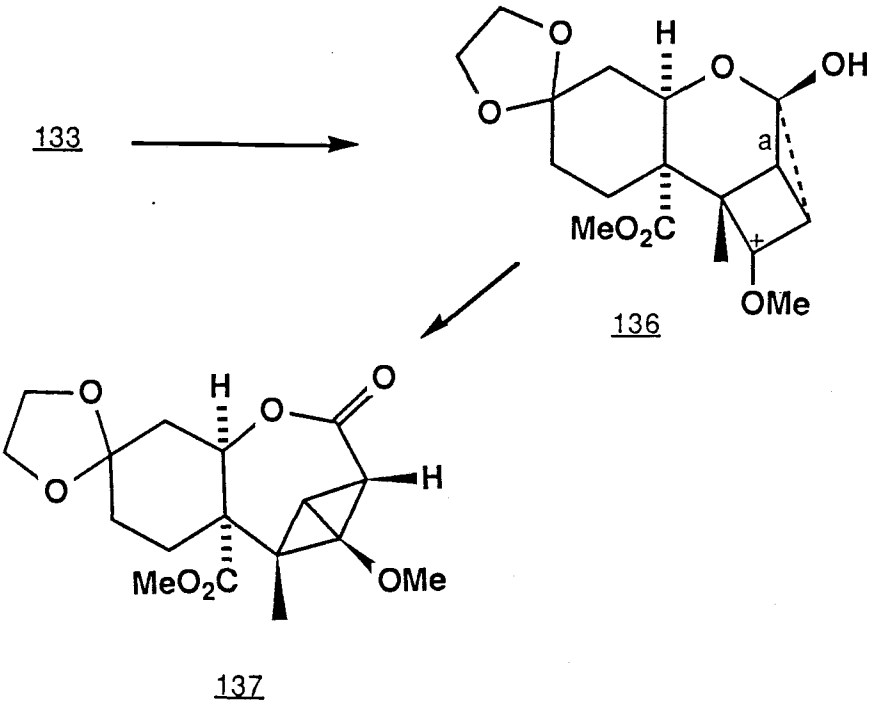


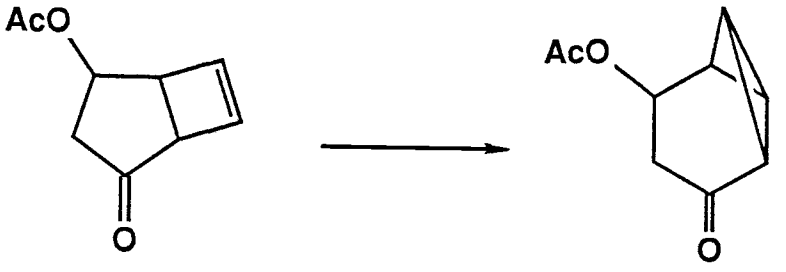
Figure 9
Mechanism of the Modified Cargill Reaction

as solvent. Only one isomer, presumably of *cis-anti-cis* configuration shown, was found in the reaction mixture. The ketal 133 was treated with potassium pyrosulfate in refluxing xylene to give a crystalline material which indeed showed loss of one equivalent of methanol. However, this was clearly not the expected 135. The carbon-13 NMR spectrum of this product showed no resonances for carbon-carbon double bonds but did show a C-methyl group at the anomolously high field of δ12.75. The spectral data is only consistent with a compound possessing one more ring than the starting material, and the very high field position of the methyl group indicates that it is attached to a cyclopropane ring. Structure 137 is consistent with the spectral data and can be derived mechanistically from 133 by a rational process. First, acid-catalyzed elimination of methanol from 133 leads to 134. Migration of the π-bond of 134 to the protonated carbonyl gives carbocation 136, and a subsequent rearrangement of cyclopropyl bond a of 136 to the carbonium ion center leads to bicyclobutane 137. A


99
H
O
O
O
O
MeO2C
OMe
OMe
133
H
O
O
O
O
MeO2C
OMe
134
H
O
O
O
O
MeO2C
OMe
135

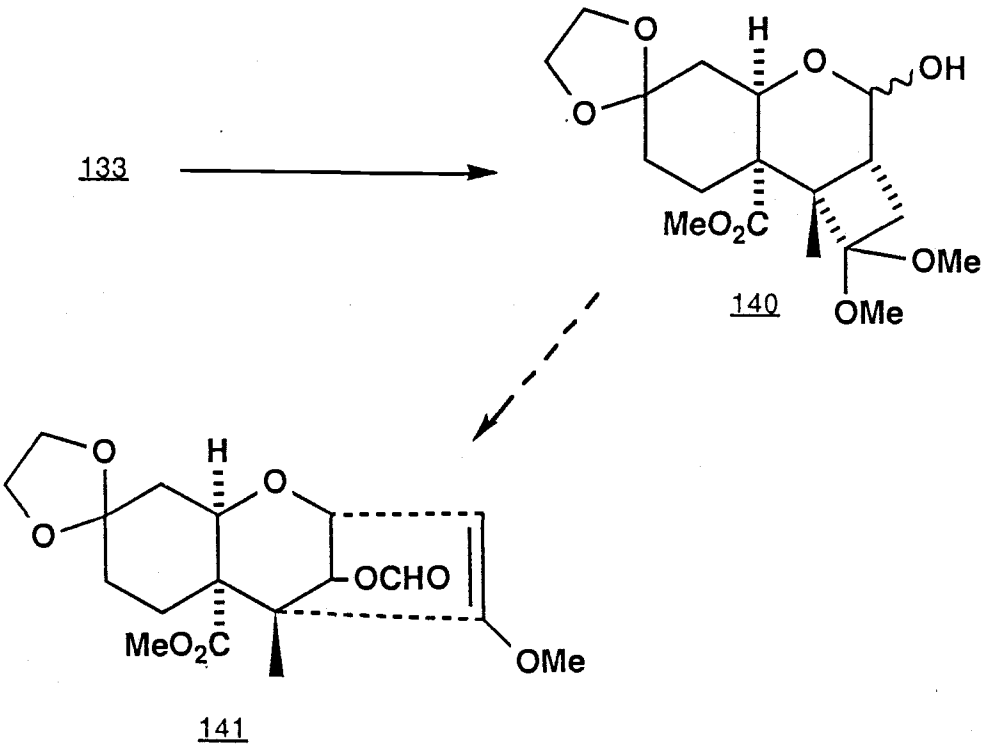

133
H
O
O
O
OH
a
MeO2C
+
OMe
136
H
O
O
O
O
H
MeO2C
OMe
137

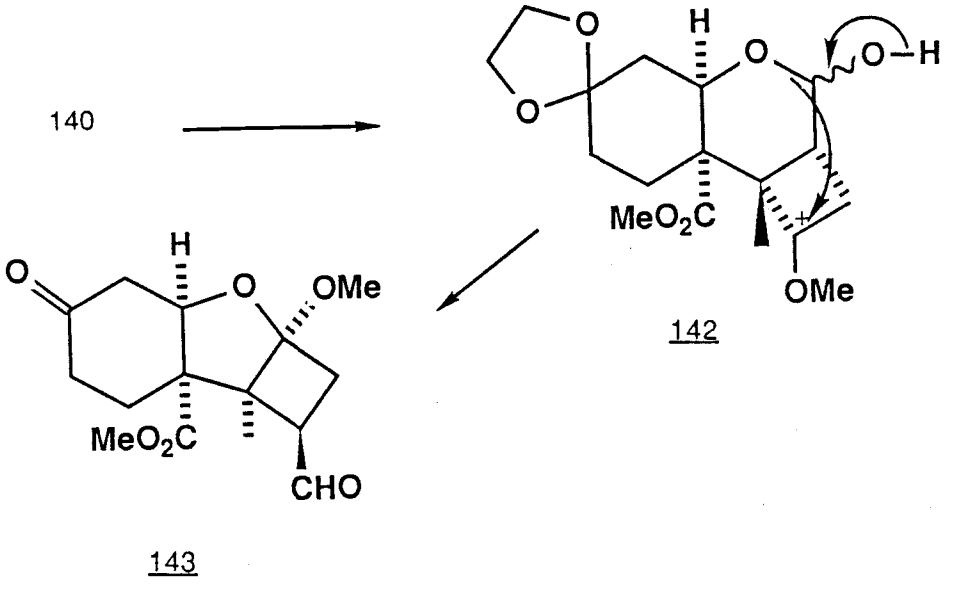
pathway of this sort is not without precedent since the cyclobutene 138 yields bicyclobutane 139 upon photolysis in acetone.[53]



138 139

In the course of a further examination of the chemistry of 133, this lactone was reduced with diisobutylaluminum hydride to give a mixture of hemiacetals 140 which was treated with 98% formic acid in the hope of producing 141. The major product of this reaction showed one methoxyl group in the proton NMR and an aldehyde proton, while the noise-decoupled carbon-13 NMR spectrum showed a total of 15 peaks with no olefinic resonances present. There was also a carbon signal for a ketone and a resonance at δ106 indicating a ketal. Structure 143 is consistent with this spectral data. The mass spectrum provides additional evidence for this structure. The base peak at m/e =180 is consistent with the furan system shown at the bottom of Figure 10, which would arise via a retro-[2+2] cycloaddition followed by loss of methyl formate accross the ring junction.


133
O
H
O
OH
O
MeO2C
OMe
OMe
140
O
H
O
O
OCHO
MeO2C
OMe
141


140
O
H
O
O—H
O
MeO2C
OMe
142
O
H
O
OMe
MeO2C
CHO
143

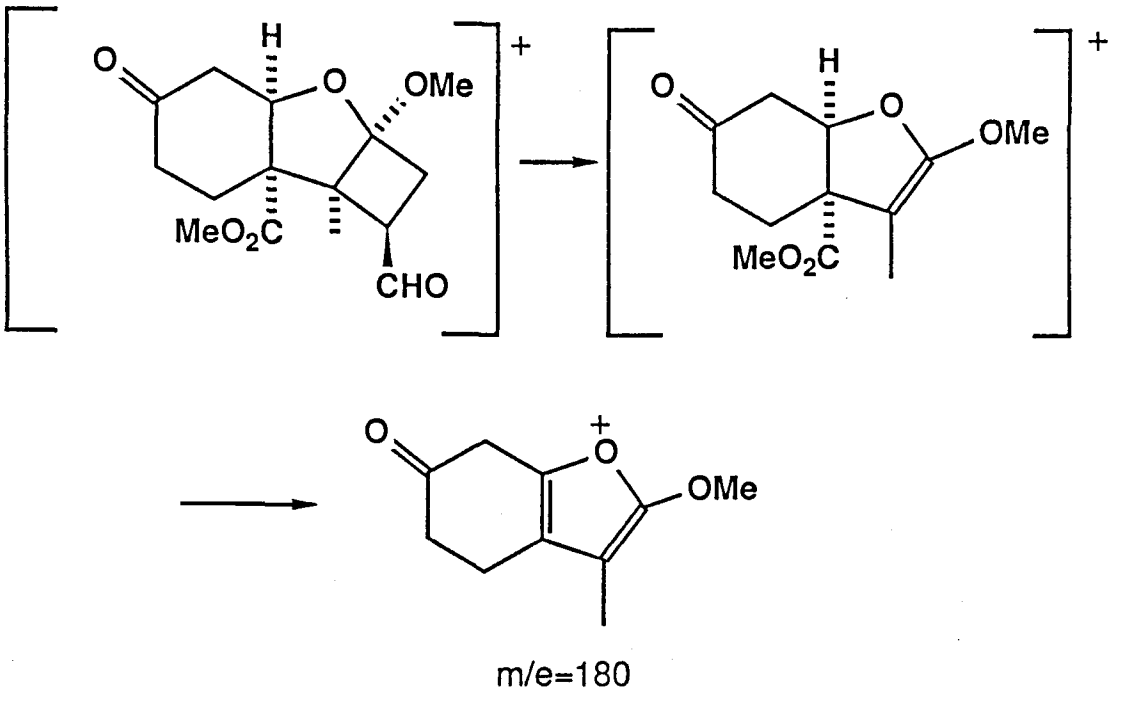


Figure 10

Mass Spectral Fragmentation of 143

Mechanistically, 143 could be derived from ionization of the dimethyl ketal carbon to give 142 followed by trapping of this carbonium ion by the ring oxygen as indicated. Acid-catalyzed hydrolysis of the ethylene ketal would complete the transformation to 143.

In conclusion, this research led to novel methods for stereospecifically emplacing several of the functional groups of verrucarol. However, the objective of a high-yielding construction of the trichothecane skeleton C ring via a cyclobutene ring expansion was not realized.

EXPERIMENTAL

Solvents used for reactions were reagent grade and were distilled before use. Ether, tetrahydrofuran, benzene, toluene, and xylene were distilled from sodium and benzophenone under nitrogen. Methylene chloride, acetonitrile, and amines were distilled from calcium hydride under nitrogen. Starting materials were obtained from commercial sources and used without further purification. "Ether" used in workups refers to anhydrous diethyl ether. For isolation of reaction products, the solvent was removed by rotary evaporation at water aspirator pressure and residual solvent was removed under vacuum at less than 1 mm. Syringes and reaction flasks were dried in an oven (at 165° C) overnight and stored before use in a dessicator over phosphorus pentoxide. Alternatively, flasks were flame-dried under a stream of nitrogen. Analytical thin-layer chromatography (TLC) was carried out on silica-coated aluminum plates (silica gel 60 F-254, 0.2 mm layer thickness, manufactured by E. Merck). Silica gel 60 from E. Merck was used for flash column chromatography. High pressure liquid chromatography (HPLC) was carried out using a Waters M-45 solvent delivery system, two Waters μ-Porasil columns in series, and a Waters refractive index detector. Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 727B spectrometer. Carbon-13 and proton NMR spectra were obtained on either Varian FT-80 or Bruker AM-400 spectrometers. Chemical shifts are expressed in ppm

downfield from internal tetramethylsilane (δ0.00). Proton NMR data are given in the following order: chemical shift, multiplicity (s, singlet;, d, doublet; t, triplet; q, quartet, m, multiplet), number of protons, coupling constants in Hertz. Ultraviolet spectra were obtained on a Varian Cary model 210 spectrophotometer. Low resolution mass spectra were obtained on either a Varian MAT CH-7 or Finnigan 4500 spectrometer. Exact mass measurements were made on either a CEC-110C or a Kratos MS50 mass spectrometer. Elemental analyses were performed by MicAnal, Tucson, AZ.

cis-3-Oxo-6-carbomethoxy-9-methylene-2-oxabicyclo[4.4.0.]dec-4-ene (105)

A flame-dried, 100mL three-neck flask equipped with nitrogen inlet and magnetic stirrer was charged with 100 mg (0.45 mmol) of 104 and 30 mL of diethyl ether and tetrahydrofuran (1:1). The solution was cooled to 0° C and 1.1 equivalent of methylenetriphenylphosphorane (from 0.175 g triphenylmethylphosphonium bromide and 0.30 mL of 1.6 M butyllithium) was added dropwise. After 20 min, 8 μL of distilled water was added and the reaction mixture was stirred for a further 10 min. Another portion of phosphorane was then added, followed after 20 min by another water quench. This cycle was repeated three times, after which 10 mL of water was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with 2x10 mL of ether and the combined organic layers were dried over magnesium sulfate. After removal of the solvent under reduced pressure there remained 95.4 mg of material which consisted of triphenylphosphine oxide, the desired product, and two other, unknown compounds. The mixture was separated by preparative TLC on a silica plate using hexane/ethyl acetate 1:1 as eluant, giving 19.7 mg (20%) of 105: IR (KBr) 3430, 2950, 1700, 1420, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.7-2.8 (m, 6), 3.90 (s, 3), 4.93 (s, 2), 5.02 (t, 1, J=4 Hz), 6.12 (d, 1, J=9 Hz), 6.85 (d, 1, J=9 Hz);

^{13}C NMR ($CDCl_3$) δ30.7, 32.3, 36.8, 47.5, 53.0, 77.7, 112.7, 121.2, 140.7, 148.1, 162.9, 172.8; MS m/e (relative abundance) 223 (4.2), 204 (22.7), 190 (83.0), 155 (100).

(4SR,2'SR)-4-Carbomethoxy-4-(1'-methyl-3'-carboxyethyl)cyclohex-2-enone (109)

A solution of 7.6 g (29.9 mmol) of 107 and 0.2 mL of 10% hydrochloric acid in 100 mL of acetone was stirred for 3 h at 0° C. Potassium carbonate (5 g, 36 mmol) was then added to the reaction mixture, which was stirred for a further 24 h. The solvent was removed in vacuo and the residue was dissolved in 50 mL of water, which was brought to pH 4 with 10% hydrochloric acid. The aqueous phase was extracted with 3 x 50 mL of methylene chloride and the organic fractions were dried over sodium sulfate. The solvent was removed in vacuo to leave 7.18 g (100%) of crude 109. A small sample was methylated with diazomethane in ether at 0° C to give the methyl ester: IR (film) 3150, 1760, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.97 (d, 3, J= 7 Hz), 1.8-2.25 (m, 4), 3.65 (s, 3), 3.70 (s, 3), 6.00 (d, 1, J=9 Hz), 6.77 (dd, 1, J= 2, 9 Hz); ^{13}C NMR ($CDCl_3$) δ15.4, 26.3, 34.8, 36.9, 37.1, 51.2, 51.7, 52.5, 130.2, 149.6, 172.5, 172.9, 198.0; MS m/e (relative intensity) 254 (10.1), 222 (71.5), 121 (100); MS (high resolution) calculated for $C_{13}H_{18}O_5$, 254.115; found, 254.117.

cis-4a-Carbomethoxy-4,7-dimethyl-3,4,4a,5,6,8a-hexahydrocoumarin (110)

A 500 mL round-bottomed flask equipped with magnetic stirrer and nitrogen inlet was charged with 2.0 g of 109 and 150 mL dry tetrahydrofuran. The solution was cooled to 0 °C and 6.7 mL of 3M methylmagnesium bromide was added dropwise. The cooling bath was removed and the solution was stirred for 3 h . It was then poured over cracked ice and acidified to pH 5 with hydrochloric acid. The resulting mixture was extracted with 4x50 mL of ether. The combined organic fractions were dried over

magnesium sulfate, filtered, and the solvent was removed in vacuo to leave 1.73 g (81%) of crude alcohol which was used without purification in the next step.

To a one-neck, 500 mL round-bottomed flask equipped with magnetic stirring was added crude 3-(1-carbomethoxy-4-hydroxy-4-methyl-2-cyclohexenyl)-3-methyl-propanoic acid (1.09 g, 4.25 mmol), 150 mL of benzene, and 100 mg of p-toluenesulfonic acid. After stirring for 1 h at room temperature, the solution was washed with 2 x 25 mL of saturated sodium bicarbonate solution and with 25 mL of brine. The organic solution was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 0.646 g of nearly pure 110, which was flash chromatographed on silica gel 60 (hexane/ethyl acetate 1:1) to yield 0.469 g (46%) of pure 110: mp 84-86° C; IR (film) 3025, 1735, 1435, 1375, 1270, 1235, 1155, 1100, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.04 (d, 3, J=7 Hz), 2.0 (m, 5), 2.5 (m, 2), 3.74 (s, 3), 5.07 (br s, 1), 5.5 (m, 1); MS m/e (relative intensity) 238 (M^+, 8.8), 210 (10.4), 168 (100); Anal. Calcd for $C_{13}H_{17}O_4$: C, 65.53; H, 7.61. Found: C, 65.32; H, 7.76.

cis-6-Carbomethoxy-5,9-dimethyl-4-dimethylaminomethylene-3-oxo-2-oxabicyclo-[4.4.0]dec-9-ene (112)

A flame-dried, one-neck 25 mL round-bottomed flask equipped with magnetic stirrer and nitrogen inlet was charged with a solution of 110 (175 mg, 0.735 mmol) in 5 mL of dry tetrahydrofuran. The solution was cooled to -78° C and a solution of lithium diisopropylamide (1.47 mmol) in 5 mL of tetrahydrofuran was added dropwise. After 45 min, dimethylformamide-dimethyl sulfate complex (0.58 g, 2.94 mmol) was added in one portion. The reaction mixture was stirred for 3 h and allowed to warm to room temperature. The contents of the flask were then transferred to a separatory funnel, diluted with 10 mL of ether, and washed with 2 x 5 mL of

saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to give 259 mg of crude product, which was flash chromatographed on silica gel 60 (ethyl acetate/methylene chloride 1:1) to yield 90.5 mg (42%) of pure 112: mp 125-126° C; IR (film) 2950, 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.07 (d, 3, J=6 Hz), 1.66 (s, 3), 1.89 (br s, 4), 3.06 (s, 7), 3.67 (s, 3), 5.08 (d, 1, J=6 Hz), 5.65 (br s, 1), 7.49 (s, 1); MS m/e (relative intensity) 293 (M^+, 94.9), 262 (12.9), 142 (100); Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90. Found: C, 65.33; H, 8.25.

6-Carbomethoxy-5,9-dimethyl-3,4-dioxo-2-oxabicyclo[4.4.0]dec-9-ene (113)

To a Pyrex test-tube equipped with magnetic stirring was added 40.5 mg (0.138 mmol) of 112 in 4 mL of methylene chloride. A stream of oxygen was bubbled through the solution, and 5 mg of methylene blue was added. The test tube was fitted with an inner, ice-filled tube and irradiated for 30 min with a 400 Watt sodium lamp. The crude reaction mixture was chromatographed on a Chromatotron (silica plate, ethyl acetate/hexane 1:1 as eluant). After removal of solvent in vacuo there was left 16.5 mg (47%) of pure 113: mp 113-114° C; IR 3840, 3000, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.72 (s, 3), 1.86 (s, 3), 2.07 (m, 5), 3.74 (s, 3), 5.26 (br s, 1), 5.45 (br s, 1); ^{13}C NMR ($CDCl_3$) δ11.4, 23.1, 26.1, 27.6, 48.7, 52.8, 76.1, 117.8, 122.8, 136.7, 142.0, 163.2, 172.0; MS m/e (relative intensity) 252 (M^+, 12.7), 193 (79.3), 91 (100); MS (high resolution, M^+) calculated for $C_{13}H_{16}O_5$, 252.100; found, 252.101.

6-Carbomethoxy-4-hydroxy-5,9-dimethyl-2-oxatetracyclo[4.4.0.$0^{1,4}0^{5,9}$]decan-3-one (118)

A solution of 113 (99 mg, 0.392 mmol) in 200 mL of reagent grade acetonitrile was placed in a photoreactor equipped with a 450 Watt medium pressure

Hanovia mercury lamp and the solution was irradiated for 70 min. After removal of the solvent under reduced pressure the crude product was flash chromatographed on silica gel 60 (hexane/ethyl acetate 1.5:1 as eluant) to give 25.6 mg (26%) of 118: mp 110-111° C; IR (film) 3450, 2960, 1790, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.10 (s, 3), 1.43 (s, 3), 1.5-2.1 (m, 4), 2.83 (d, 1, J= 3.4 Hz), 3.30 (br s, 1), 3.71 (s, 3), 4.66 (d, 1, J= 3.0 Hz); MS m/e (relative intensity) 252 (M^+, 4.4), 221 (29.0), 193 (100), 147 (36.1); MS (high resolution, M^+) calculated for $C_{13}H_{16}O_5$, 252.100; found, 252.102.

cis-4a-Carbomethoxy-3-dimethylaminomethylene-4-methyl-7,7-ethylenedioxy-4,4a,-5,6,7,8,8a-heptahydrocoumarin (119)

To an oven-dried 100 mL round-bottomed flask equipped with a nitrogen inlet and mechanical stirrer was added cuprous bromide-dimethyl sulfide complex (2.0 g, 9.76 mmol) and 20 mL of dry tetrahydrofuran. The flask was immersed in an ice water bath and stirring was commenced as 14 mL of 1.55 M methyllithium solution in ether (21.7 mmol) was added over 15 min. A solution of 66 (2.0g, 7.5 mmol) in 10 mL of tetrahydrofuran was added to the reaction flask over a 20 min period. The reaction mixture was stirred for a further 2 h after which methyl sulfate-dimethyl formamide complex (4.2 g, 21 mmol) was added. The ice water bath was removed and the stirred reaction mixture was allowed to reach room temperature. Stirring was continued for a further 2 h and the mixture was then treated with 30 mL of ammonia-ammonium chloride buffer (1:10) and extracted with 3 x 50 mL of ether. The organic fractions were washed with 3 x 20 mL of saturated sodium bicarbonate solution and dried over sodium sulfate. Filtration and solvent removal under reduced pressure left 1.77 g (70%) of 119: IR (film) 1720, 1690, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.03 (d, 3, J=7 Hz), 1.15-2.25 (m, 6), 3.07 (s, 6), 3.72 (s, 3), 3.85 (br s, 4), 5.0 (br s, 1), 7.55 (s, 1); MS

m/e (relative intensity) 339 (M^+, 87.8), 324 (35.4), 280 (25.7); MS (high resolution, M^+) calculated for $C_{17}H_{25}NO_6$, 339.168; found, 339.167.

cis-3-Hydroxy-4a-carbomethoxy-4-methyl-7,7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin (120)

An apparatus consisting of three concentric Pyrex test tubes of sizes 200 x 30 mm, 200 x 25 mm, and 150 x 20 mm was constructed and the innermost tube was filled with powdered Dry Ice. The middle tube was equipped with a stir bar and oxygen inlet and was charged with a solution of 119 (1.33 g, 3.92 mmol) and Rose Bengal (20 mg) in 20 mL of methylene chloride. The space between the middle and outer tubes was purged with dry nitrogen. A vigorous flow of oxygen through the methylene chloride solution was commenced and the reaction apparatus was irradiated for 30 min with a 400 Watt sodium lamp. Solvent was removed from the reaction mixture under reduced pressure and the crude product was flash chromatographed on silica gel 60 (hexane/ethyl acetate 1:1) to leave 0.96 g (82%) of 120: IR (film) 3425, 2950, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.5-2.25 (m, 9), 3.71 (s, 3), 3.94 (s, 4), 5.00 (t, 1, J=7 Hz), 6.33 (br s, 1); MS m/e (relative intensity) 298 (M^+, 39.2), 239 (42.4), 225 (34.2); MS (high resolution, M^+) calculated for $C_{14}H_{18}O_7$, 298.105; found, 298.106.

cis-3-Acetoxy-4a-carbomethoxy-4-methyl-7.7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin (121)

A dry 25 mL round-bottomed flask equipped with nitrogen inlet was charged with 120 (0.23 g, 0.783 mmol) in 10 mL of tetrahydrofuran, 1 mL of 1.0 M tetra-N-butylammonium fluoride in tetrahydrofuran (1 mmol) and 2.0 mL of acetic anhydride (19 mmol). After an initial swirling, the flask was allowed to stand for 48 h at room

temperature. Volatiles were removed under reduced pressure and the residue taken up in 20 mL of ether. The solution was washed with 3 x 5 mL of saturated calcium chloride solution and with 5 mL of aqueous sodium bicarbonate solution. After drying, the ethereal solution was filtered and the solvent was removed to give 0.215 g (80%) of 121 as a clear glass: IR (film) 1750, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.7 (m, 2), 1.95 (s, 3), 2.15 (m, 4), 2.29 (s, 3), 3.75 (s, 3), 3.95 (s, 4), 5.0 (dd, 1, J=5, 8 Hz); MS m/e (relative intensity) 340 (M^+, 1.8), 298 (28.0), 239 (21.9).

cis-3-Allyloxy-4a-carbomethoxy-4-methyl-7,7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin (122)

A 10 mL flask equipped with a magnetic stirrer was charged with 120 (30.6 mg, 0.121 mmol) in 2 mL of methylene chloride, anhydrous potassium carbonate (500 mg, 3.62 mmol), 0.5 mL of 1M tetra-N-butylammonium fluoride in tetrahydrofuran (0.5 mmol), and allyl bromide (0.5 mL, 5.8 mmol). The flask was stoppered and the mixture was stirred overnight. After removal of volatiles under reduced pressure, the residue in the flask was triturated with ethyl acetate/hexane (1:1). The extracts were filtered through a short column of silica gel 60 to leave 23.4 mg (67%) of 122: IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.5-2.5 (m, 4), 1.96 (s, 3), 3.72 (s, 3), 3.94 (s, 4), 4.46 (d, 2, J=8 Hz), 4.95 (t, 1, J=9 Hz), 5.1-6.5 (3H, m); MS m/e (relative intensity) 338 (M^+, 25.7), 279 (33.9), 235 (20.8), 99 (100); MS (high resolution, M^+) calculated for $C_{17}H_{22}O_7$, 338.137; found, 338.135.

cis-anti-cis-7-Methyl-8-carbomethoxy-2-oxatricyclo[6.4.0.$0^{4,7}$]dodec-5-ene-3,11-dione (126)

A solution of 125 (21.5 mg, 0.070 mmol) in 2 mL of acetone was stirred overnight with a few crystals of p-toluenesulfonic acid. The solvent was removed and

the residue was taken up in 10 mL of methylene chloride. The organic layer was washed with 5 mL of saturated sodium bicarbonate solution and the aqueous layer back-washed with 5 mL of methylene chloride. The combined organic layers were dried over magnesium sulfate. After removal of solvent there was left 16.8 mg (91 %) of 126 slightly contaminated with 125. A pure sample of 126 was obtained using Waters HPLC equipment and two μ-Porasil columns in series (ethyl acetate/hexane 1:1): IR (film) 1725, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.32 (s, 3), 1.6-3.25 (m, 6), 3.81 (s, 3), 5.0 (m, 3), 6.19 (m, 2); ^{13}C NMR ($CDCl_3$) δ22.0, 26.7, 38.7, 43.8, 50.7, 52.2, 52.4, 78.41, 133.9, 143.4, 170.3, 172.6, 205.1; MS m/e (relative intensity) 264 (M^+, 11.1), 204 (13.4), 105 (100); MS (high resolution, M^+) calculated for $C_{14}H_{16}O_5$, 264.100; found, 264.100.

(4RS, 1'RS, 4'SR)-4-Carbomethoxy-4-(4'-(1'-carbomethoxy-4'-methylcyclobut-2'-enyl))cyclohex-2-enone (127)

A 25 mL round-bottom flask equipped with a reflux condenser was charged with 126 (54 mg, 0.227 mmol), 10 mL of anhydrous methanol, and anhydrous potassium carbonate (100 mg, 0.725 mmol, 3.2 eq). The mixture was refluxed with stirring for 3 h, cooled, and poured into 10 mL of water. The solution was acidified to pH 5 with potassium dihydrogen phosphate and extracted with three 5 mL portions of methylene chloride. After the combined organic fractions were dried over magnesium sulfate, they were filtered and the solvent was removed under reduced pressure to leave 41 mg (76%) of 127 in nearly pure condition. An analytical sample was prepared by methylation of 127 with diazomethane in ether at 0° C: ^1H NMR ($CDCl_3$) δ1.48 (s, 3), 2.3-2.4 (m, 4), 3.39 (br s, 1), 3.57 (s, 3), 3.72 (s, 3), 6.0 (d, 1, J=10.4 Hz), 6.17 (dd, 1, J=1, 3 Hz), 6.32 (dd, 1, J=1.5, 3 Hz), 6.98 (d, 1, J= 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ23.6, 29.5, 35.5, 51.3, 52.3, 52.4, 56.6, 57.4, 129.1, 132.6, 143.7,

148.4, 171.6, 173.0, 198.0; MS m/e (relative intensity) 278 (M^+, 1.16), 159 (44.25), 125 (100). MS (high resolution, M^+) calculated for $C_{15}H_{18}O_5$, 278.115; found, 278.115.

cis-anti-cis-8-Carbomethoxy-7,11-dimethyl-2-oxatricyclo[6.4.0.$0^{4,7}$]dodec-5-diene-3-one (128)

A flame-dried 10 mL round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet was charged with 127 (25.4 mg, 0.097 mmol) and 5 mL of dry tetrahydrofuran. The solution was cooled to 0° C and methylmagnesium bromide (2.85 M in ether, 2.2 eq) was added dropwise by syringe. After 2 h the reaction mixture was poured into ice water and brought to pH 5 with potassium dihydrogen phosphate. The solution was extracted with 3 x 5 mL of ether, and the collected organic fractions were dried over magnesium sulfate. Solvent removal at reduced pressure gave 21.5 mg of crude hydroxy acid which was lactonized by stirring in 5 mL of methylene chloride containing a few crystals of p-toluenesulfonic acid at room temperature for 12 h. After solvent removal under reduced pressure the crude 128 was flash chromatographed on silica gel 60 (hexane/ethyl acetate 1.5:1) to leave 15.2 mg (42%) of pure 128. An analytical sample was prepared by recrystallization from ether/hexane: IR (film) 2650, 1735, 1720, 1440, 1240, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.29 (s, 3), 1.68 (s, 3),1.95 (m, 4), 3.22 (s, 1), 3.72 (s, 3), 5.02 (d, 1, J=4.7 Hz), 5.70 (m, 1), 6.15 (dd, 1, J=0.9, 2.8 Hz), 6.25(dd, 1, J=0.9,2.8 Hz); MS m/e (relative intensity) 262 (M^+, 10.9), 206 (29.6), 159 (100.0), 91 (73.6); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.91. Found: C, 68.69; H, 6.92.

cis-anti-cis-8-Carbomethoxy-7,11-dimethyl-3-hydroxy-2-oxatricyclo[6.4.0.$0^{4,7}$]-dodec-5,11-diene (129)

A solution of 128 (10 mg, 0.08 mmol) in 2 mL of dry tetrahydrofuran was added by syringe to a flame-dried 5 mL round-bottomed flask equipped with magnetic stirring and argon inlet. The flask was cooled to -78° C and diisobutylaluminum hydride (1M, 0.2 mL, 5.2 eq) was added dropwise. After 1.5 h methanol (0.5 mL) was added and the mixture was poured into 10 mL of water. The mixture was extracted with 3 x 10 mL of ether and the combined organic fractions were dried over magnesium sulfate and filtered. After removal of solvent under reduced pressure there was left 9.0 mg (90%) of the desired product as a roughly 1:1 mixture of diastereoisomers: IR (film) 3450, 2930, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.23 (s), 1.26 (s), 1.67 (s), 2.0 (m), 2.52 (s), 2.75 (dd, J= 1.0, 4.4 Hz), 2.85 (d, J=3.5 Hz), 3.03 (d, J=6.7 Hz), 3.67 (s), 4.34 (d, J=5.0 Hz), 4.71 (d, J=5.5 Hz), 5.22 (dd, J=4.5, 6.9 Hz), 5.35 (d, J=3.3 Hz), 5.53 (m), 6.02 (dd, J=1.4, 2.9 Hz), 6.10 (d, J=2.8 Hz), 6.22 (d, J=2.8 Hz), 6.35 (d J=2.8 Hz); MS m/e (relative intensity) 251 (1.3), 219 (3.8), 167 (14.0).

cis-anti-cis-3-Acetoxy-8-carbomethoxy-7,11-dimethyl-2-oxatricyclo[6.4.0.$0^{4,7}$]-dodec-5,11-diene (130)

A 5 mL round-bottomed flask equipped with a magnetic stirrer was charged with 129 (6.2 mg, 0.024 mmol), 1 mL of acetic anhydride, and 5 drops of pyridine. The reaction mixture was stoppered and stirred for 25 h. Volatiles were then removed under reduced pressure and the residue was filtered through a 2 cm column of silica gel 60 using methylene chloride as eluant. After removal of solvent there was left 7.6 mg (100%) of the product as a mixture of diastereoisomers: IR (film) 2950, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.23-1.26 (2 s, 3), 1.65 (s, 3), 1.97 (br s, 4), 2.11 (s, 3), 2.6 (m, 1), 3.67 (s, 3), 4.46 (m, 1), 5.53 (m, 1), 6.15 (m, 3); MS m/e (relative intensity) 306 (M^+, 4.8), 246 (21.3), 164 (56.9).

cis-anti-cis-6,6-Dimethoxy-7-methyl-8-carbomethoxy-11,11-ethylenedioxy-2-oxa-tricyclo[6.4.0.0^{4,7}]dodec-3-one (133)

A solution of 99 (1.0g, 3.55 mmol) in 125 mL of spectrograde acetonitrile was placed in a quartz photoreactor and irradiated with a 450 Watt mercury lamp through a Vycor filter for 75 min. The solvent was then removed in vacuo and the residue flash chromatographed on silica gel 60 (ethyl acetate/hexane 1:1) to yield 954 mg (72%) of 133 as a white semisolid: IR 2940, 1725, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.26 (s, 3), 1.30 (dd, 1, J=3.25, 14.3 Hz), 1.82 (m, 1), 2.15 (dt, 1, J=3.3, 14.4 Hz), 2.31 (m, 4), 2.54 (td, 1, J=3.2, 14.4 Hz), 2.68 (dd, 1, J=2.7, 12.4 Hz), 3.15 (s, 3), 3.21 (s, 3), 3.75 (s, 3), 3.9-4.1 (m, 4), 4.74 (dd, 1, J=2.8, 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ19.5, 22.0, 25.4, 31.8, 33.9, 36.4, 37.5, 48.7, 50.2, 51.6, 52.5, 55.3, 63.8, 64.9, 106.6, 107.2, 172.9, 173.1; MS m/e (relative intensity) 370 (M^+, 1.6), 99 (48.6), 88 (100); MS (high resolution, M^+) calculated for $C_{18}H_{26}O_8$, 370.163; found, 370.162.

(1RS, 4SR, 5SR, 6SR, 8RS)-5-Methoxy-6-methyl-7-carbomethoxy-10,10-ethylene-dioxy-2-oxatetracyclo[5.4.0.1^{4,6} 0^{5,12}]dodecan-3-one (137)

A one-neck 100 mL round bottom flask equipped with a magnetic stirrer and a dropping funnel filled with 4A molecular sieves surmounted by a reflux condenser was charged with 161.5 mg (0.44 mmol) of 128, 100 mg (0.40 mmol) of oven-dried potassium pyrosulfate, and 30 mL of dry o-xylene. The mixture was refluxed vigorously for 26.5 h. After removal of suspended solids by filtration and of solvent by evaporation under reduced pressure, the crude material was flash chromatographed on silica gel 60 (hexane/ethyl acetate 2.5:1). The yield of 137 was 64.3 mg (44%): mp 171-172° C; IR (film) 2940, 1750, 1725, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.26 (s, 3),

1.48 (m, 1), 1.85 (m, 1), 2.0-2.25 (m, 3), 2.68 (m, 2), 2.82 (dd, 1, J = 1.7, 11.3 Hz), 3.20 (s, 3), 3.70 (s, 3), 3.8-4.1 (m, 4), 4.97 (d, 1, J= 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ12.3, 25.0, 28.1, 32.4, 40.3, 49.9, 51.5, 52.2, 55.3, 55.5, 63.7, 64.7, 81.3, 85.4, 110.6, 172.0, 173.4; MS m/e (relative intensity) 338 (M^+, 20.6), 294 (15.3), 149 (29.4), 99 (100); MS (high resolution, M^+) calculated for $C_{17}H_{22}O_7$, 338.138; found, 338.137.

cis-anti-cis-3-Hydroxy-6,6-dimethoxy-7-methyl-8-carbomethoxy-11,11-ethylenedioxy-2-oxatricyclo[4.4.0.0^{4,7}]dodecane (140)

A flame-dried 25 mL round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet was charged with a solution of 133 (71 mg, 0.191 mmol) in 8 mL of dry tetrahydrofuran. The flask was cooled to -78° C and 0.4 mL of 1M diisobutylaluminum hydride solution (0.4 mmol) was added dropwise. The reaction mixture was stirred for 1h and then poured into 20 mL of water. The gelatinous mixture was extracted with 3x10 mL of ether. The combined organic fractions were dried over magnesium sulfate, filtered, and the solvent was removed in vacuo to leave 43.3 mg (60%) of crude lactol as an inseparable mixture of diastereoisomers. A sample for spectral analysis was prepared by acetylation of 140 with pyridine and acetic anhydride followed by separation of the diastereomeric acetates by HPLC (μ-Porasil column, ethyl acetate/hexane 1:1). Spectral data were obtained on the less polar acetate: IR (film) 2950, 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.13 (s, 3), 1.85-2.3 (m, 7), 2.10 (s, 3), 2.41 (dt, 1, J= 4.4, 13.5 Hz), 2.51 (dd, 1, J= 5.9, 12.6 Hz), 3.16 (s, 1), 3.22 (s, 3), 3.71 (s, 3), 3.95 (m, 4), 4.28 (dd, 1, J= 4.5, 9.0 Hz), 6.23 (d, 1, J= 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ21.0, 21.3, 24.5, 27.6, 33.7, 35.8, 36.7, 49.1, 50.0, 51.2, 51.8, 54.0, 63.8, 64.2, 74.4, 93.0, 104.4, 108.6, 169.4, 175.3; MS m/e (relative intensity) 414 (0.3, M^+), 225 (10.8), 99 (32.3).

(2SR,3RS,5SR,6RS,7SR)-*cis-anti-cis*-7-Carbomethoxy-10-oxo-3-methoxy-2-oxa-tricyclo[5.4.0.0^{3,6}]undecan- 5-carboxaldehyde (143)

A solution of 140 (15.8 mg, 0.425 mmol) was dissolved in 1 mL of 98% formic acid and allowed to stand for 27 min at room temperature. Volatiles were then removed in vacuo. The residue was taken up in methylene chloride (10mL) and the solution was washed with two 10 mL portions of water. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to leave 10.8 mg (86%) of 143 as a clear glass: IR (film) 2950, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.49 (s, 3), 2.0-2.9(m, 9), 3.27 (s, 3), 3.73(s, 3), 4.77(t, 1, J=4 Hz), 9.68 (d, 1, J=2.6 Hz); ^{13}C NMR ($CDCl_3$) δ18.3, 28.4, 28.8, 36.0, 42.8, 48.9, 50.4, 52.4, 53.7, 59.8, 78.6, 106.0,173.4, 200.8, 208.6; MS m/e (relative intensity) 296 (M^+, 0.4), 239 (16.1), 180 (100), 43(96); MS (high resolution, M-1) calculated for $C_{15}H_{19}O_6$, 295.118; found, 295.119.

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