

AN ABSTRACT OF THE THESIS OF

James Anthony Thomas for the degree of Doctor of Philosophy
in Chemistry presented on March 12, 1979 .

Title: APPROACHES TO THE SYNTHESIS OF TRICHOTHECANE SESQUI-
TERPENES.

Abstract approved:

Redacted for Privacy


Dr. James D. White

Synthetic studies were initiated with the ultimate goal of an efficient synthesis of a member of the trichothecane class of sesquiterpenes. Two different approaches to this problem were explored.

The first approach entailed a [3,3] sigmatropic rearrangement of an appropriately substituted 1,5 diene in an attempt to stereospecifically generate the key C₄-C₁ carbon-carbon bond of trichodiene. Suitable 1,5 dienyl substrates were prepared and subjected to Cope, alkoxy-Cope, and Claisen rearrangement conditions, although in no case was a product obtained suitable for conversion to trichodiene. A rare example of the Claisen rearrangement of a 1,1,6,6 tetrasubstituted 1,5 diene was demonstrated, namely the conversion of 2,5-dimethylcyclohexenyl 3-methyl-2-butenyl ether to 2-(2-methylbut-3-en-2-yl)-2,5-dimethylcyclohexanone in 31% yield.

The second approach utilized sequential cycloaddition reactions to generate the C₅-C₆ bond of verrucarol with the

correct relative stereochemistry. Thus, methyl coumalate was converted via a Diels-Alder reaction with 2-ethoxybutadiene followed by treatment with ethylene glycol and acid to 4a-carbomethoxy-7,7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin. The latter was treated with lithium dimethylcuprate, followed by phenylselenation-oxidation-elimination to furnish 4a-carbomethoxy-3-methyl-7,7-ethylenedioxy-4a,5,6,7,8,8a-hexahydrocoumarin, which was subjected to photocycloaddition with acetylene to yield the key tricyclic compound cis-anti-cis-8-carbomethoxy-7-methyl-11,11-ethylenedioxy-2-oxatricyclo[6.4.0.0^{4,7}]dodec-5-en-3-one.

The latter tricyclic compound was reduced with diisobutylaluminum hydride to furnish the corresponding hydroxy hemiacetal, 8-hydroxymethyl-7-methyl-11,11-ethylenedioxy-2-oxatricyclo[6.4.0.0^{4,7}]dodec-5-en-3-ol. Treatment of the latter with acid prompted isomerization to spiro[1-methyl-4-oxabicyclo[4.2.0]oct-7-en-5-ol-2,1'-4,4-ethylenedioxcyclohexan-2-ol]. Further acid treatment at 70°C led to the cyclobutylcarbinol rearrangement product spiro[1-methyl-8-formyloxy-4-oxabicyclo[3.2.1]oct-6-ene-2,1'-cyclohex-2-en-4-one], thus demonstrating the feasibility of this reannulation step to form the bicyclo[3.2.1] portion of verrucarol.

APPROACHES TO THE SYNTHESIS OF TRICHOTHECANE SESQUITERPENES

by

James Anthony Thomas

A THESIS

submitted to

Oregon State University

in partial fulfillment of

the requirements for the

degree of

Doctor of Philosophy

Completed March 12, 1979

Commencement June 1979

ACKNOWLEDGEMENTS

I wish to thank Dr. J. D. White for his patience, guidance and numerous helpful suggestions during my tenure at Oregon State University. I also wish to express my gratitude to Dr. J. P. Carter and Mr. John Chronic for helping build my stocks of synthetic intermediates. A special debt of gratitude is owed to Ms. Susan Randall for her unceasing supply of NMR and mass spectral data, and to Mr. Mario Boschetto for his wizardry with glassware. Finally, I wish to acknowledge the N. L. Tartar Foundation for the partial support of this work.

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APPROACHES TO THE SYNTHESIS OF TRICHOHECANE SESQUITERPENES

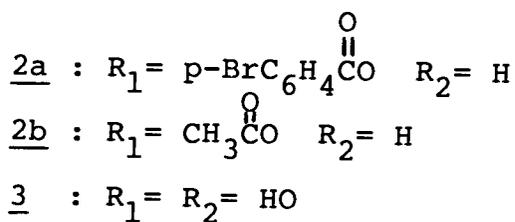
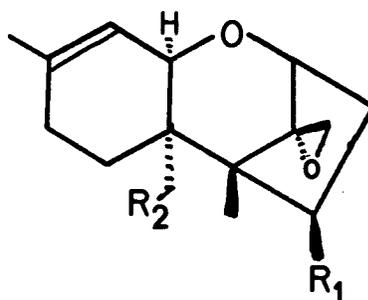
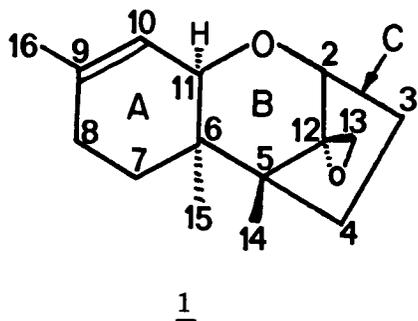
CHAPTER I: INTRODUCTION

The trichothecanes and trichothecane containing compounds are mold metabolites derived from various fungal species. These substances have been implicated as the causative agents in a number of mycotoxin diseases originating from molding corn or grain.¹ Studies by Brian and Hemming² showed that culture filtrates from various strains of Fusarium, Trichothecium, and Mycothecium also displayed significant antifungal activity. Substances containing the trichothecane structure have since been shown to exhibit several forms of biological activity, typically phytotoxic, cytotoxic, insecticidal, and antibiotic.³ Of particular significance is the fact that they have been shown to inhibit the growth of Ehrlich ascites tumors in mice^{3b} and Walker carcinoma in rats.⁴ It is these properties that have sparked interest in first, the structure elucidation and second, the synthesis of members of the trichothecanes.

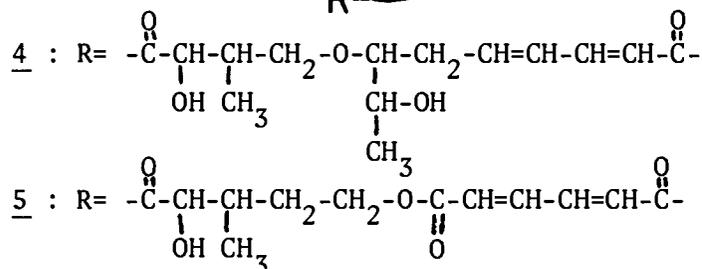
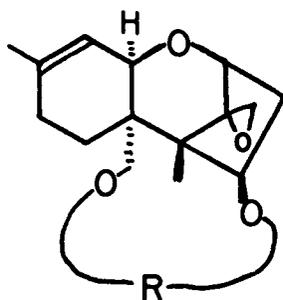
The work of Brian and Hemming, noted above, prompted efforts at the isolation of the active principals responsible for the antifungal activity that they had discovered. One compound, trichothecin, was isolated in 1948. During the period 1949 to 1959 there were no reports of new members of the trichothecanes. However, from 1959 to the present, there have been numerous disclosures of new and varied members of the trichothecane class of terpenes.

The early literature dealing with the structure elucidation of this family was fraught with incorrect structural assignments. The definitive structural proof was supplied by Abrahamsson and Nilsson,⁵ who performed an X-ray crystallographic analysis on the p-bromobenzoate ester of

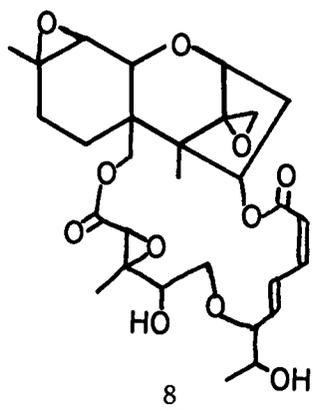
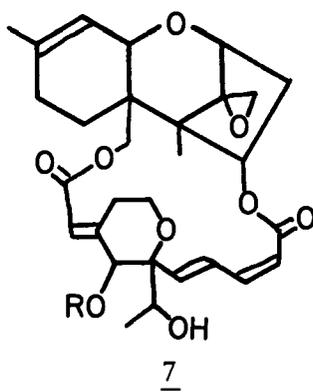
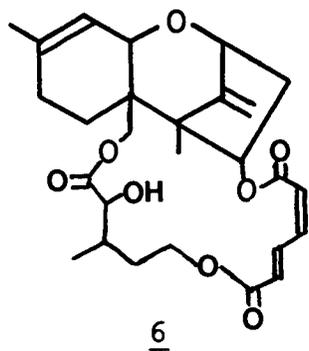
trichodermol (2a), thus fixing the structure as shown below on the representative examples trichothecene 1,⁶ trichodermin 2b,⁷ and verrucarol 3.⁸



Some examples of trichothecane containing compounds are the macrolide structures of the roridins⁹ and the verrucarins,¹⁰ exemplified by roridin A 4 and verrucarin A 5.



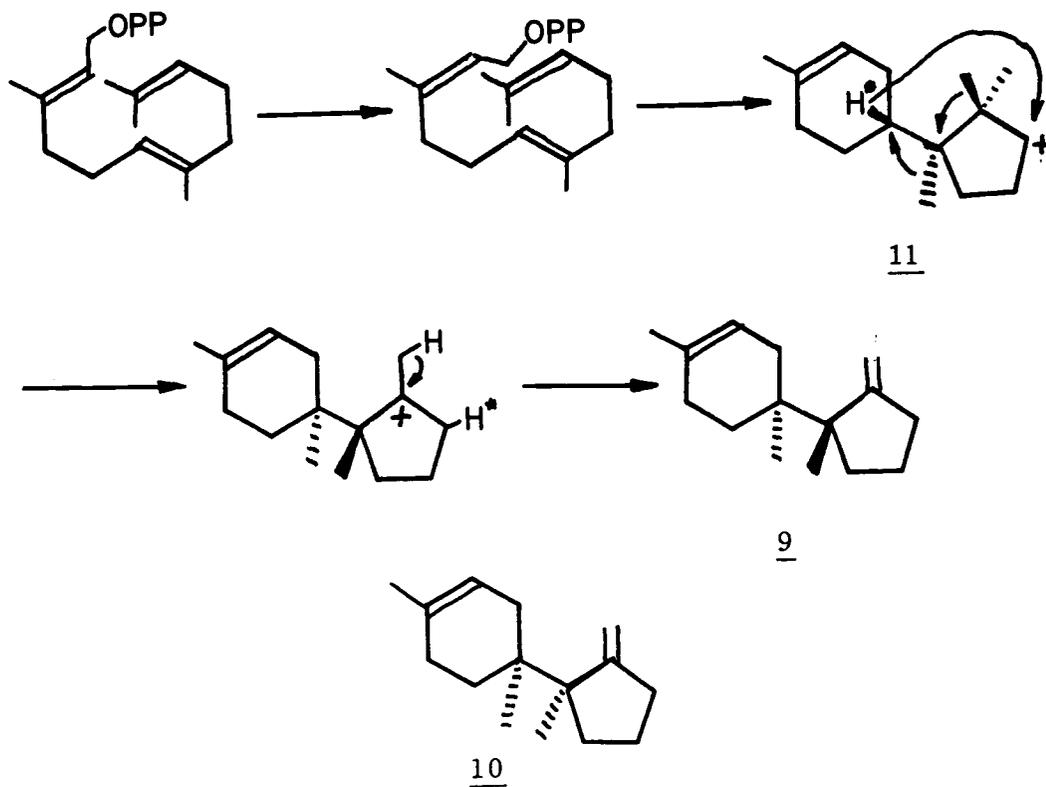
A number of macrolides related to the verrucarins and roridins are known which are modified in the tricyclic nucleus, as in verrucarin K 6,¹¹ in the linear diacid portion, as in satratoxin H 7¹² or in both, as in baccharin 8.¹³



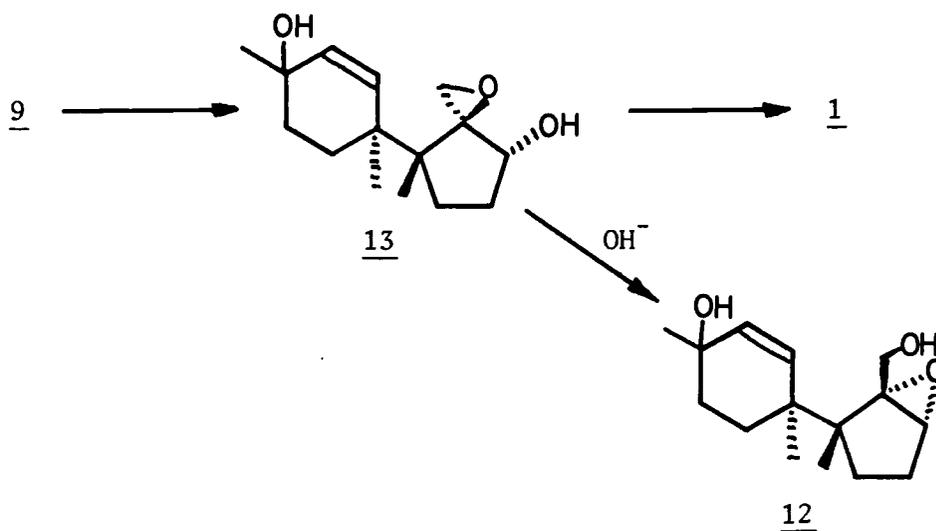
The mechanism of action responsible for the mycotoxic effects and the biological properties is not certain, although it appears that the spiroepoxy pyran moiety plays a key role.¹⁴ It is known that trichothecanes can bind reversibly and irreversibly to ribosomes and polyribosomes, thereby blocking protein synthesis.¹⁵ Binding appears to specifically block the enzyme peptidyl transferase.^{15c,16} The reversibility of binding depends on the presence and nature of oxygen substitution at carbons 3, 4, 8, and 15 of the trichothecane skeleton (trichothecane numbering).¹⁷

The trichothecanes were originally thought to be derived biosynthetically from all trans farnesyl pyrophosphate via an α -bisabolene intermediate,¹⁸ but they have since been shown to be derived from trichodiene 9. Although the latter had been hypothesized as a key intermediate in the biosynthesis of trichothecanes, this was only recently substantiated by its isolation¹⁹ and appropriate labeling studies.^{6,20} The stereochemistry about the bond joining the two rings of 9 was assumed to be the same as in the trichothecanes, however, this was put on firmer ground by the isolation and characterization of bazzanene 10,²¹ the C₄ epimer of 9. The formation of 9 was shown to occur by the following stages:

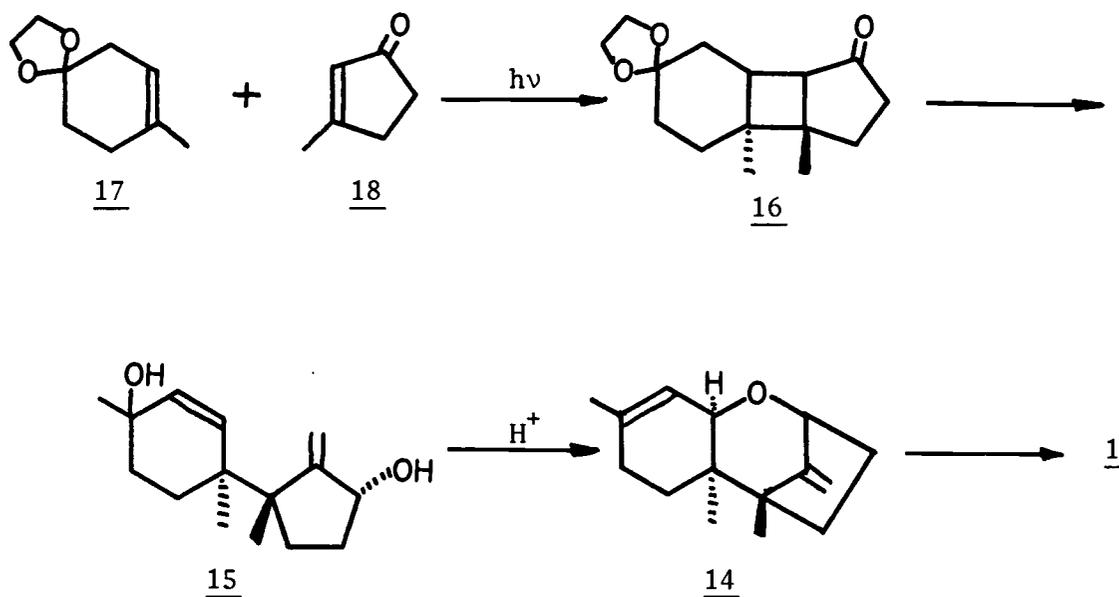
- (1) Isomerization of all-trans farnesyl pyrophosphate to the 2-cis isomer²²
- (2) cyclization of cis, trans farnesyl pyrophosphate to carbonium ion 11
- (3) sequential or concerted shift of H^* to the carbonium ion center of 11 (enzyme assisted),²³ and the stereospecific Wagner-Meerwein shifts of the two methyl groups²⁴
- (4) loss of a proton to give 9.



The further transformation of 9 into the trichothecene skeleton had been rationalized to proceed via 12, but it was subsequently shown¹⁹ that 12 was actually an artifact of the true intermediate, trichodiol 13.



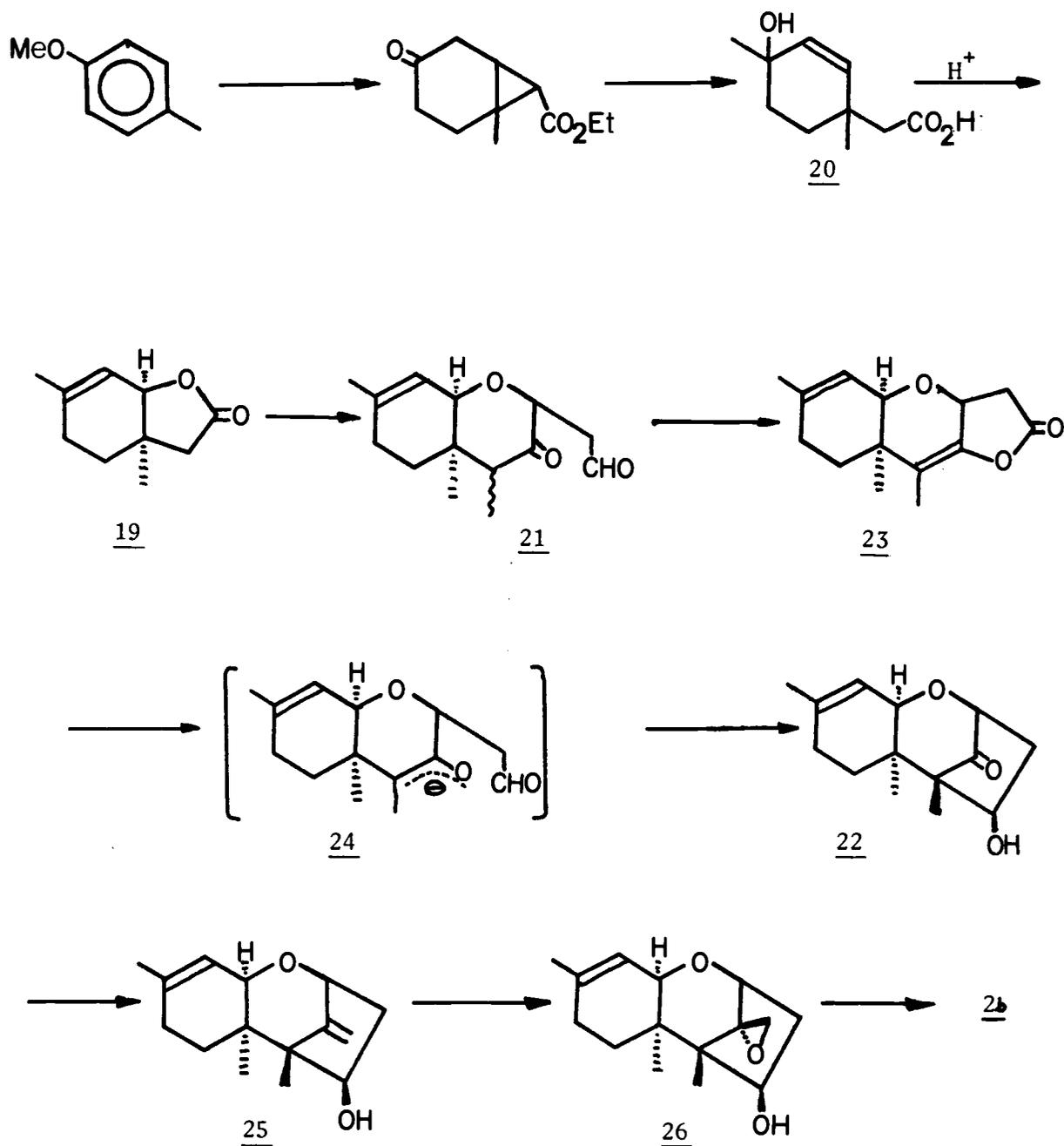
The viability of 13 as a biosynthetic intermediate was shown by an interesting synthesis of 1 by Kamikawa et al.²⁵ The key biomimetic step of their synthesis was the acid promoted formation of ether 14 from diol 15. This diol was obtained from tricyclic ketone 16 which was prepared from olefin 17 and enone 18 by photocycloaddition.



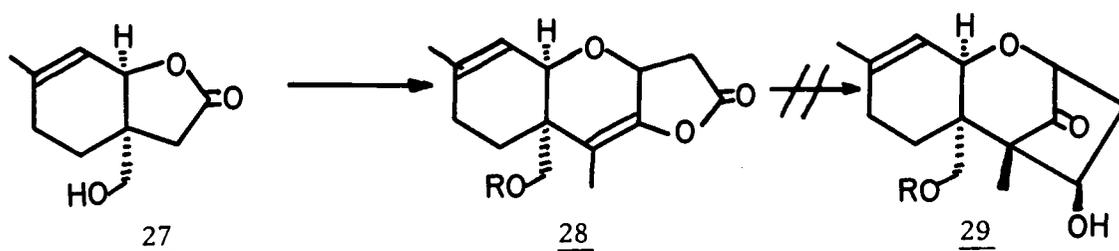
The first synthesis²⁶ of a member of the trichothecane class was accomplished by Raphael and co-workers.²⁷ Their synthesis of trichodermin 2b, proceeds in a linear fashion beginning with ring A, and sequentially adding rings B and C. The first key compound, cis fused lactone 19,²⁸ was obtained by acid treatment of hydroxy acid 20. Lactone 19 was then transformed into keto aldehyde 21, which was projected to undergo aldol condensation to give the trichothecane skeleton of 22. However, all attempts to effect the desired condensation failed.²⁹ This was circumvented by transformation of 21 into enol lactone 23, which was reduced

with lithium tri-*t*-butoxyaluminum hydride to yield 22 directly.

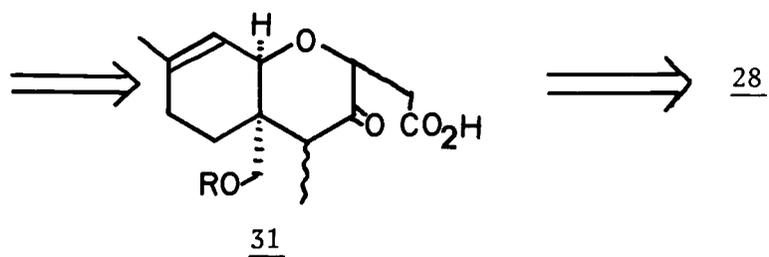
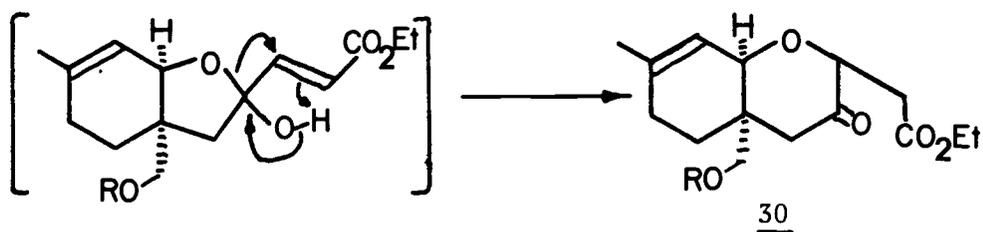
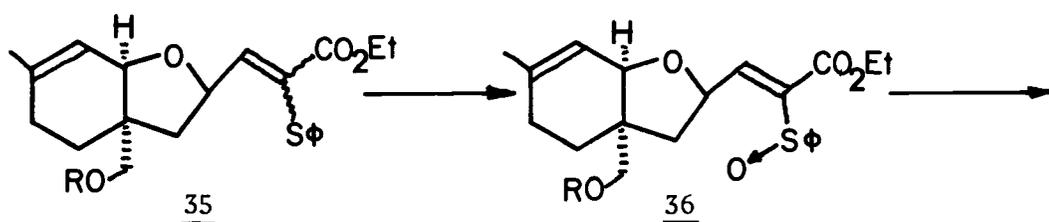
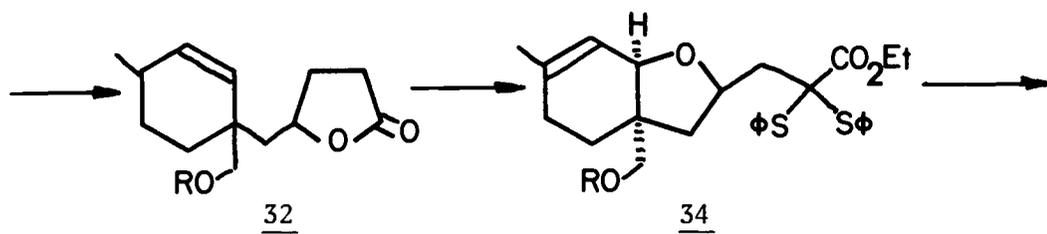
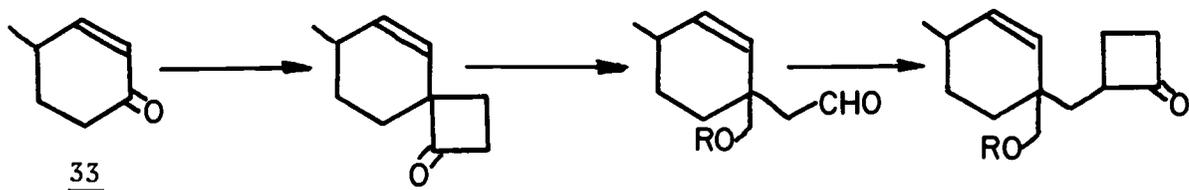
Apparently the regiospecifically generated enolate 24 underwent aldol condensation while still coordinated to aluminum. Keto alcohol 22 was converted to the methylene compound 25 and regiospecifically epoxidized to 26 utilizing the C-ring hydroxyl function to direct the epoxidation. Subsequent acetylation yielded 2b.



Synthetic efforts aimed at verrucarol 3 have been reported by two groups. The first, that of Colvin et al,³⁰ pursued a route strictly analogous to that of the Raphael trichodermin synthesis. The key intermediate in their scheme is cis fused lactone 27 (analogous to 19). This was converted to a number of hydroxyl protected derivatives which were carried to the stage of the enol lactone 28. All efforts to bring about the reduction-aldol sequence to 29, analogous to the conversion of 23 to 25, failed.

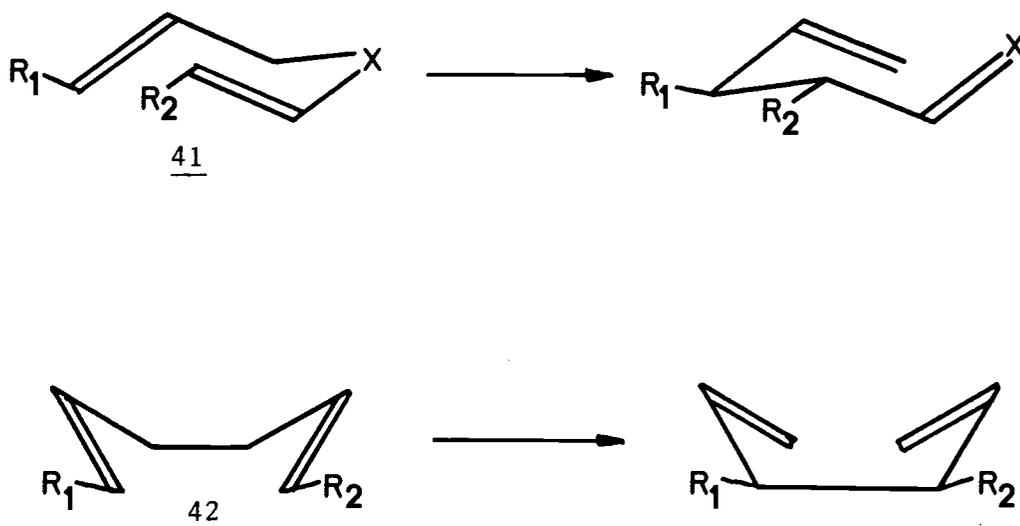


The second approach to 3 is that of Trost and Rigby,³¹ which proceeded along unique lines to yield keto ester 30. It was anticipated that the conversion of 30 into 29 (via 31 and 28) would proceed without incident, however, Colvin's results contradict this expectation. The key intermediate in this synthesis is the lactone 32, obtained from enone 33 via spiroannulation, cyclobutanone ring opening, annulation to a new cyclobutanone and Baeyer-Villiger oxidation. The desired lactone 32 was then converted to the cis-fused ether 34, which underwent elimination to the α,β -unsaturated ester 35, and, in a truly unique step, 30 was obtained upon formation of sulfoxide 36 and thermal rearrangement in refluxing methanol.



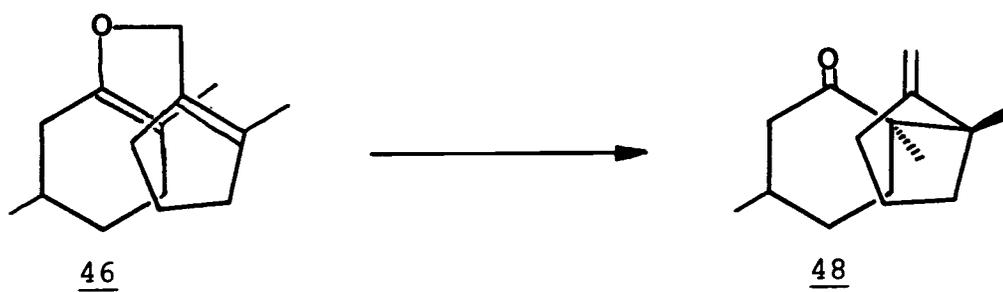
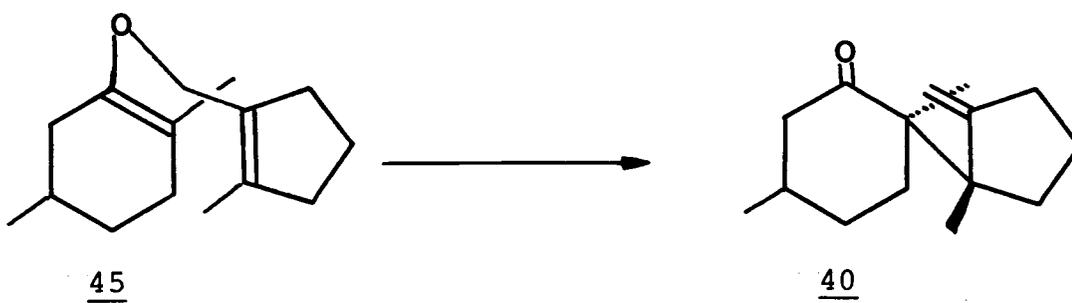
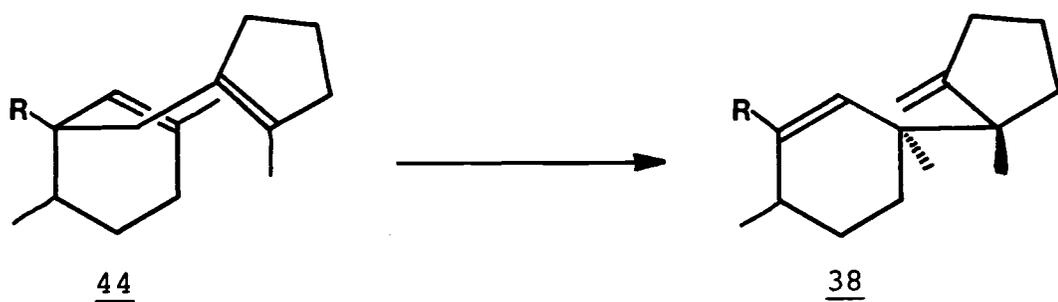
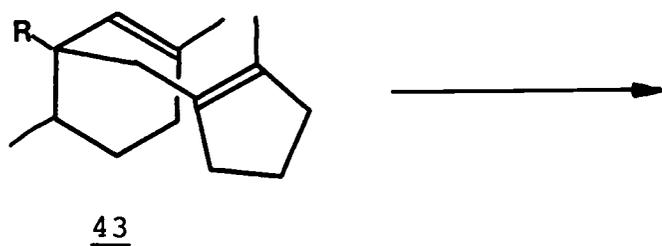
It was the goal of this work to develop synthetic approaches to two members of the trichothecanes, namely trichodiene 9 and verrucarol 3. The synthetic routes that were explored were intended to be efficient and to generate the molecule with the correct relative stereochemistry. Through pursuit of these objectives, it was hoped that the groundwork might be laid to a general approach to the trichothecane sesquiterpenes, by which the large variation in functional group patterns in this class could be accommodated. In particular, it was hoped that this work could eventually be extended toward a synthesis of a macrocyclic member of the verrucaridin group.

the chair is not accessible.³² It is also known that the degree of substitution at the termini of the 1,5-dienyl substrate has a marked effect on the rate of rearrangement.³³ Fully substituted dienes³⁴ and conformationally strained molecules³⁵ can successfully undergo the rearrangement although their rates are generally slow.



In the present study, the requisite dienes 37a, 37b, and 39 are all fully substituted at the termini of the reactive 1,5-dienyl system, hence the rearrangement is expected to be slow. The available reactive conformations for 37 and 39 are those shown below. These are (1) the chair and boat conformers of 37, namely 43 and 44 respectively and (2) the chair and boat forms of 39 shown as 45 and 46.

From a study of molecular models of these four systems, the following conclusions can be drawn. Conformation 44 is favored over 43 due to several unfavorable steric interactions between the two rings of the latter. Conformation 44 is probably less strained even though the



molecule must attain the boat transition state. Conformation 45 is clearly favored over conformation 46 due to two factors. First, there are fewer steric interactions between the two rings of 45 than in 46 and second, 45 is in the preferred chair conformation. Either conformation 44 or 45 would be expected to lead to the correct relative stereochemistry at the incipient carbon-carbon bond linking the two rings of 38 or 40. The verification of these arguments would be the successful transformation of 38 or 40 into 9, thereby demonstrating the stereochemical integrity of the rearrangement.

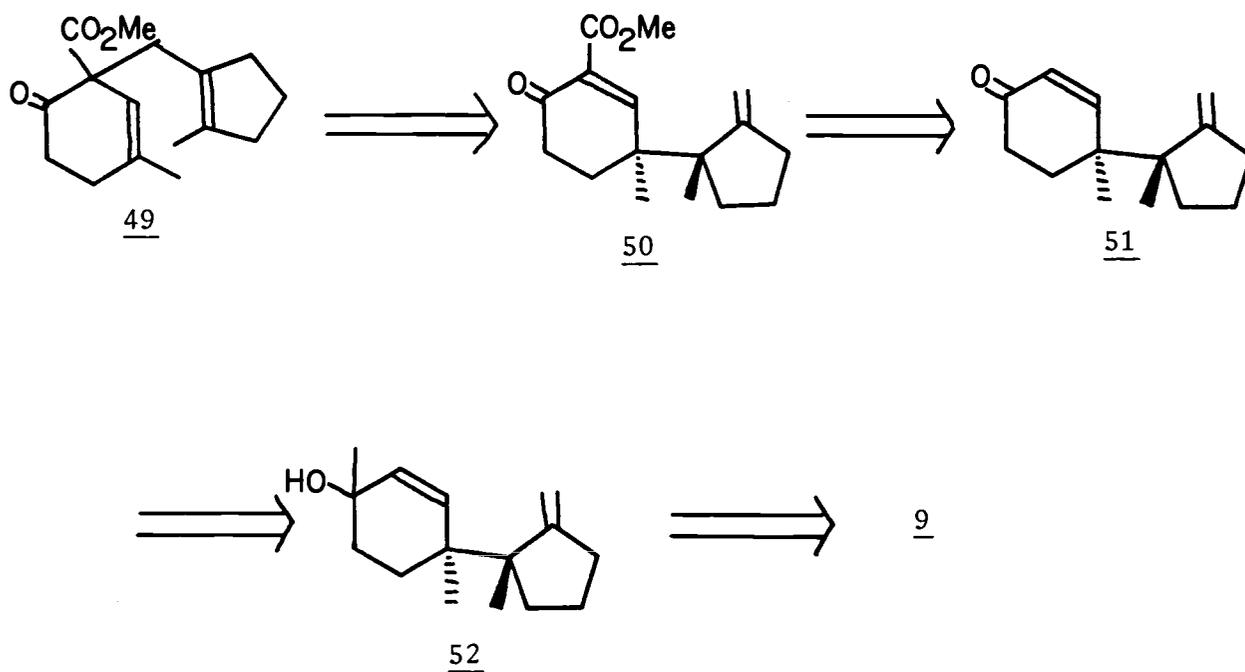
The only potential problem in this scheme would be the intervention of one of the less favored reactive conformations, 43 or 46. However, inspection of the products expected from these conformations, 47 or 48, shows that upon further transformation, the C₄ isomer of 9 would be obtained, which is the known compound bazzanene 10. Therefore the possible products are all known and the problem of product identification is simplified.

The three sections which follow describe approaches to trichodiene based on the precepts outlined above.

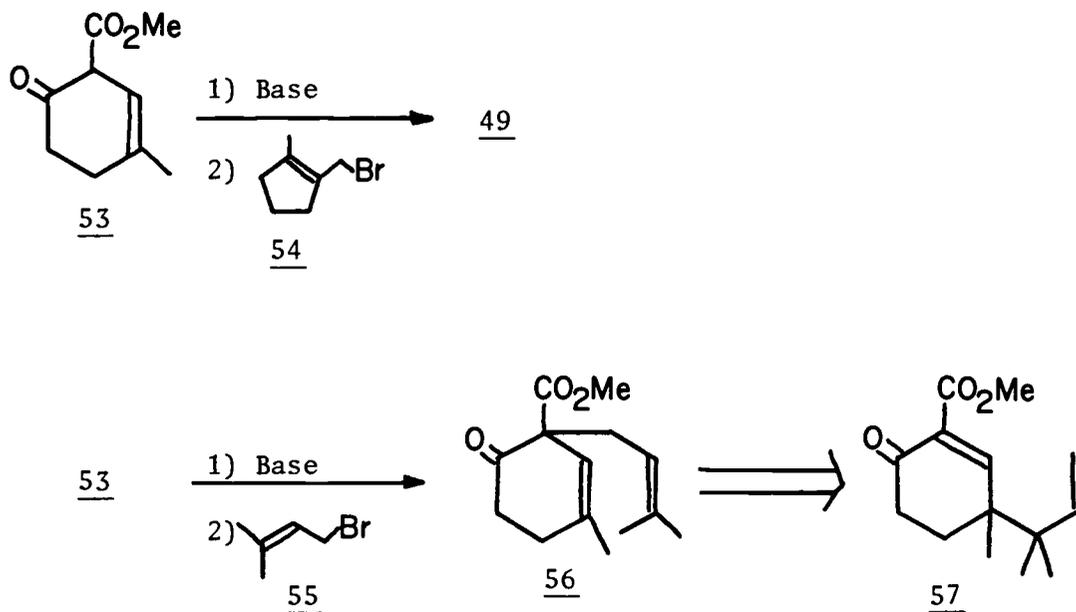
A. THE COPE REARRANGEMENT ROUTE

The simple bicyclic diene 37a, discussed above, was deemed unsuitable as an actual synthetic intermediate for the reason that the corresponding rearrangement product 38a lacks functionality for modifying the cyclohexene ring without disturbing the methylenecyclopentane moiety. Therefore a substrate was chosen in which functionality present would allow subsequent transformation to 9 after rearrangement. A second consideration in choosing a substrate was the activation energy of the

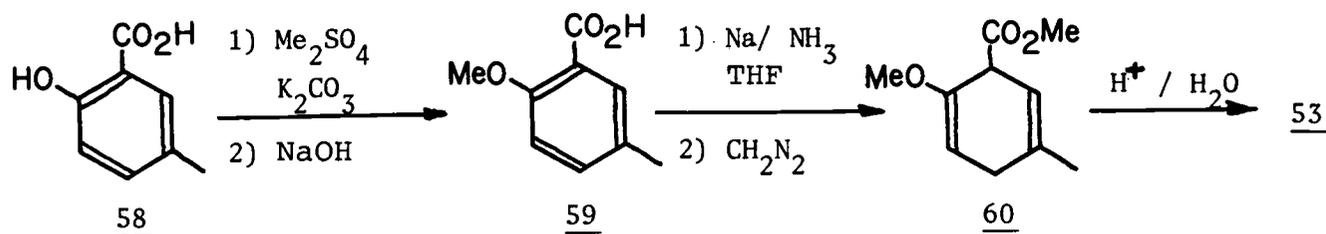
rearrangement which we wished to maintain as low as possible in order to maximize the rate of reaction. The substrate selected was ketoester 49. The corresponding rearrangement product 50 would contain a carbonyl group which could eventually become the C₁ methyl group of 9. The factor incorporated into the rearrangement of 49 which would potentially increase the rate of reaction is a shift of the β,γ double bond to the more stable α,β position. Keto ester 50 would then be decarbomethoxylated to give enone 51, which would be treated with methyllithium and then reduced with lithium aluminum hydride/aluminum trichloride³⁶ to yield 9.



The formation of 49 was envisaged via alkylation of ketoester 53 with bromide 54. However, before investigating this particular alkylation, it was decided to test both the alkylation and subsequent rearrangement steps with 3,3-dimethylallyl bromide 55,³⁷ a model for bromide 54.

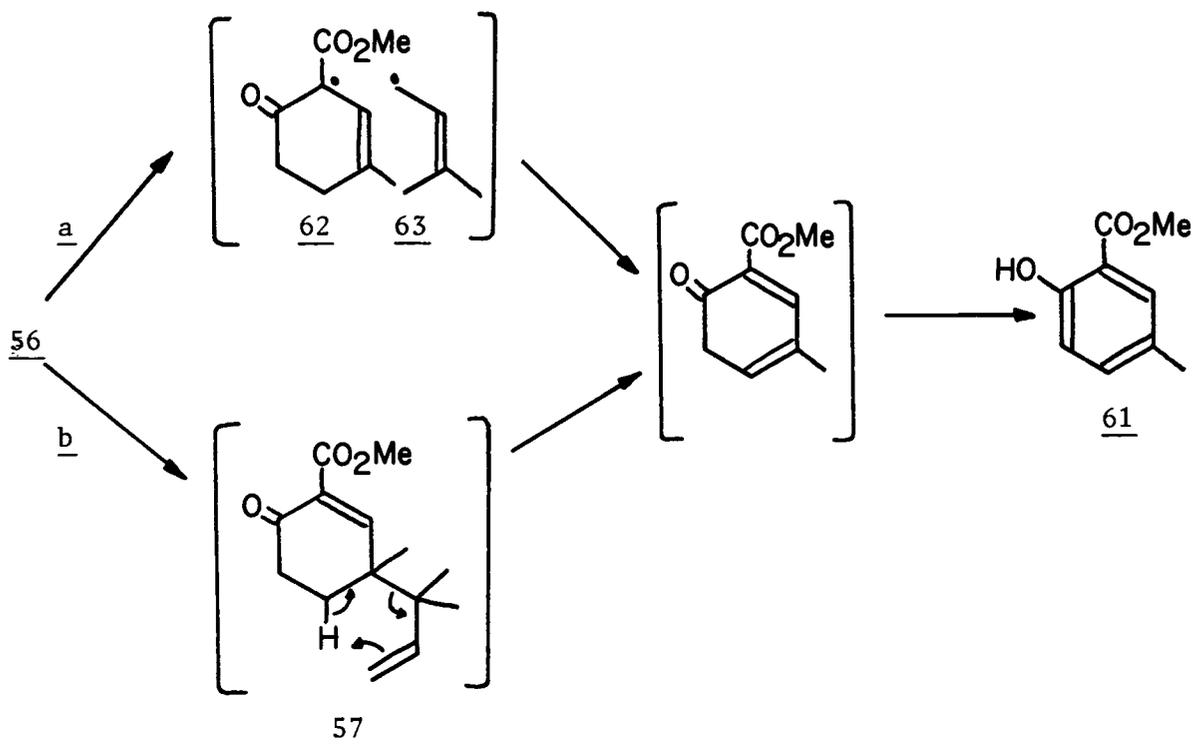


Ketoester **53** was readily obtained from 5-methylsalicylic acid (**58**)³⁸ by the following steps. Methylation of **58** with dimethylsulfate, followed by saponification, gave 64% of **59**, which was reduced with sodium in liquid ammonia in the presence of tetrahydrofuran and then esterified with diazomethane to furnish **60** in 72% from **59**. It is of interest to note that in this Birch reduction, a modification of the literature procedure, in which the sodium metal is added to a solution of all the other components, led exclusively to the desired product. It was previously reported that the Birch reduction of 2-methoxybenzoic acids leads to substantial amounts of dihydrobenzoic acids in which the methoxy substituent is lost.³⁹ Enol ether **60** was hydrolyzed with aqueous acid to furnish **53** in 68% yield.



The alkylation of 53 with 3,3-dimethylallyl bromide (55) in the presence of sodium hydride led to 59% of ketoester 56. The Cope rearrangement of 56 was attempted by heating a benzene solution of the diene in a sealed tube at 200°C for 3 hours, which returned only starting material. Further heating at 250°C for 16 hours led to an aromatic product identified as 61. This result can be explained by a radical pathway (a), in which 56 suffers homolysis to the allylic radicals 62 and 63, with 62 losing a hydrogen atom via intermolecular hydrogen abstraction and tautomerizing to 61. Alternatively, a two-step, concerted pathway (b), where the first step is the desired Cope rearrangement to give 57, which further undergoes a retro-ene reaction to yield 61 after tautomerization, is also possible.

To distinguish these possibilities, varying amounts of the radical inhibitor 2,6-di-*t*-butyl-*p*-cresol were added to the heated solution of 56 in benzene. Addition of 1.7% inhibitor (w/w) and heating at 220°C for 14 hours led to a mixture of 56 and 61. Addition of one full equivalent of inhibitor and heating at 225°C for 16 hours returned exclusively 56. Further heating of the solution containing one equivalent of inhibitor at 250°C for 16 hours led only to 61. These results lend support to a radical mechanism, at least up to 225°C, but above this temperature either or both mechanisms could be in force. This question was not

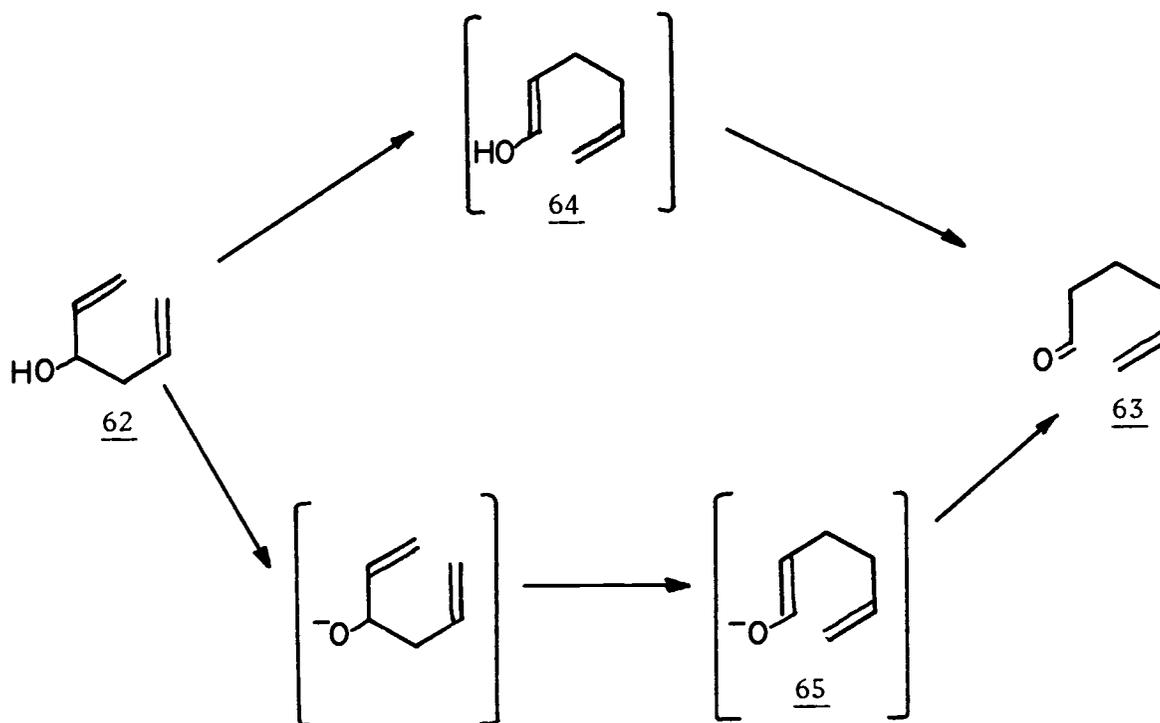


pursued further. The lack of any indication that the desired product 57 was being formed from 56 led us to investigate a variation of this route based on the alkoxy-Cope rearrangement described below.

B. THE ALKOXY-COPE ROUTE

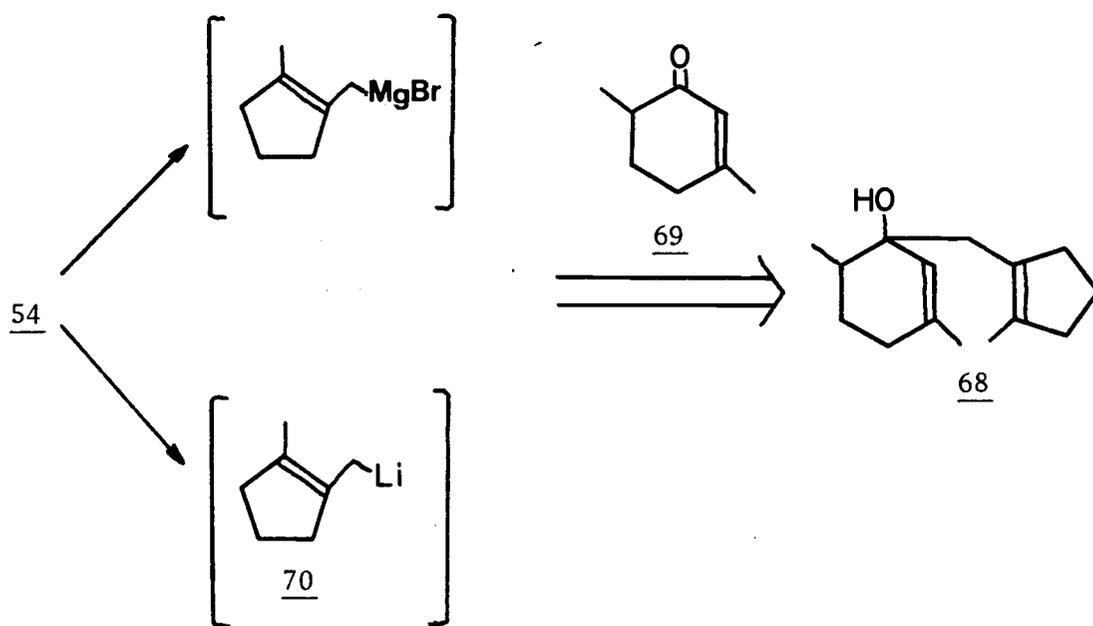
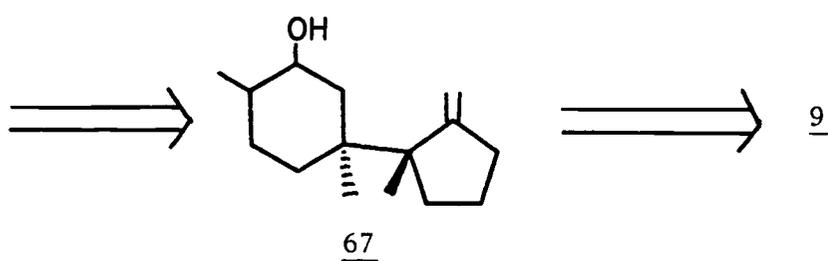
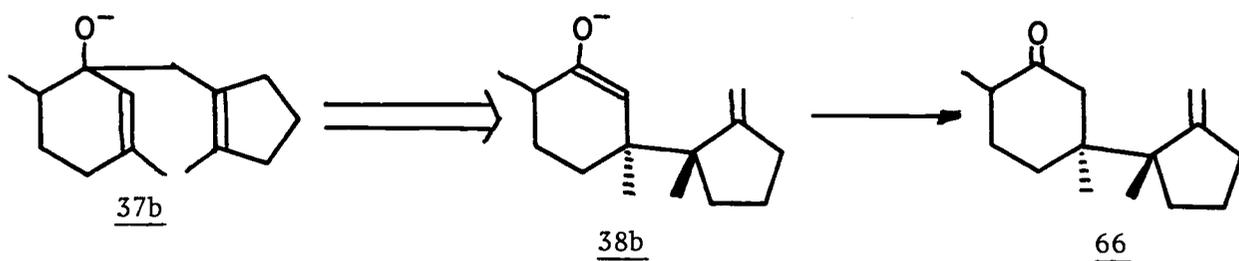
One of the classical variants of the Cope rearrangement involves a 1,5-diene containing a hydroxyl group at the 3 or 4 position. This is termed the oxy-Cope rearrangement.³³ The inclusion of a hydroxyl group at the indicated position provides a means of "trapping" the rearranged product, an enol, by ketonization, as shown below in the conversion of 62 to 63 via 64. Evans and Goleb³⁵ extended this idea to the

corresponding alkoxide, where the product of rearrangement is an enolate. They found typical rate enhancements relative to the corresponding oxy-Cope rearrangement of 10^{10} - 10^{17} times using this modification. This process is shown in the conversion of 62 to 63 via 65.

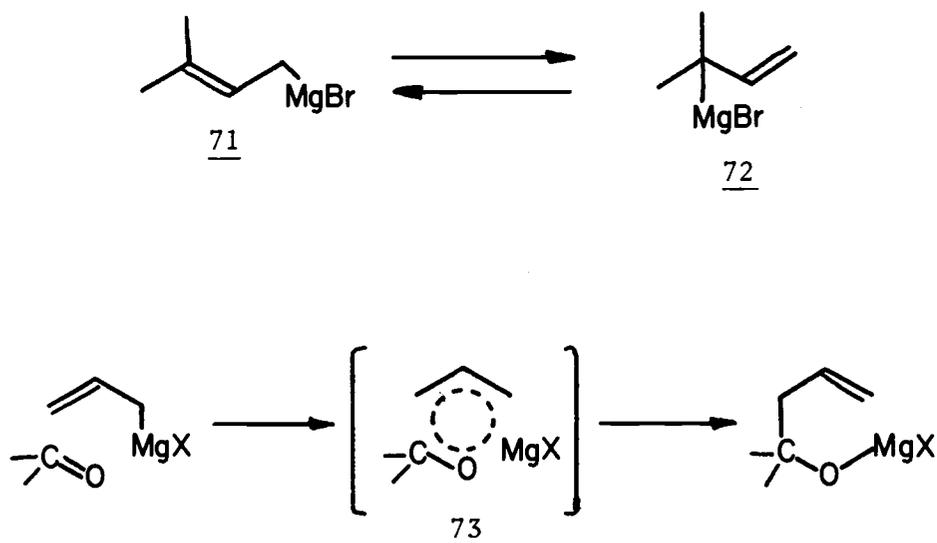


The alkoxide 37b discussed previously was judged to be a viable synthetic intermediate in the synthesis of 9, as the rearrangement product 38b is the enolate of ketone 66. The latter could in principle be reduced to alcohol 67 and dehydrated to 9.

It was anticipated that the substrate for the alkoxy-Cope rearrangement, alcohol 68, would be obtainable from enone 69 and bromide 54 via either a Grignard reaction or a 1,2-addition of allyllithium species 70.

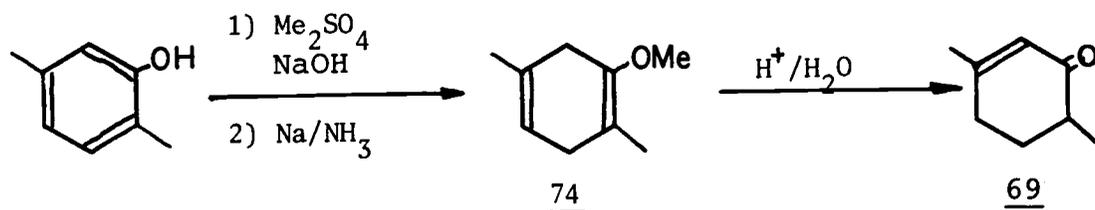


An inherent problem existed with the proposed Grignard reaction of a 3,3-dialkylsubstituted allylic bromide, namely the fact that the corresponding organomagnesium reagent is known to exist as a mixture of the rapidly interconverting isomers 71 and 72.⁴⁰ Further, allylic Grignard reagents can react with a carbonyl group via the cyclic, six-membered transition state 73. The net effect is that very little regioselectivity is expected in the Grignard reaction of a non-symmetric allylic system. Therefore it was decided to investigate the lithio species (i.e., 70) first, in the hope that regioselectivity in the addition reaction could be obtained.

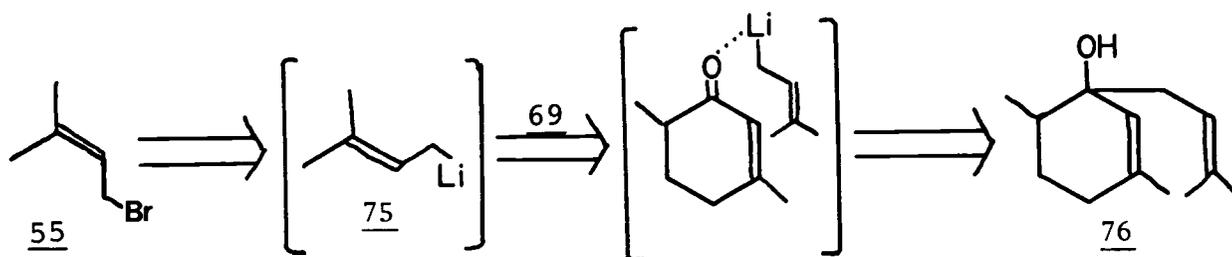


3,6-Dimethylcyclohex-2-enone (69) was prepared in 60% overall yield from 2,5-dimethylphenol by treatment with dimethylsulfate, followed by Birch reduction to 74 and finally acid-catalyzed hydrolysis.

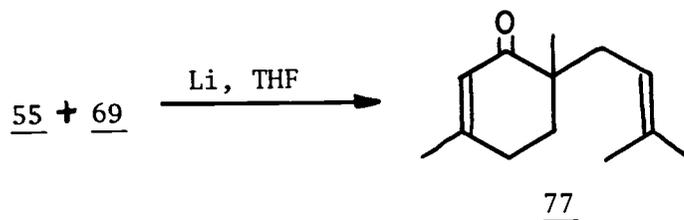
As with the Cope route discussed above, the model bromide 55 was used in preliminary studies, and this was converted to 3,3-dimethylallyllithium (75) by treatment with lithium metal. It was hoped that



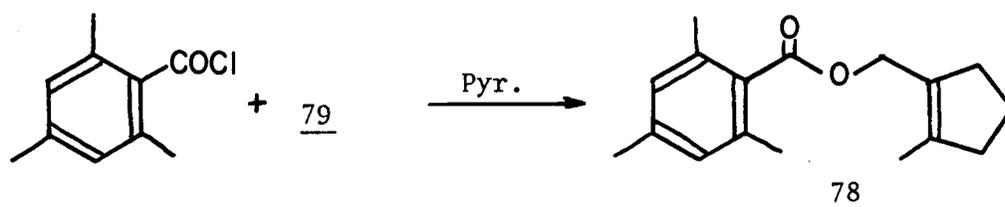
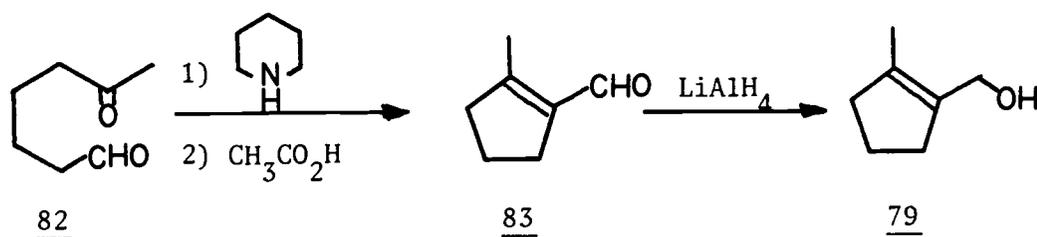
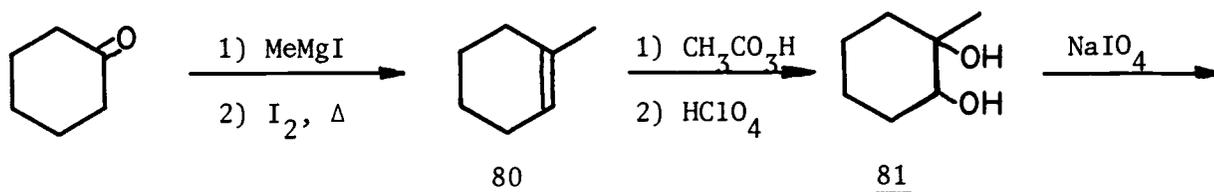
coordination of lithium in this reagent to the carbonyl oxygen of 69 would enhance the prospects for a non-transposed product by promoting a normal 1,2-carbonyl addition.



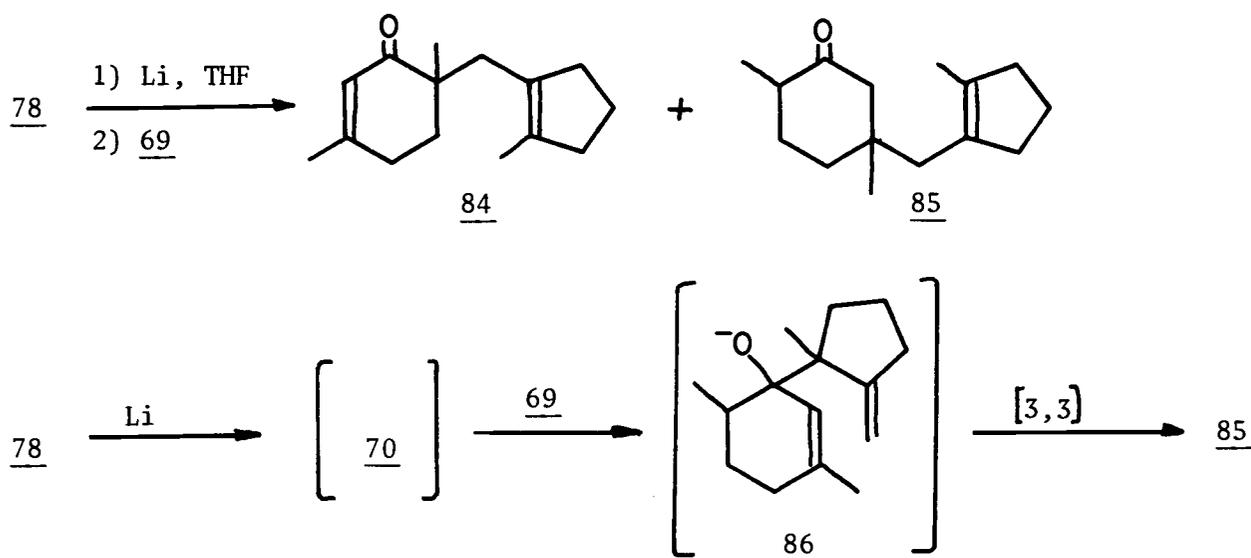
The first attempts at producing 75 by direct metalation of 55, or by reduction of 3,3-dimethylallyl phenyl ether⁴¹ with lithium were unsuccessful, leading to intractable mixtures. In one run where 55 and 69 were simultaneously added to a mixture of lithium metal in tetrahydrofuran, the alkylation product 77 was obtained, but otherwise no characterizable products were obtained.



This prompted the search for a better method for the preparation of the organometallic reagent. Mesitoate esters of allylic alcohols have been shown to undergo efficient reductive fission with lithium metal in tetrahydrofuran to generate the mesitoate anion and the corresponding allyllithium species.⁴² Mesitoate ester 78 was prepared from mesitoyl chloride⁴³ and allylic alcohol 79. The latter was prepared in 25% overall yield from cyclohexanone by a sequence, shown below, based on work by Ruppert.⁴⁴



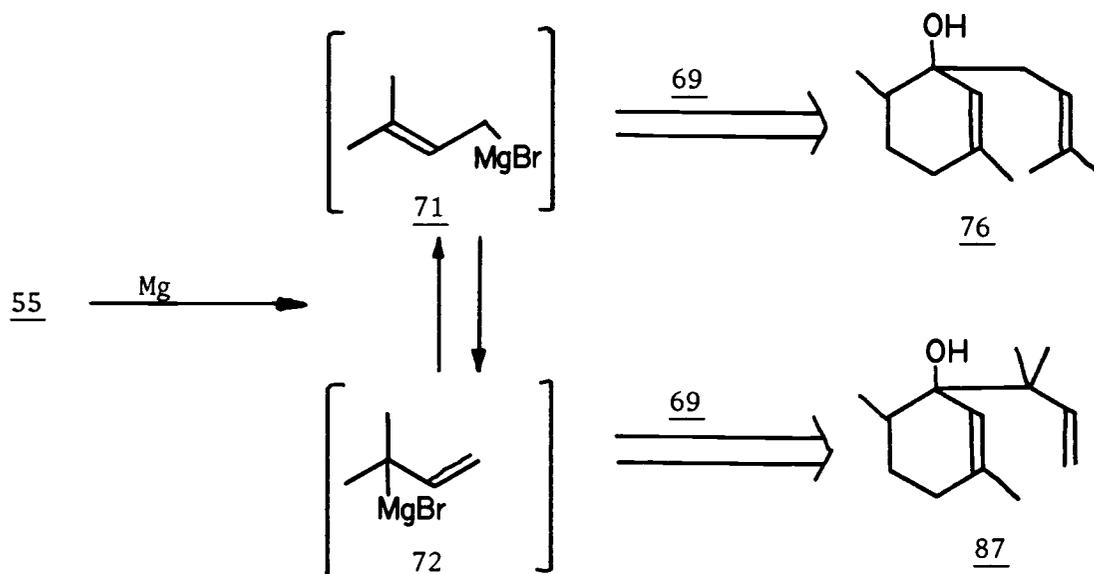
Treatment of ester 78 with lithium metal, followed by enone 69 led to two products isolated by preparative gas chromatography, namely, enone 84 (4.1%) and ketone 85 (5.6%). Enone 84 undoubtedly arises from alkylation of 69 with unreduced 78, the enolate of 69 being generated with either residual lithium or the allylic anion 70 acting as the base. The ketone 85 though, is most likely produced via an alkoxy-Cope rearrangement of intermediate 86.



This result was indeed discouraging. The lack of any of the desired alcohol 68 (or its alkoxy-Cope rearrangement product 66) therefore led us to investigate the Grignard reaction of 54 with 69 as a means to procure 68.

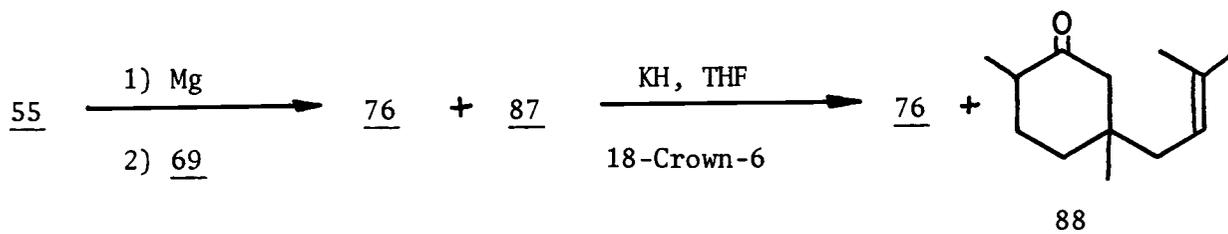
Since a mixture of regioisomers was expected from the Grignard reaction, it was decided to again simplify the process by utilizing the model bromide 55. The expected alcohols 76 and 87 would be easy to differentiate by a comparison of their olefin hydrogen resonances in

their NMR spectra. Alcohol 76 would be expected to display two absorptions in this region, one from the cyclohexenyl olefin proton and one from the side chain olefin hydrogen, while alcohol 87 would be expected to show four proton absorptions in this region, one from the cyclohexenyl olefin hydrogen and three in the characteristic pattern of a terminal vinyl group.



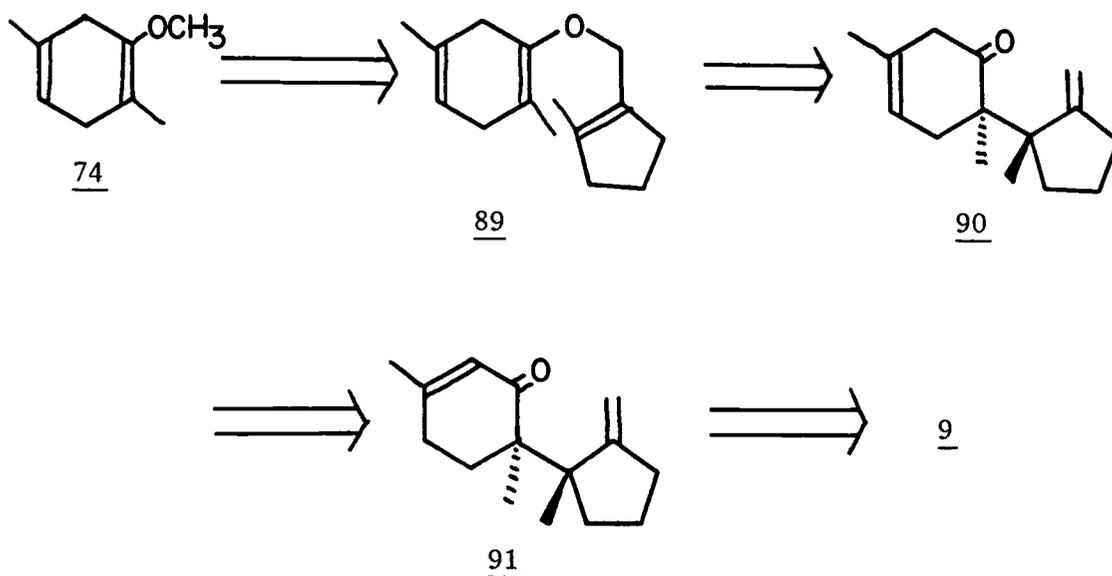
The formation of the Grignard reagent from 55 proceeded smoothly and, upon addition of 69, a nearly quantitative yield of alcohols 76 and 87 was produced. The NMR spectrum revealed that the ratio of 76 to 87 was 40 to 60 by comparison of the integrations for the olefinic hydrogens. Attempted separation of the crude alcohols failed, and it was therefore decided to attempt the oxy-Cope rearrangement on the mixture. The mixture was converted to the corresponding alkoxides by stirring with potassium hydride and 18-crown-6 polyether in tetrahydrofuran, after which a new mixture consisting of an alcohol component

(IR 3400 cm^{-1}) and a ketone component (IR 1710 cm^{-1}) was obtained. The NMR spectrum of this mixture displayed a new methyl singlet at δ 1.1, an increase in signals for the 3,3-dimethylallyl moiety, a decrease in signal for the cyclohexenyl olefin proton, and virtual disappearance of signal for the terminal vinyl group. The conclusion drawn from this data is that the alcohol component of the mixture is recovered 76 and that the ketone component is 88, the alkoxy-Cope rearrangement product of 87. This is consistent with the proposed formation of ketone 85, but deals the decisive blow to an approach to the trichothecanes based on the alkoxy-Cope route, as the desired alcohol 76 apparently did not rearrange.

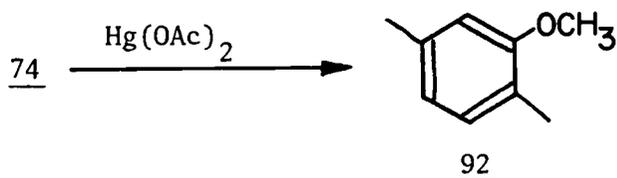


C. THE CLAISEN REARRANGEMENT ROUTE

In principle the allyl vinyl ether 39 is an ideal precursor to trichodiene, since its rearrangement product 40 contains functionality which would permit easy conversion to 9. However, an attractive alternative was potentially available from diene 74, an intermediate in the synthesis of enone 69. Conversion of 74 to the allyl vinyl ether 89 followed by rearrangement could produce ketone 90, which could be converted to 9 in two steps. These would be first, isomerization of the β,γ double bond to the α,β position, and second, reduction of the carbonyl group to a methylene unit.

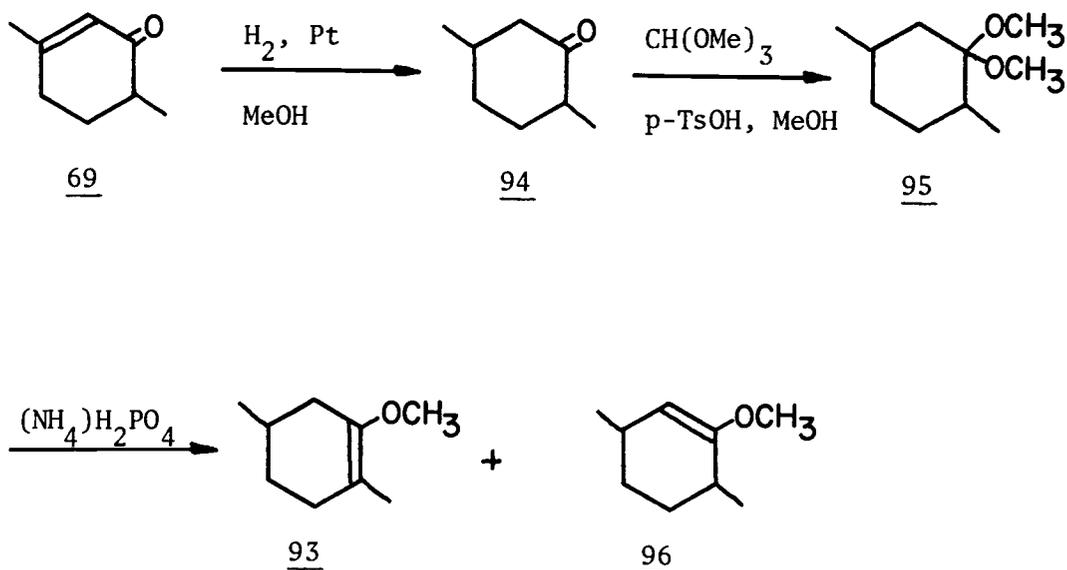


To this end a transesterification reaction was attempted on enol ether 74 with alcohol 79 using mercuric acetate as catalyst in refluxing benzene. The only isolable product was determined to be 2,5-dimethylanisol (92). This presumably arises by mercuric acetate mediated allylic oxidation of 74, followed by the loss of the elements of acetic acid.



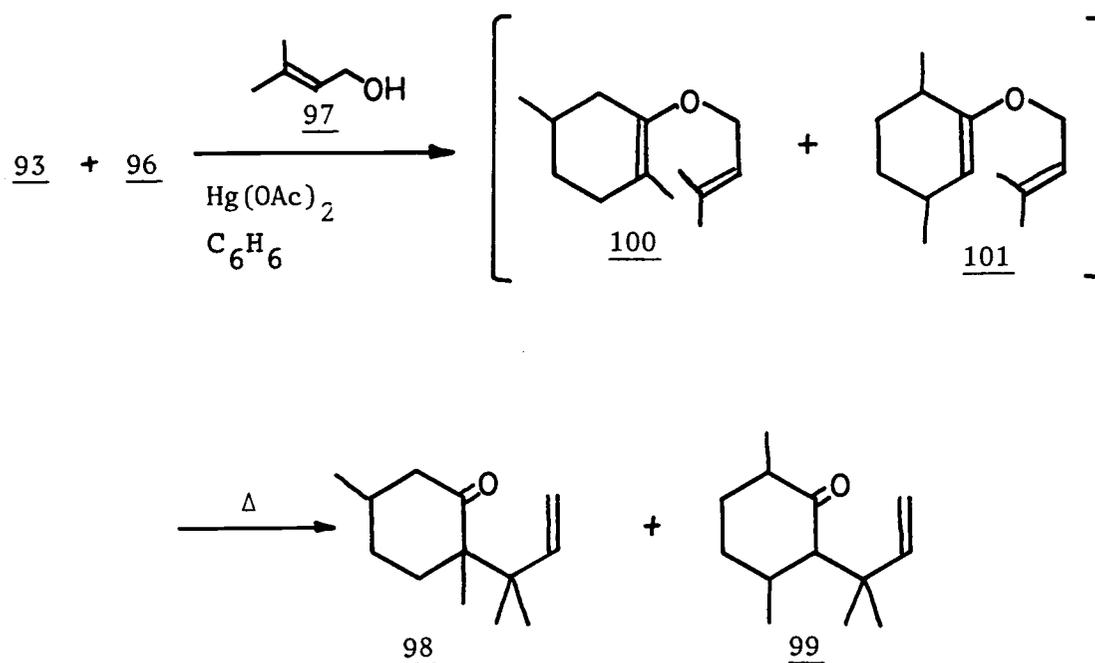
We then returned to the original proposal, the synthesis and rearrangement of 39 to give 40. Ketone 40 would be converted to enone 91 which could be reduced to 9. Again a transesterification reaction was anticipated to yield 39. This scheme would require preparation of enol ether 93. A number of attempts were made to selectively reduce the

trisubstituted double bond of 74 by catalytic hydrogenation but without success. The enol ether 93 was subsequently obtained in 23% yield from enone 69. Thus, catalytic reduction of 69 with hydrogen and platinum catalyst gave 94, which was converted to ketal 95 with trimethylorthoformate. Acid-catalyzed elimination of methanol from 95 gave a mixture of enol ethers 93 and 96 in a ratio of 47:53 (gas chromatography) respectively. The mixture was separable by gas chromatography, however, the separated isomers reattained the equilibrium composition in spite of precautions taken to exclude factors which might catalyze isomerization (base washed glassware, freezing, exclusion of oxygen). Therefore the mixture was carried on in the hope that separation could be realized at a later stage.

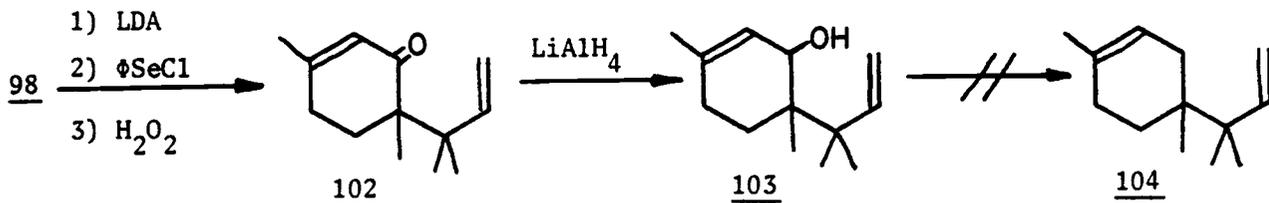


As with the previous routes examined, the initial studies were performed using 3,3-dimethylallyl alcohol 97 as a model for alcohol 79. Alcohol 97 was prepared by aluminum hydride reduction of 3,3-dimethylacrylic

acid. Refluxing a mixture of enol ethers 93 and 96 together with alcohol 97 and mercuric acetate in benzene, followed by refluxing the crude product in toluene, led to a mixture of two products which were separated by column chromatography and identified as 98 (31%) and 99 (5%). Separation of the intermediate allyl vinyl ethers 100 and 101 was not attempted as it was anticipated that the purified isomers would reestablish the equilibrium composition, as enol ethers 93 and 96 had done.



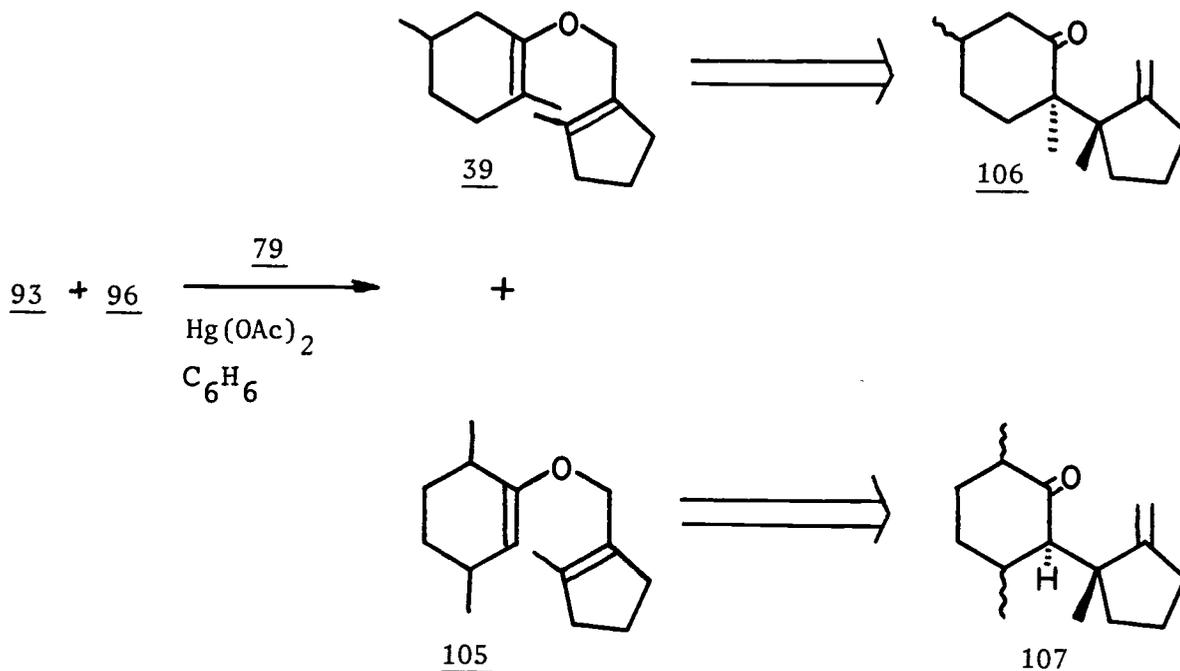
Ketone 98 was converted to enone 102 in 45% yield by the phenylselenation-oxidation procedure of Reich et al,⁴⁵ and 102 was reduced to allylic alcohol 103 in 87% yield with lithium aluminum hydride. An attempt to convert 103 to 104 by reduction with lithium aluminum hydride/titanium tetrachloride⁴⁶ led to an uncharacterizable mixture.



Since the model series had proved successful, at least in terms of the Claisen rearrangement of an appropriately substituted allyl vinyl ether, our efforts were turned to the analogous sequence using alcohol 79. Treatment of the mixture of enol ethers 93 and 96 with 79 and mercuric acetate in refluxing benzene led to a mixture of allyl vinyl ethers 39 and 105, determined to be 37% of 39 and 63% of 105 by a careful comparison of the NMR integration for the olefinic proton of 105 with the total methylene signal α to oxygen at δ 3.6. The change in ratio of allyl vinyl ethers in favor of the trisubstituted olefin 105 compared to that of enol ethers 93 and 96 can be attributed to an equilibration catalyzed by traces of acetic acid generated during the transesterification reaction. The trisubstituted olefin is presumably favored for steric reasons when the ether substituent is bulky.

The mixture of 39 and 105 was taken up in xylenes and refluxed for 20 hours to yield 23.7% of carbonyl containing compounds with molecular weight 220, thereby showing them to be isomeric with the allyl vinyl ethers. Column chromatography led to two isolable products. These were 108, which exhibited in its NMR spectrum one methyl singlet at δ 0.96, two methyl doublets at δ 0.98 and δ 1.00, and two exo-methylene triplets (one proton each) at δ 4.72 and δ 4.91 ($J=2.0\text{Hz}$); and 109, which showed one methyl singlet at δ 0.98, two methyl doublets at δ 0.94 and δ 0.96, and two exo-methylene triplets (one proton each) at δ 4.67 and δ 4.81

($J=2.0\text{Hz}$) in its NMR spectrum. These data indicated that 108 and 109 were probably pure compounds and were isomers of structure 107. It could not be determined unambiguously whether 108 and 109 were rearrangement products of allyl vinyl ether 39 or 105, but further transformation in the forward synthetic direction appeared likely to decide this crucial question.

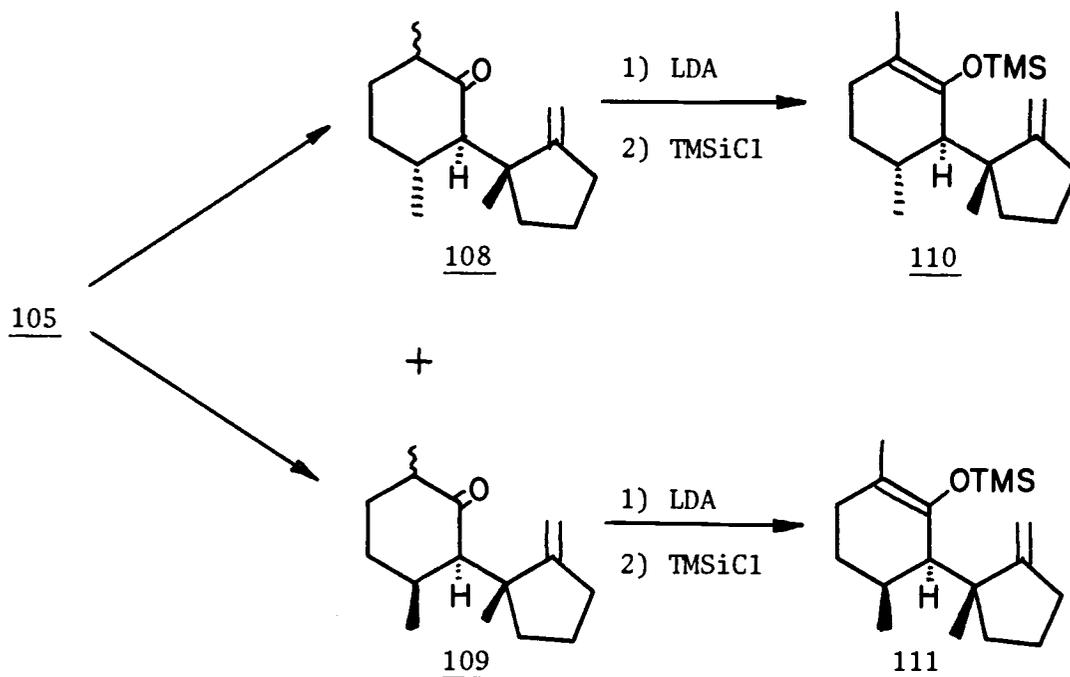


Ketone 108, when submitted to the phenylselenation-oxidation procedure utilized to transform 98 to 102, failed to yield an enone, and returned only starting material or a number of products (identifiable only as fragments of starting material) depending on the reaction conditions. Attempted dehydrogenation of 108 using DDQ⁴⁷ or selenium dioxide⁴⁸ also failed to yield an enone. However, treatment of 108 with lithium diisopropylamide (LDA), followed by trimethylsilyl chloride, led to a silyl enol ether (110) whose NMR spectrum displayed a new

allylic methyl group at δ 1.6 and no enol ether olefin proton. Analogous treatment of ketone 109 led to silyl enol ether 111. The NMR spectra of silyl ethers 110 and 111 were very similar but not superimposable on each other, suggesting that they were isomeric. The NMR data are clearly inconsistent with silyl enol ethers derived from 106, but can be accommodated by enol ethers derived from structure 107 where enolization has occurred towards the α -methyl substituent (enolization towards the alternate site would place the silyl group coplanar with the bulky cyclopentyl substituent).

The conclusion to be drawn from these data are that both 108 and 109 are Claisen rearrangement products of allyl vinyl ether 105 and not of 39. Also, since the silyl ethers 110 and 111 are not identical, they are reasonably inferred to be stereoisomers in which the methyl and cyclopentyl substituents are oriented cis and trans on the cyclohexane ring. This is based on the expectation that the Claisen rearrangement proceeded through a chair transition state, since it is known to be clearly favored where possible.⁴⁹ Although there is not enough data to unequivocally assign stereochemistry to 108 and 109, examination of molecular models reveals that one of the transition states has fewer steric interactions associated with it than the other. The prime offending interaction is between the 3-methyl group of the cyclohexene ring and the methyl group of the cyclopentene ring in 105. The less sterically hindered transition state would lead to 108, and consequently this stereochemistry is assigned to the major product from 105.

It was now apparent that, whereas rearrangement of the model system 100 proceeded in the desired direction, that of allyl vinyl ether 39 did not. The difference must be inherent in the extra steric bulk of the



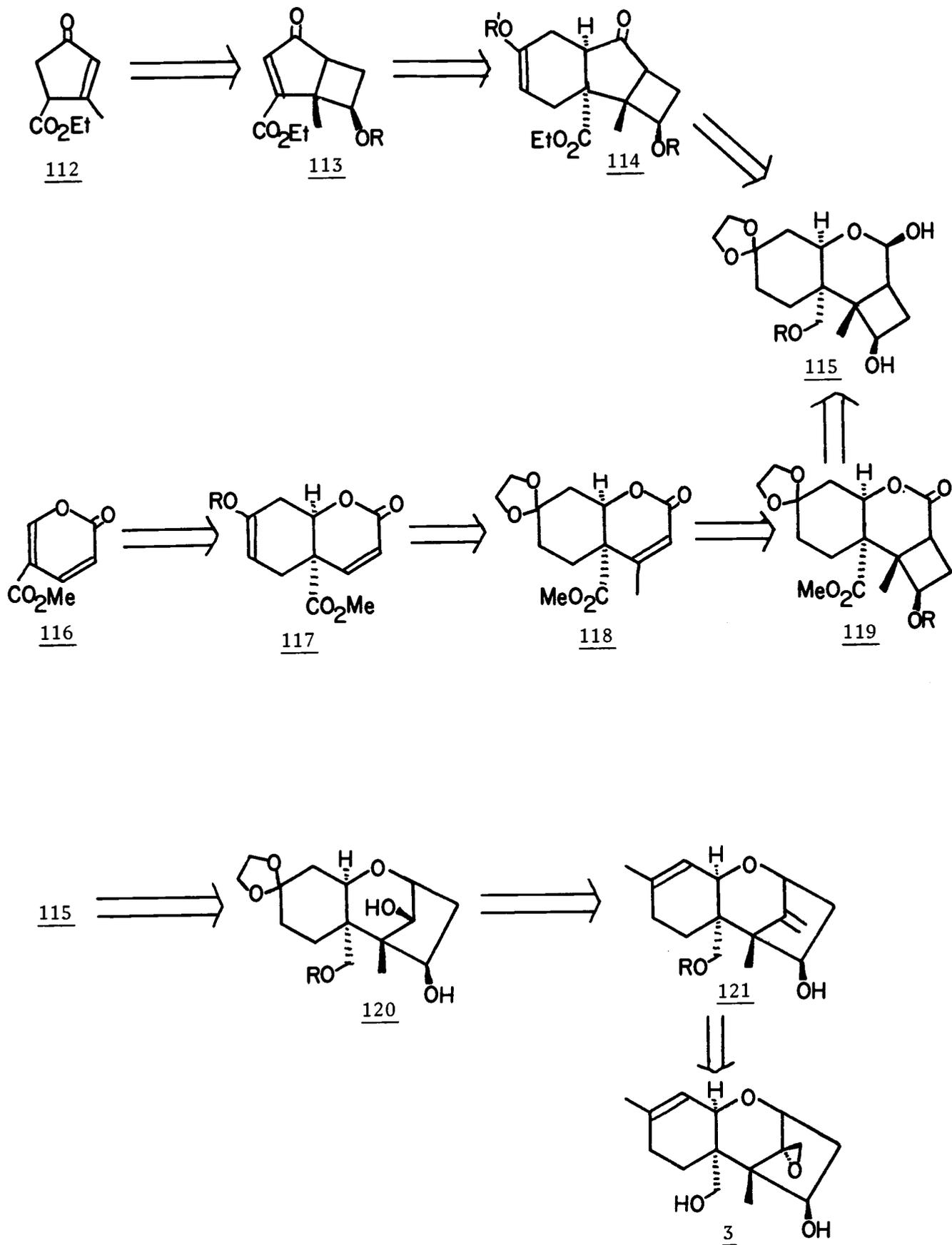
cyclopentene substituent relative to that of the allyl system, rendering the activation energy for the rearrangement of **39** so high that the intervention of side reactions, such as radical cleavage and olefin isomerization, prevail. The fact that **105** does yield rearrangement products attests to the difference in activation energy that one less substituent at the terminus of the reactive 1,5-diene can make.

In conclusion we find that the three sigmatropic rearrangements studied herein do not provide a means for construction of the key C_4-C_1 bond of the trichodiene system. The substitution pattern and relative stereochemistry associated with this linkage in trichothecane sesquiterpenes must therefore be assembled by a different plan. An alternative strategy for dealing with this problem is embodied in an approach to verrucarol discussed in the following chapter.

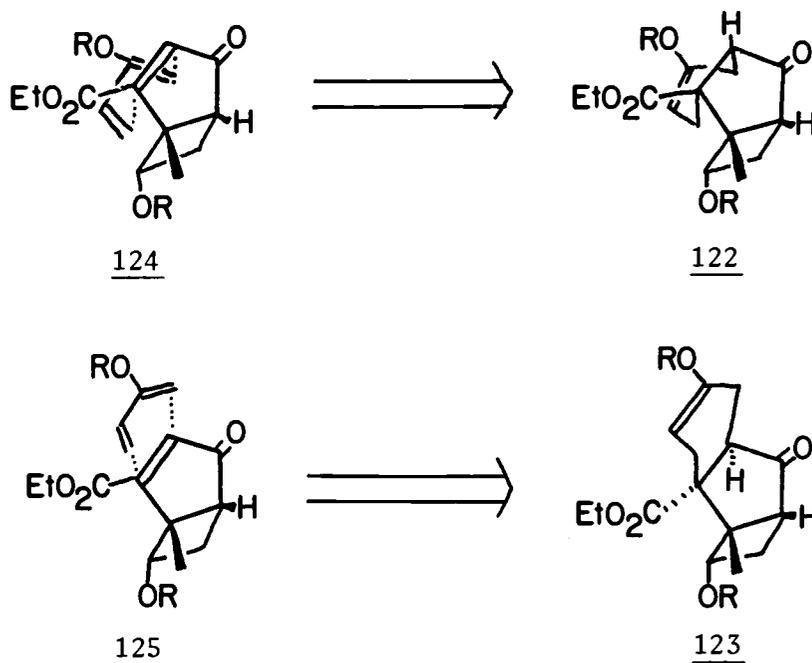
CHAPTER III: AN APPROACH TO VERRUCAROL 3

As with any synthesis of the trichothecane skeleton, a primary objective in the synthesis of verrucarol (3) must be the generation of the C₅-C₆ bond with the correct relative stereochemistry. The plan described below approaches this problem by generating the required stereochemistry via sequential cycloaddition reactions on a suitably substituted B-ring precursor. This scheme allows the pursuit of two distinctly different routes. In the first, termed the "B-C-A route", an initial photocycloaddition of a vinyl ester and enone 112 furnishes bicyclo[3.2.0]hept-2-enone 113, which is converted to tricyclic ketone 114 via a Diels-Alder reaction from the less sterically hindered exo side of 113. Subsequent modifications to 114 would be expected to yield hemiacetal 115, the key intermediate in this approach. The alternative route, dubbed the "B-A-C route" would pursue 115 beginning with a Diels-Alder reaction with methyl coumalate 116 to yield tetrahydrocoumarin 117. Introduction of a β -methyl substituent at the lactone of 117 would give 118, to which a vinyl ester would be added from the less hindered, exo side of 118 via photocycloaddition to give 119. The latter would be converted to 115 by reduction.

The key intermediate 115, when subjected to acid, should undergo a cyclobutylcarbinol rearrangement with expansion of the cyclobutane ring to yield the desired trichothecane skeleton of 120. Alcohol 120 would be converted to diolefin 121 and epoxidized regioselectively, using the C-ring hydroxyl group to direct the reaction. Completion of the verrucarol plan is based on the Raphael trichodermin synthesis (see page 6).

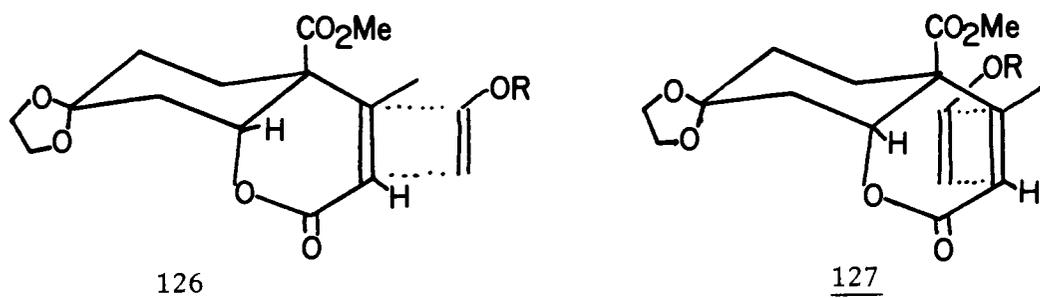


The Diels-Alder reaction has been thoroughly studied as to its regio- and stereochemistry.⁵⁰ It is known to proceed in a concerted fashion and exhibits a preference for suprafacial addition of the dienophile to the diene where possible. The cycloaddition reaction requires a favorable overlap between the diene and dienophile components, hence the reaction is sensitive to steric factors. In the proposed Diels-Alder reaction of a 2-alkoxybutadiene with 113, there are two possible cis-fused products which could be obtained (the regiochemistry is dictated by the steric interactions between the alkoxy substituent and the methyl and ester groups on 113). One adduct would be the sterically crowded cis-syn-cis isomer 122, and the other the cis-anti-cis isomer 123. These derive from transition states 124 and 125 respectively. Transition state 124 is clearly the less favorable one, with the diene approaching the dienophile from the sterically hindered endo side of 113. Thus, adduct 123 is expected to predominate.



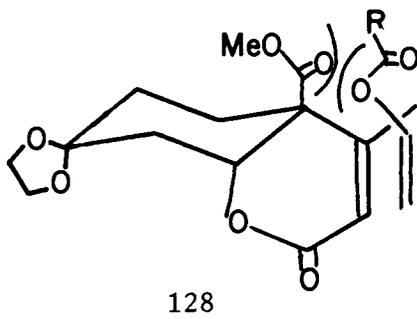
Clear precedent exists for the Diels-Alder reaction of a butadiene with methyl coumalate 116,⁵¹ hence no problems were expected with this step. However, it was anticipated that by utilizing a 2-alkoxybutadiene, which is known to exhibit a higher degree of regioselectivity than simple alkyl substituted butadienes,^{50c} improved regioselectivity would be obtained.

The $[\pi^2 + \pi^2]$ photocycloaddition step in either route was expected to yield a cis-fused cyclobutane, i.e., 113 or 119.^{52,53} The cycloaddition of a vinyl ester to lactone 118 should proceed to give the desired cis-anti-cis ring system of 119, since the necessary orbital overlap is most easily attained when the vinyl ester approaches the lactone from the exo side of 118, as in transition state 126. The alternative transition state 127 requires that orbital overlap be attained from the endo side of 118, which molecular models show to be very sterically hindered.

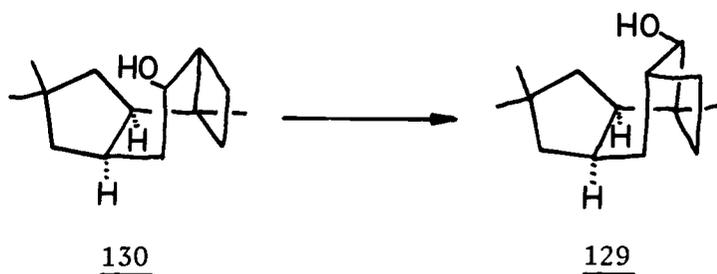


The regiochemistry depicted in 113 is based on a preference for the oxygen bearing carbon of a vinyl ester to bond to the β -carbon of an enone in a photocycloaddition, as noted by Corey et al.⁵³ A similar preference was noted by Kosugi and co-workers⁵⁴ in the photocycloaddition reactions of α,β -unsaturated lactones, hence the regiochemistry shown for 119.

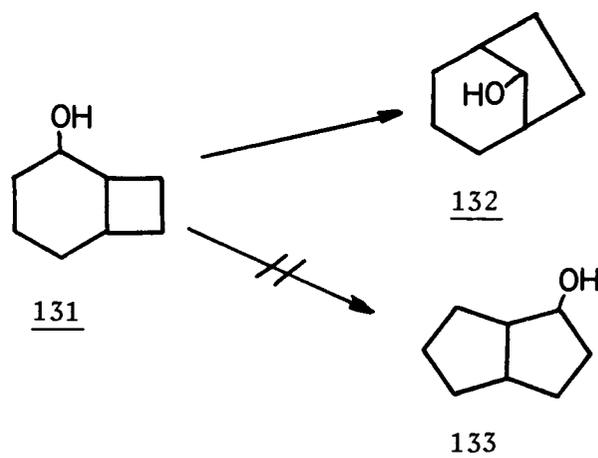
The configurations of the ester bearing carbon of the cyclobutane ring in both 113 and 119 derive from a sterically favored "exo" addition, as in transition state 126. In transition state 128, there are unfavorable steric interactions between the ester carbonyl of 118 and the ester group of the vinyl ester. A similar argument holds for the stereochemistry of 113.



The cyclobutylcarbinol rearrangement has found limited use in natural products chemistry, even though it can be a high yield and very stereoselective process. It has been shown⁵⁵ that the acid catalyzed rearrangement of a chiral cyclobutylcarbinol can lead to a high yield of a single product. Thus, only cyclopentanol 129 was obtained upon acid treatment of endo alcohol 130.^{55c} The implications from this and similar experiments are twofold, first, that the cyclobutane bond that is closest to being anti-periplanar to the departing hydroxyl group is most likely to migrate, and second, the intermediate cyclopentylum ion is "captured" from the face of the new cyclopentane ring opposite to that of the migrating bond.

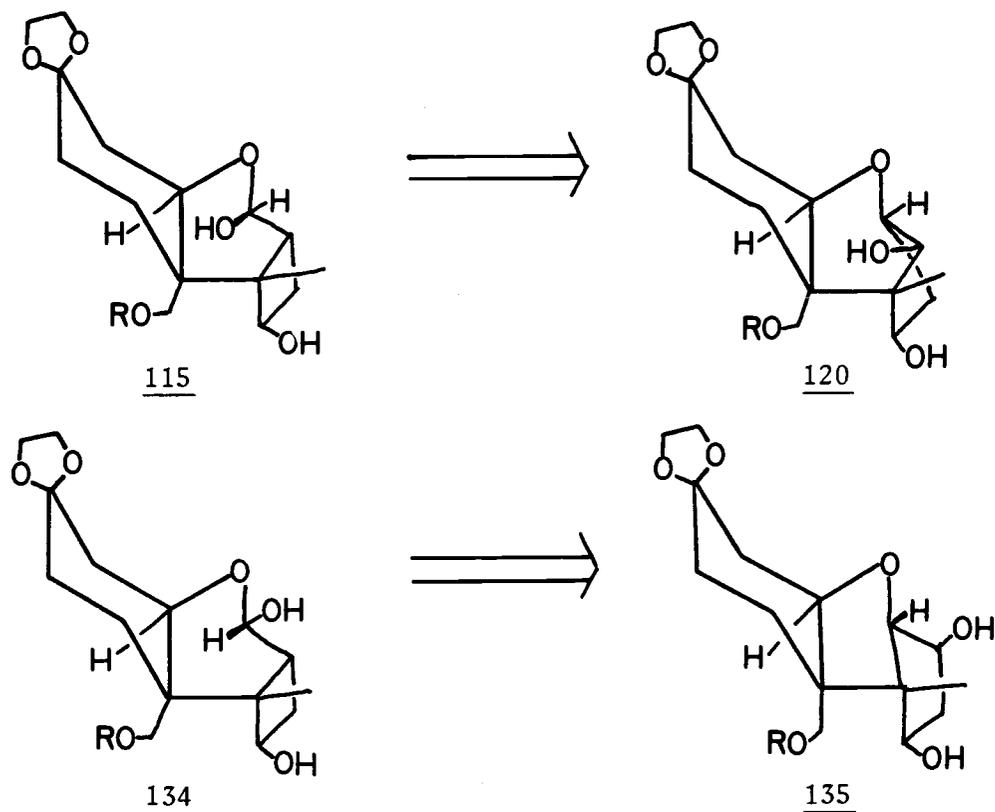


It is also of particular interest to note that in all cases noted above where the cyclobutyl substrate was a substituted bicyclo[4.2.0]octan-1-ol such as 131, the only product obtained was the corresponding bicyclo[3.2.1]octan-7-ol (132), with none of the alternate rearrangement product, the bicyclo[3.3.0]octan-1-ol (133) observed.



Application of these observations to the cyclobutylcarbinol rearrangement of 115 leads to the expected product, 120. The stereoelectronic requirement (anti-periplanarity) is met by the thermodynamically favored endo hemiacetal 115, which would lead to 120. The rearrangement of exo hemiacetal 134 would be expected to yield the bicyclo[3.3.0]octanol 135

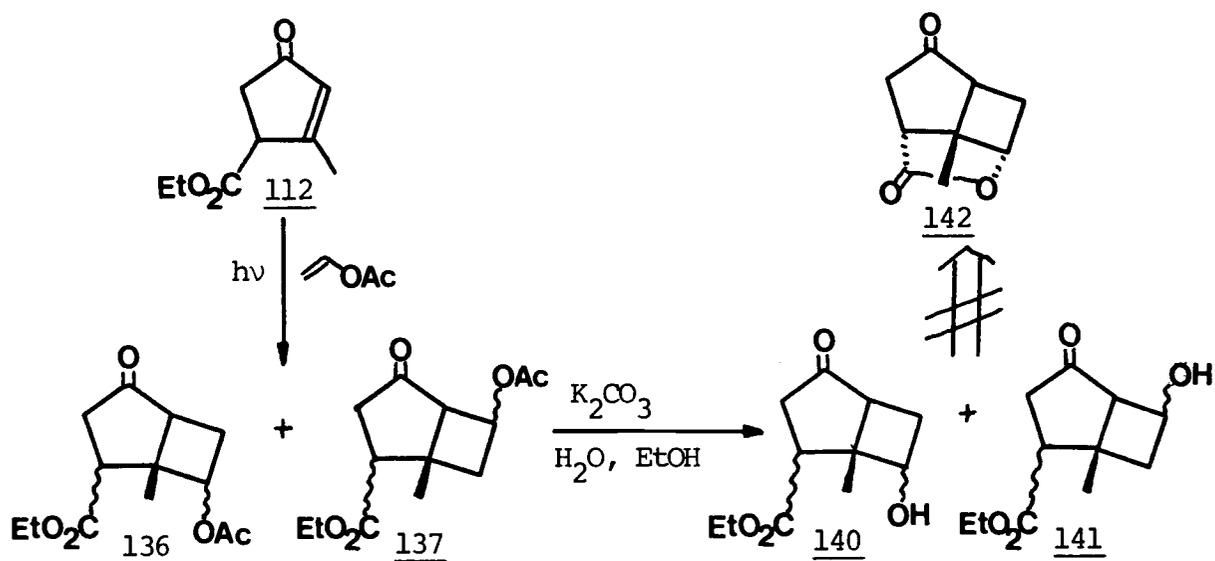
which, as noted above, is not favored. Acid catalyzed equilibration of the hemiacetal carbon should drive the rearrangement toward the favored bicyclo[3.2.1]octanol system of 120.

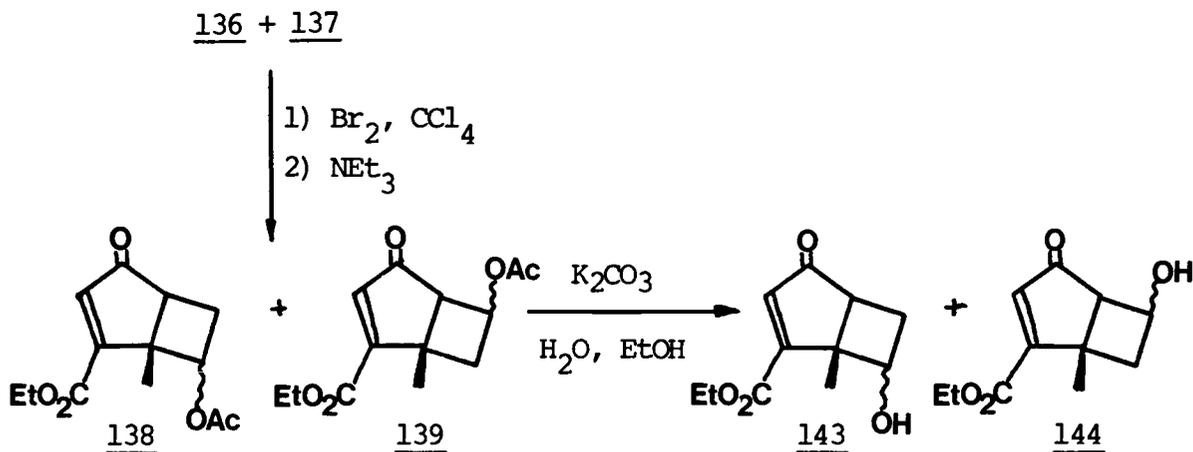


A. THE B-C-A ROUTE

As outlined above, the B-C-A route began with ester 112, which was prepared by the method of Dolby et al.⁵⁶ Cyclopentenone 112 and vinyl acetate were irradiated with a Pyrex-filtered medium pressure 450 W mercury lamp in hexane to furnish a mixture of ketones 136 and 137. The NMR spectrum of the mixture displayed eight acetoxy peaks, corresponding to all of the possible cis-fused isomers. Treatment of the mixture with bromine in carbon tetrachloride, followed by triethylamine led to a 67%

yield (from 112) of a mixture of regioisomers 138 and 139, which exhibited four acetoxy and four olefin hydrogen peaks in the NMR spectrum. All attempts to separate the isomers by chromatographic methods failed. Separation was also attempted by modification of the functional groups of 136 and 137, and 138 and 139, although without success. Ketones 136 and 137 were converted to alcohols 140 and 141 by treatment with aqueous potassium carbonate and the latter were treated with tosyl chloride in pyridine, followed by alcoholic potassium hydroxide, in the hope that this would lead to lactone 142. However, only polymer was obtained. The enones 138 and 139 were converted to alcohols 143 and 144 in like manner, however, on treatment of the latter with p-nitrobenzoyl chloride in pyridine, only an uncharacterizable mixture was obtained. Neither mixture of alcohols was resolvable into isomers. The attempted oxidation of alcohols 140 and 141, or 143 and 144 also failed to yield characterizable products.



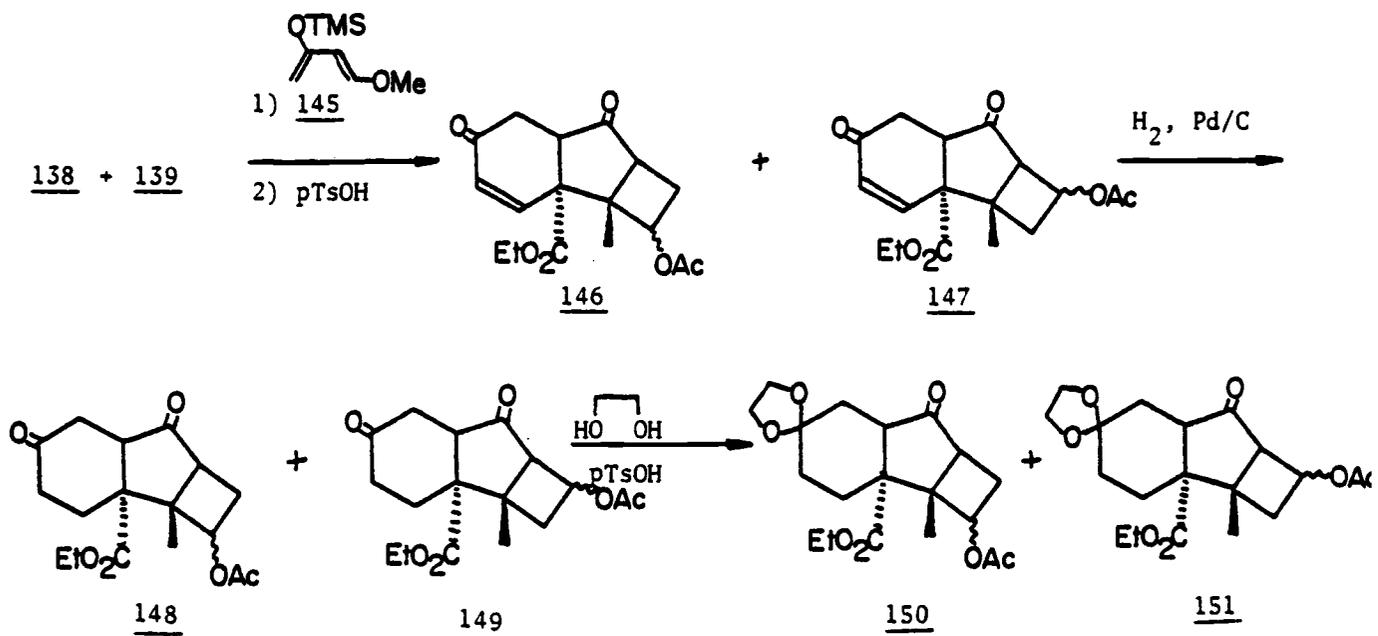


In spite of the presence of four isomers, it was decided to test the feasibility of the A-ring annulation via a Diels-Alder reaction with 138 and 139. A secondary goal was to find a point in the forward synthetic direction where chromatographic separation of isomers could be realized.

To this end the mixture of 138 and 139 was heated in benzene solution with isoprene and 2-ethoxybutadiene⁵⁷ in separate trials. In both cases, the acetates were recovered unchanged along with polymeric material, the latter undoubtedly arising from the diene. Clear precedent existed for the Diels-Alder reaction of dienes with β -formylacrylic esters,⁵⁸ and therefore it was hypothesized that the 3a-methyl group of 138 and 139 presented a steric barrier that could not be overcome at temperatures low enough to prevent the competitive polymerization of the diene. This would require a diene that was both more reactive towards dienophiles and less prone to polymerization. The diene 2-trimethylsilyloxy-4-methoxybutadiene (145) has been shown to possess these desirable properties.⁵⁹

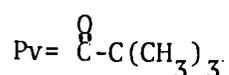
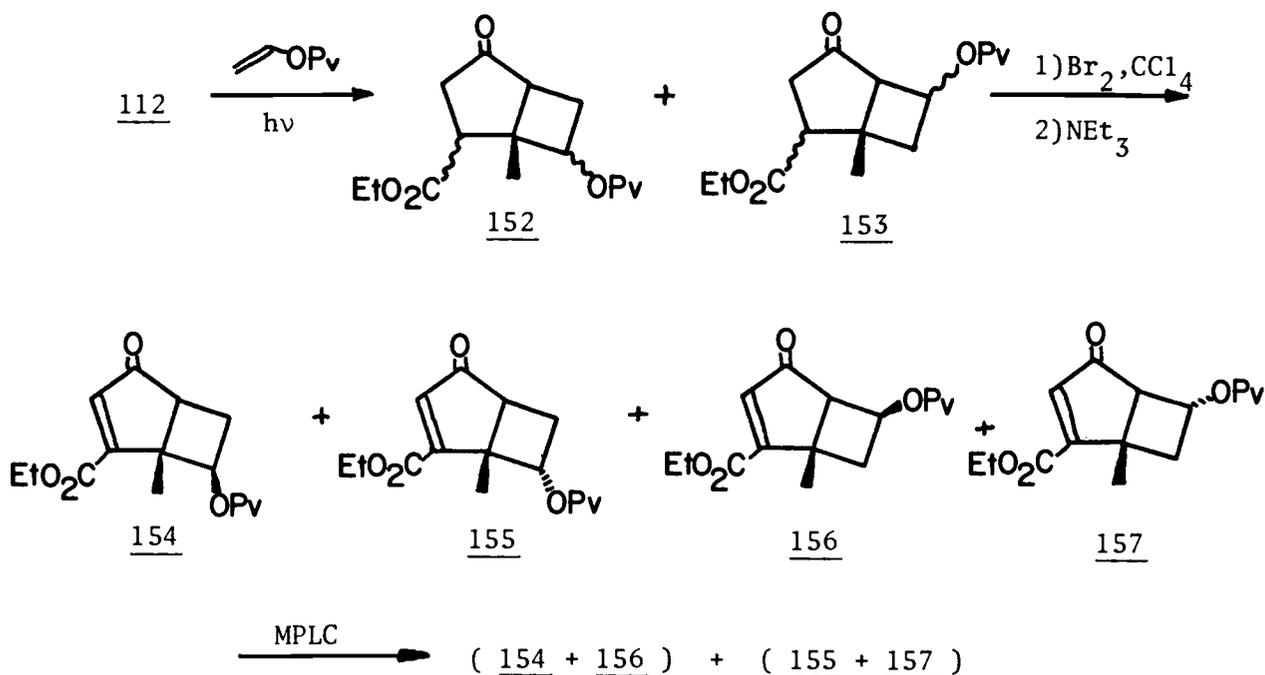
Upon heating a benzene solution of 138, 139 and 145 in a sealed tube at 200°C for 20 hours, followed by acidic hydrolysis, a 38% yield of enones 146 and 147 was obtained. The regiochemical sense of the Diels-Alder reaction was subsequently shown to be as indicated for

structures 146 and 147. The latter were reduced with hydrogen and palladium on carbon to ketones 148 and 149, and further converted to ketals 150 and 151, in 40% yield from 146 and 147. Unfortunately, the desired chromatographic separation of isomers could not be achieved at any point along this path.

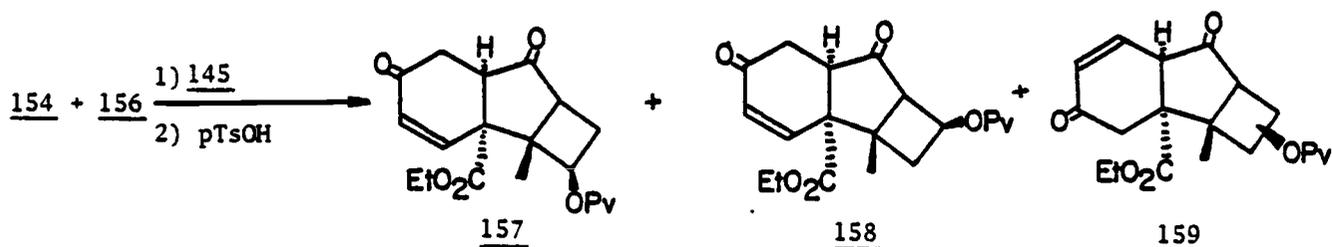


With the inability to effect an isomer separation in the acetate series in mind, it was decided to utilize a vinyl ester with more steric bulk in the initial photocycloaddition step, in an attempt to improve the isomer ratio towards the exo series. Vinyl pivalate was chosen for this purpose. Irradiation of a pentane solution of 112 and vinyl pivalate at ca -40°C ⁶⁰ produced a mixture of ketones 152 and 153, which were converted to enones 154, 155, 156 and 157 by treatment with bromine

in carbon tetrachloride followed by triethylamine. Medium pressure liquid chromatography on silica gel using 10% ethyl acetate/cyclohexane as eluent led to separation of the exo isomers 154 and 156 (26%) from the endo isomers 155 and 157 (21%). The exo and endo assignments are based on analogy with the 2-acetoxy-5-norbornene system, in which the endo 2-hydrogen (exo acetate) resonates upfield (δ 4.57) relative to the exo 2-hydrogen (endo acetate) (δ 5.19) in the NMR spectrum.⁶¹ The NMR absorptions of the C₄ hydrogens of 154 and 155 are each doubled doublets (154: δ 4.90, 155: δ 5.14), and the signals for the C₅ hydrogens of 156 and 157 are each eight line multiplets (156: δ 4.65, 157: δ 5.38) as expected for the respective regioisomers. Thus the goal of an enhancement of the isomer composition in favor of the exo isomers was realized, with the added benefit of a partial separation of isomers.



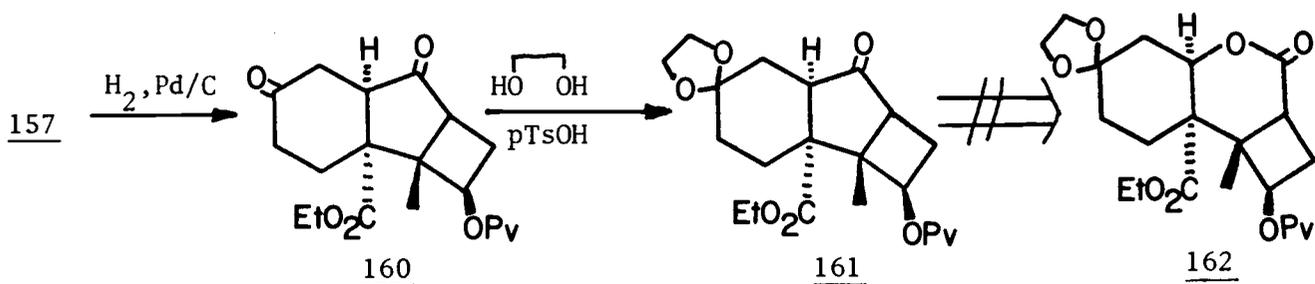
A benzene solution of exo isomers 154 and 156 and diene 145 in a sealed tube was heated to 200°C for 20 hours. Acidic hydrolysis and chromatography of the product led to 32% of recovered starting pivalates and 45% of a semicrystalline mixture of 1:1 adducts, which the NMR spectrum showed to be comprised of 157, 158 and 159. Recrystallization afforded a single crystalline product, 157, in 14% yield from 154 and 156.



A detailed analysis of the NMR spectrum of 157 revealed the relative stereochemistry shown above. The regiochemical sense of the cycloaddition was shown by the presence of an AA'M spin system (δ 2.60 (dd, $J=7.0, 17.5\text{Hz}$), 3.05 (dd, $J=2.5, 17.5\text{Hz}$), and 3.90 (ddd, $J=1.5, 2.5, 7\text{Hz}$)) corresponding to the methylene group α to the enone carbonyl and the adjacent ring junction proton. This spin system is clearly inconsistent with isomer 159. Further support for this assignment is gained from the resonances of the enone olefin hydrogens. The β -hydrogen's signal is a doublet of doublets, coupled to both the α -hydrogen of the enone ($J=10\text{Hz}$) and to the ring fusion proton of the AA'M system ($J=1.5\text{Hz}$). The latter coupling constant is inconsistent with structure 159, but readily explained by a "W-coupling",⁶² thus delineating the conformation of the four bonds linking the two hydrogens. This conformation can only

be attained if the cycloaddition had given a cis-anti-cis geometry of the three rings of 157. Further evidence for the cis-anti-cis configuration was obtained from observation of the change in chemical shift of the C₅ methyl group of 157 upon reduction of the enone double bond with hydrogen and palladium on carbon to yield 160. The methyl group in question is situated in the deshielding region of the enone double bond,⁶³ with a chemical shift of δ 1.52. This requires the cis-anti-cis configuration, which is consistent with the W-coupling noted above. Upon reduction of 157 to 160, the chemical shift of the methyl group predictably moves upfield to δ 1.36, again consistent with loss of the deshielding effect. Had the alternative cis-syn-cis configuration been obtained, the chemical shift of the methyl group would not have been so profoundly affected by the double bond reduction.

The reduced product 160 was converted to ketal 161 in 78% yield from 157 and was treated with 3,5-dinitroperbenzoic acid⁶⁴ in an attempt to bring about Baeyer-Villiger oxidation to lactone 162. However, this led to either recovered starting material or uncharacterizable mixtures depending on reaction conditions. In cases where mixtures were obtained, a mass spectrum showed no trace of a molecular ion corresponding to the desired lactone 162.



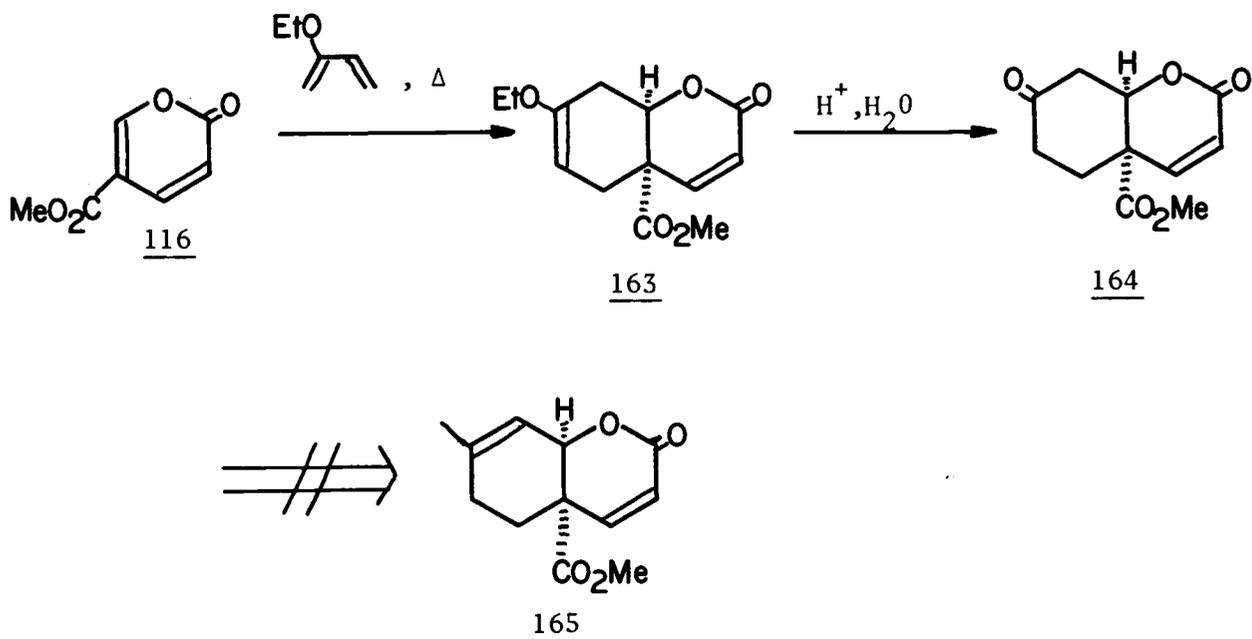
The failure of the Baeyer-Villiger oxidation of 161, coupled with the low yield of 157 (3.6% from 112) prompted us to set this route aside in favor of the B-A-C route described in the following section.

B. THE B-A-C ROUTE

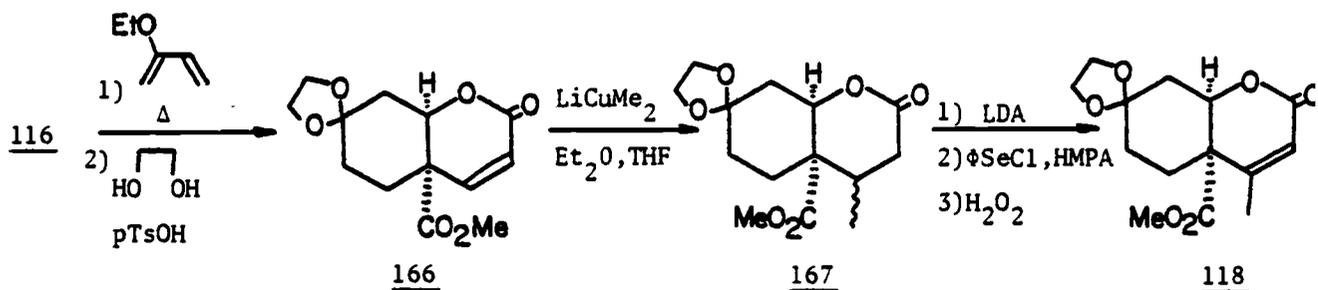
Two noteworthy features incorporated into the B-A-C route distinguish it from the B-C-A route described above, namely the fact that the starting material, pyrone 116, already contains the B-ring oxygen atom that caused the B-C-A route to fail, and the precedent for the facile Diels-Alder reaction using 116 as the dienophile.

Methyl coumalate (116) and 2-ethoxybutadiene were heated at 100°C in benzene in a sealed tube for 20 hours to furnish tetrahydrocoumarin 163 in 79% yield. The latter was hydrolyzed in 77% yield to ketone 164 which was characterized by its NMR spectrum. In addition to the expected AB quartet for the olefin hydrogens of the α,β -unsaturated lactone moiety, there was an AA'M spin system consisting of the ring fusion hydrogen and the adjacent α -methylene hydrogens (δ 2.75 (dd, $J=3,16\text{Hz}$), 2.99 (dd, $J=4,16\text{Hz}$), and 5.22 (ddd, $J=1.5,3,4\text{Hz}$)). Thus the regiochemical sense of the Diels-Alder reaction is as shown. The 1.5Hz coupling of the ring fusion hydrogen is a W-coupling to the exo C_4 hydrogen. The cis fusion of the two rings is the only configuration that is consistent with the requisite planar five atom system responsible for the W-coupling.

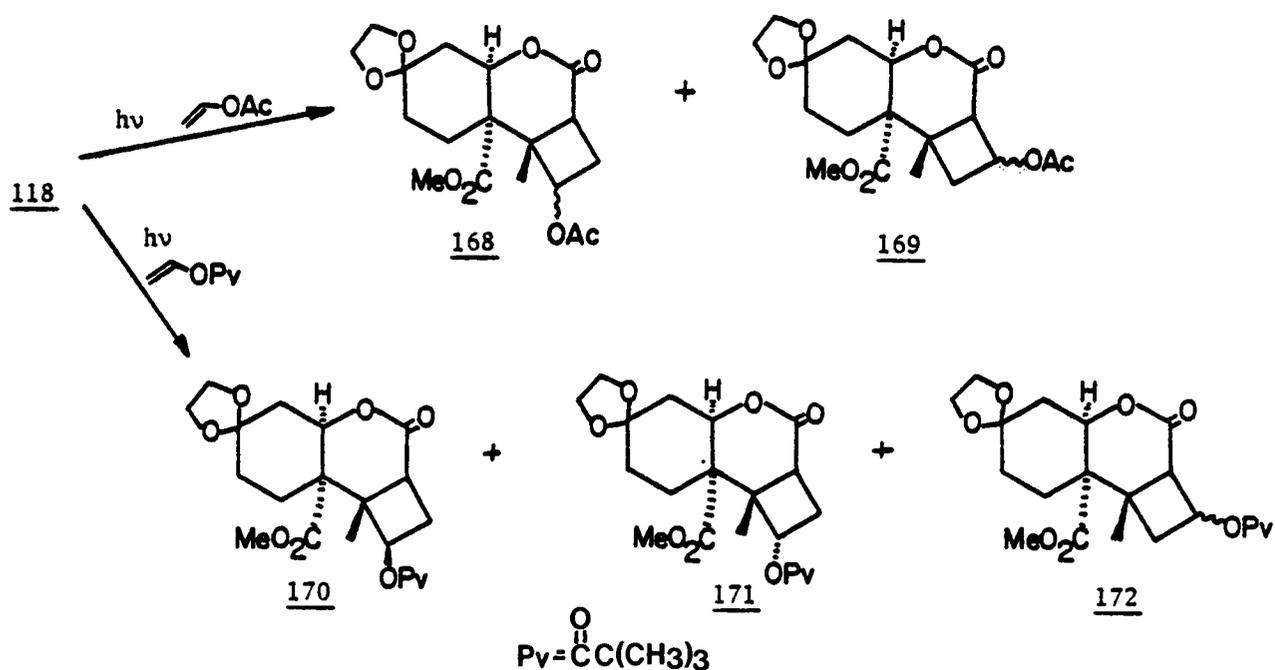
A number of unsuccessful attempts were made to transform 164 into 165, via a Wittig reaction followed by acid treatment, and by addition of methylmagnesium iodide followed by dehydration. Since the next stage of the synthetic plan involved reactions that were incompatible with the A-ring ketone, it became mandatory that the carbonyl function be protected.



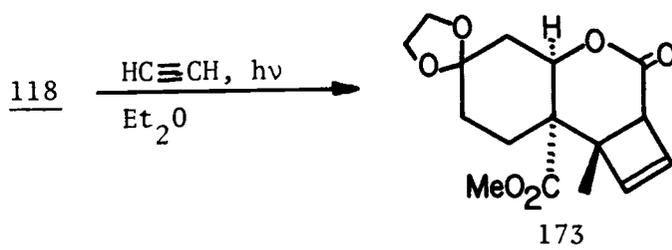
Attempts to form ketal 166 from 164 using standard procedures were unsuccessful, but this problem was circumvented by the direct transformation of 163 to 166 (in 50% recrystallized yield from 116) with ethylene glycol, acid, and azeotropic removal of ethanol. Ketal 166 was treated with lithium dimethylcuprate⁶⁵ to afford lactone 167 in 80% yield. This was converted to α,β -unsaturated lactone 118 in 79% yield by a modification of the phenylselenation-oxidation procedure of Grieco and Miyashita.⁶⁶



The photocycloaddition reaction of 118 and vinyl acetate was performed by irradiation with a Vycor-filtered 450 W medium pressure mercury lamp to yield a mixture of regioisomers 168 and 169 which was unresolvable by chromatography. Similar irradiation of 118 and vinyl pivalate led to a 74% yield of a mixture of isomers 170, 171 and 172. Medium pressure liquid chromatography afforded fractions which were enriched in one isomer or the other, implying that repeated chromatography would resolve the mixture. However, the desired isomer 170 was shown to be a minor component of the isomer mixture by the yield of the fraction enriched in 170 (8.3% from 118, 15.6% of material isolated after one chromatography cycle). This is apparently a result of steric hindrance in the transition state leading to 170, caused by interference of the pivalate group with either or both the methyl group and ester function of 118.



The impractical yield of the correct regio- and stereoisomer from the photocycloaddition of 118 with unsymmetrical olefins prompted a search for a partner which would simplify the isomer problem and yet would permit the introduction of the C₄-hydroxyl function of 3 at a later stage of the synthesis. Acetylene filled this need quite satisfactorily. Irradiation of 118 in ether through a Vycor filter with acetylene bubbling through the solution produced a 50.9% yield of cyclobutene 173 and some 33% of uncharacterized material after chromatography. The NMR spectrum of 173 showed that the A and B rings were in a conformation analogous to that of 164 by the presence of a similar AA'M spin system with W-coupling to the exo C₆-hydrogen. One of the cyclobutene olefin hydrogen's resonance was shifted 0.12 δ units downfield from that of the other, which can be attributed to a net deshielding effect of the methyl ester function, consistent with the expected cis-anti-cis configuration of the three rings.



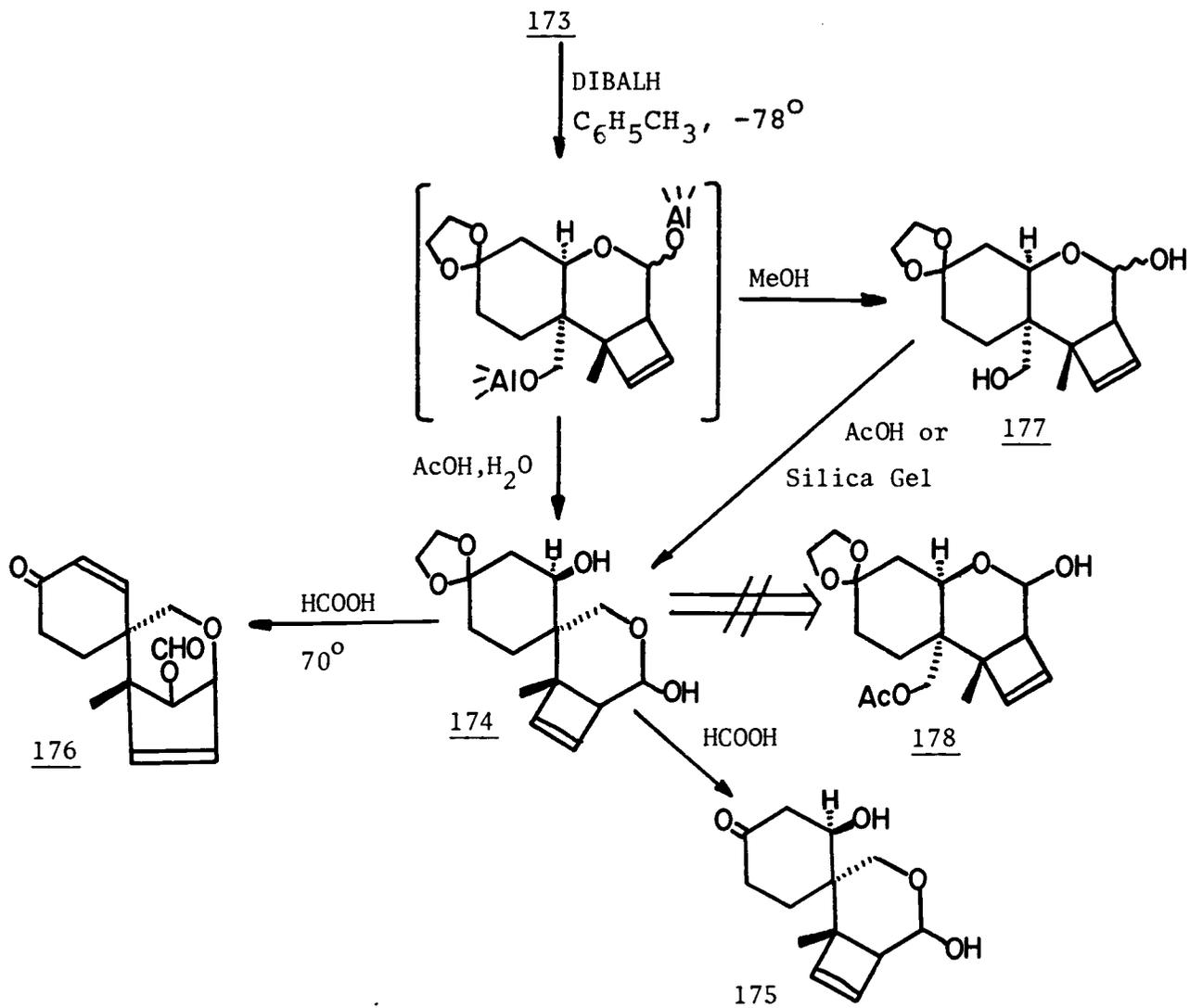
With a suitable precursor now in hand, the cyclobutylcarbinol rearrangement was investigated. To this end, 173 was treated with diisobutylaluminum hydride and the product, hemiacetal 174, was subjected to various acidic systems. On stirring a solution of 174 in 97% formic acid, ketone 175 was obtained by ketal hydrolysis and (presumably) isomerization.

Stirring a solution of 174 in anhydrous formic acid at 70°C led to rearranged product 176, as evidenced by its NMR spectrum, which displayed an ABM spin system for the cyclopentenyl olefin hydrogens and the adjacent bridgehead proton (δ 4.64 (dd, J=3,9Hz), 6.16 (dd, J=3,6Hz), and 6.36 (d, J=6Hz)), in addition to an AB quartet for the enone olefin hydrogens (δ 6.03 (d, J=10Hz) and 6.45 (d, J=10Hz)), and an AB quartet for the methylene group of the tetrahydropyran ring (δ 3.60 (d, J=12Hz) and 3.82 (d, J=12Hz)). The coupling constant of the non-enone olefin hydrogens (6Hz) is clearly incompatible with a cyclobutene, but well within range of a cyclopentene ring.⁶⁷

At this stage the true nature of the initial hydride reduction product was not certain, but was assumed to be the expected primary alcohol, 177. Thus it was reasoned that protection of the primary hydroxyl function of 177 immediately upon its formation would prevent the undesirable isomerization to the spiro system of 174, 175 or 176. However, treatment of 174 with acetic anhydride in pyridine failed to yield acetate 178. This result led to a reexamination of the reduction of 173. The explanation for the anomalous results soon became apparent when it was noted that aqueous acetic acid had been used to dissolve the aluminum salts, and it was this brief acid treatment that caused the isomerization of 177 to 174.

To test this hypothesis, lactone 173 was treated with diisobutylaluminum hydride, with a non-acidic workup procedure. The NMR and IR spectra of the product so obtained (177), were clearly different from those of 174. Yet, chromatography of 177 on silica gel was sufficient to cause the isomerization to 174 and stirring a solution of 177 in chloroform with one drop of glacial acetic acid for 5 minutes, led to

complete isomerization to 174. Thus, it is clear that the acidic workup procedure after reduction is responsible for the appearance of the spiro ring system of 174, 175 and 176.



The unexpectedly facile isomerization of 177 to the spiro hemiacetal 174 places yet another obstacle in the route to verrucarol. Successful negotiation of this problem and an eventual synthesis of the natural sesquiterpene by this pathway will depend upon a method, such as blocking the primary alcohol of 177, which would suppress the undesired reorganization.

CONCLUSIONS

The [3,3] sigmatropic rearrangement was shown to be an impractical method to construct the C₄-C₁ bond of trichodiene 9. The Claisen rearrangement of model allyl vinyl ether 100 furnished ketone 98 in 31% yield, providing a rare example of a Claisen rearrangement of a 1,1,6,6 tetra-substituted 1,5 diene.

The synthesis of alcohol 177 comprised the completion of the first stage of the synthesis of verrucarol 3, namely the procurement of a molecule containing the correct cis-anti-cis configuration of the three rings and suitable functionality to allow for the conversion to 3. However, the facile isomerization of 177 to 174 prevented the realization of the trichothecane carbon skeleton, via a cyclobutylcarbinol rearrangement of 177. Hemiacetal 174 was successfully converted to cyclopentene 176, thereby demonstrating the feasibility of the proposed cyclobutylcarbinol rearrangement to obtain the oxabicyclo[3.2.1]octane portion of 3.

CHAPTER IV: EXPERIMENTAL

GENERAL

Infrared spectra (IR) were obtained with a Perkin-Elmer 137 or 727B infrared spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Varian EM-360, EM-360A, or HA-100 spectrometer and are reported in δ units with tetramethylsilane (TMS) as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, bs=broad singlet, m=multiplet, etc. are used throughout. Mass spectra (MS) were obtained on a Varian MAT CH-7 spectrometer. Exact mass determinations were carried out using a CEC-103B spectrometer, using an ionization potential of 70 eV. Column chromatography was performed using neutral silica gel (Activity I). Preparative thin layer chromatography (TLC) plates were obtained from Analtech and were prepared from silica gel GF-254. All boiling points (BP) and melting points (MP) are uncorrected. Dry tetrahydrofuran (THF) was obtained by distillation from lithium aluminum hydride. Dry benzene was obtained by distillation from sodium wire. Other solvents were purified using standard procedures. All organic solutions were dried with MgSO_4 and filtered prior to rotary evaporation at water aspirator pressure unless otherwise noted.

2-Methoxy-5-methylbenzoic acid (59)

A mixture of 13.05 g (0.085 mol) of 5-methylsalicylic acid, 39 g (0.28 mol) of K_2CO_3 and 40 g (0.32 mol) of dimethylsulfate in 225 mL of acetone was refluxed for 21.5 h. The reaction was cooled and the solvent

was evaporated. The residue was taken up in 225 mL of 5N NaOH and refluxed for 2.5 h. The cooled mixture was washed with ether, acidified to pH=1 with conc. HCl and the precipitate was collected and dried to leave 11.2 g of white solid. Recrystallization from benzene/pet. ether furnished 9.1 g (64%) of white needles, 59: MP 68.5-69.5°C; IR (CHCl₃ film) 3500-2700 (br), 3020, 1735 cm⁻¹; NMR (CCl₄) δ 2.3 (3H, s), 3.9 (3H, s), 6.7 (1H, d, J=9Hz), 7.2 (1H, dd, J=2,9Hz), 7.7 (1H, d, J=2Hz).

Methyl 2-methoxy-5-methyl-1,4-dihydrobenzoate (60)

To 250 mL of liq. NH₃ was added 4.0 g (23.8 mmol) of 59 and 40 mL of dry THF. Small hexane washed chunks of metallic sodium were added slowly until a permanent blue endpoint was reached. The reaction was stirred at NH₃ reflux for 30 m, then NH₄Cl(s) was added until the blue color was discharged, the NH₃ was evaporated and 100 mL of water was added. The mixture was acidified with conc. HCl to pH=1. The mixture was extracted with ether and the combined ether extracts washed with brine, and the solvent was evaporated. The residue was taken up in 50 mL of ether and a solution of diazomethane in ether was added at RT until no more N₂ evolution was evident. The solvent was evaporated to leave 4.0 g of an orange liquid, which was chromatographed (CH₂Cl₂ elution) to give 2.90 g (72%) of 60: IR (neat) 3010, 1740, 1700 cm⁻¹; NMR (CDCl₃) δ 1.74 (3H, d, J=1.5Hz), 2.70 (2H, m), 3.52 (3H, s), 3.63 (3H, s), 3.78 (1H, d, J=5.5Hz), 4.72 (1H, t, J=3.5Hz), 5.32 (1H, dq, J=1.5,5.5Hz).

2-Carbomethoxy-4-methylcyclohex-3-ene-1-one (53)

A solution of 2.90 g (17.0 mmol) of 60, 10 mL of 10% HCl and 50 mL of acetone was stirred under N₂ at RT for 4 h. Then 1.1 g of NaHCO₃(s) was added and the mixture stirred until homogeneous. The acetone was evaporated and 20 mL of water was added. The mixture was extracted with ether and the extracts were washed with brine, and the solvent evaporated to leave a green oil which was distilled to give 1.95 g (68%) of a clear liquid, 53: BP 85–88°C/0.85 mm; IR (neat) 3000, 1665, 1620 cm⁻¹; NMR (CCl₄) δ 1.76 (3H, d, J=1.5Hz), 2.1–2.6 (4H, m), 3.72 (3H, s), 3.84 (1H, d, J=4Hz), 5.86 (1H, dq, J=1.5,4Hz).

2-Carbomethoxy-4-methyl-2-(3-methyl-2-butenyl)-
cyclohex-3-ene-1-one (56)

To a mixture of 0.52 g (10.8 mmol) of 50% sodium hydride in 50 mL of dry THF was added dropwise a solution of 1.50 g (9.6 mmol) of 53 in 25 mL of THF. The mixture was stirred at RT for 1 h, then cooled to -10°C and a solution of 1.49 g (10.0 mmol) of 3,3-dimethylallyl bromide (55) in 25 mL of THF was added dropwise. The mixture was stirred at -5°C for 1 h, then at RT for 30 m. The reaction was quenched with 100 mL of water and extracted with ether. The ether extracts were washed with brine, and the solvent was evaporated. The residual oil was distilled to give 1.26 g (59%) of a clear oil, 56: BP 125–131°C/1.05 mm; IR (neat) 1740, 1720, 1700 cm⁻¹; NMR (CCl₄) δ 1.60 (3H, s), 1.66 (3H, d, J=1.5Hz), 1.84 (3H, s), 2.2–2.8 (6H, m), 3.64 (3H, s), 4.91 (1H, tq, J=1.5,7Hz), 5.33 (1H, q, J=1.5Hz); MS m/e (relative intensity) 236 (M⁺, 14.4), 168 (39.5), 136 (100), 69 (39.6).

Cope Rearrangement of 56

Run A. A solution of 23 mg (0.097 mmol) of 56 and 2 mL of dry benzene was sealed in an ampule and heated to 250°C for 16 h. The tube was cooled, opened and the solvent was evaporated to leave 16 mg (99%) of a yellow oil, 61: NMR (CCl₄) δ 2.3 (3H, s), 3.7 (1H, bs), 3.9 (3H, s), 6.8 (1H, d, J=9Hz), 7.2 (1H, dd, J=2,9Hz), 7.55 (1H, d, J=2Hz).

Run B. A solution of 130 mg (0.55 mmol) of 56 and 2.3 mg of 2,6-di-t-butyl-p-cresol in 2 mL dry benzene was sealed in an ampule and heated to 220°C for 14 h. The tube was cooled, opened and the solvent was evaporated to leave 124 mg of yellow oil. The NMR spectrum shows 35% of 56 and 65% of 61 by comparison of the methyl ester absorptions.

Run C. A solution of 105 mg (0.42 mmol) of 56 and 95 mg (0.42 mmol) of 2,6-di-t-butyl-p-cresol in 3 mL of dry benzene was sealed in an ampule and heated to 225°C for 16 h. The tube was cooled, opened and the solvent was evaporated to leave 217 mg of yellow oil consisting of 56 and inhibitor (NMR).

Run D. The product from run C was taken up in 3 mL of dry benzene and heated to 250°C for 16 h. The tube was cooled, opened and the solvent was evaporated to leave 200 mg of an orange-yellow oil, which the NMR spectrum showed to consist of inhibitor and 61.

2-Methoxy-1,4-dimethylcyclohexa-1,4-diene (74)

To 150 mL of liq. NH₃ was added 5.0 g (0.037 mol) of 2,5-dimethylanisol, 40 mL of dry THF and 10 mL of abs. ethanol. Small hexane washed chunks of sodium metal were slowly added to a permanent blue endpoint,

and then $\text{NH}_4\text{Cl}(\text{s})$ as added to dissipation of the blue color. The NH_3 was evaporated, 75 mL of water was added, and the aqueous portion saturated with $\text{NaCl}(\text{s})$. The mixture was extracted with ether and the combined ether extracts washed with brine, and the solvent was evaporated. The residue was distilled to yield 3.62 g (72%) of clear oil, 74: BP 62–63°C/4.8 mm; IR (neat) 3010, 1715, 1680 cm^{-1} ; NMR (CCl_4) δ 1.65 (3H, s), 1.70 (3H, s), 3.65 (4H, bs), 3.6 (3H, s), 5.35 (1H, bs).

3,6-Dimethylcyclohex-3-en-1-one (69)

A solution of 2.0 g (0.0145 mol) of 74, 10 mL of 10% H_2SO_4 and 5 mL of dioxane was refluxed for 3 h. The reaction was cooled, $\text{K}_2\text{CO}_3(\text{s})$ added to pH=7.0 and 10 mL of water was added. The mixture was extracted with ether and the combined ether extracts were washed with sat. NaHCO_3 , brine and the solvent was evaporated. The residue was distilled to furnish 1.52 g (84%) of clear oil, 69: BP 71–72°C/5 mm; IR (neat) 3080, 1675, 1635 cm^{-1} ; NMR (CDCl_3) δ 1.15 (3H, d), 1.6 (2H, m), 1.9 (3H, s), 2.1–2.4 (3H), 5.8 (1H, bs).

6-(3-Methylbut-2-enyl)3,6-dimethylcyclohex-2-ene-1-one (77)

To a mixture of 50 mg (7.0 mmol) of lithium metal in 2.5 mL of dry THF at -10°C was added dropwise a solution of 0.27 g (2.2 mmol) of 69 and 0.39 g (2.6 mmol) of 55 in 3.5 mL of dry THF. The reaction was maintained at -10°C for 1.5 h. The reaction was filtered and the solvent was evaporated. To the residue, 10 mL of sat. NH_4Cl was added and the mixture was extracted with ether. The combined ether extracts were dried and the solvent was evaporated to leave 336 mg of yellow oil. The oil

was distilled by bulb to bulb distillation, and the fraction boiling at 75–120°C (5.0 mm) was submitted to preparative gas chromatography (5' x 1/4' 10% OV-17, 200°C) to yield 77: IR (neat) 1670, 1210 cm^{-1} ; NMR (CDCl_3) δ 1.05 (3H, s), 1.1–1.6 (2H), 1.65 (3H, s), 1.75 (3H, s), 1.95 (3H, d, $J=1.5\text{Hz}$), 2.2 (4H, m), 5.1 (1H, dt, $J=1.5, 7\text{Hz}$), 5.8 (1H, q, $J=1.5\text{Hz}$).

1-Methylcyclohexene (80)

To a mixture 36.5 g (1.5 mol) of magnesium turnings in 200 mL of dry ether was added dropwise a solution of 177 g (1.25 mol) of methyl iodide in 100 mL of dry ether. An ice water bath was installed and a solution of 100 g (1.02 mol) of cyclohexanone in 150 mL of dry ether was added dropwise. The reaction was warmed to RT and added to 120 mL of conc. HCl in 450 g of ice. The mixture was filtered, the organic layer removed, the aqueous phase saturated with NaCl(s) and extracted with ether. The combined ether extracts and organic layer were washed with sat. NaHSO_3 , brine and the solvent was evaporated. The residue was distilled (BP 52.5–53°C/8.5 mm) to give 93.3 g of clear liquid. The liquid (85.7 g) and 1 g of iodine crystals were heated to 130°C in a flask fitted with a heated column carrying a still head. The distillate was collected and the aqueous phase saturated with NaCl(s) and removed. The organic layer was washed with sat. NaHSO_3 , brine, dried and filtered to leave 63.1 g (88%) of clear liquid, 80: IR (neat) 3050, 1660, 1370 cm^{-1} ; NMR (CDCl_3) δ 1.3–1.7 (4H), 1.6 (3H, s), 1.7–2.1 (4H), 5.3 (1H, bs).

1-Methylcyclohexane-1,2-diol (81)

To an ice cold mixture of 32.7 g (0.34 mol) of 80, 55 g (0.55 mol) of Na_2CO_3 and 250 mL of CH_2Cl_2 was added 102 g (0.54 mol) of 40% peracetic acid. The reaction was allowed to come to RT and stirred for 7 h, then 250 mL of water was added and the aqueous phase saturated with NaCl(s) . The organic layer was removed and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layer and CH_2Cl_2 extracts were washed with sat. NaHCO_3 , brine, and the solvent was evaporated. The residue was taken up in 100 mL of THF, the solution was cooled to ice temperature and 7.5 mL of 3% HClO_4 added. After stirring for 3 h the aqueous phase was saturated with NaCl(s) , and extracted with CH_2Cl_2 . The combined extracts were dried and the solvent was evaporated to leave 40.1 g (89%) of white solid, 81: MP 82-84°C (recrystallized from EtOAc); IR (nujol mull) 3470, 3420, 1120, 1075 cm^{-1} ; NMR (CDCl_3) δ 1.2 (3H, s), 1.2-1.9 (8H), 2.4 (1H, s), 2.65 (1H, bs), 3.5 (1H, m).

6-Oxoheptanal (82)

To a solution of 56.9 g (0.44 mol) of 81 in 500 mL of 95% ethanol was added a solution of 109 g (0.51 mol) of sodium meta-periodate in 1 L of water in one portion. The reaction was stirred for 2.75 h, then 200 mL of water was added, the aqueous phase was saturated with NaCl(s) and extracted with ether. The combined ether extracts were washed with brine, and the solvent was evaporated. The residue was distilled to give 31.0 g (55%) of yellow oil, 82: BP 49-51°C/0.2 mm; IR (neat) 2880, 2770, 1725 cm^{-1} ; NMR (CDCl_3) δ 1.6 (4H, m), 2.2 (3H, s), 2.45 (4H, m), 9.8 (1H, t, $J=1.5\text{Hz}$).

2-Methylcyclopentenylcarboxaldehyde (83)

To an ice cold solution of 10.0 g (0.08 mol) of 82 in 60 mL of ether was added 7.5 g (0.087 mol) of piperidine over 30 m. The reaction was stirred at ice temperature for 3 h, then at RT for 2 h. The reaction was washed with brine, and the solvent was evaporated to leave 14.6 g of a light green oil. To a solution of 21.98 g of the oil in 350 mL of dry ether was added a solution of 17 g of glacial acetic acid in 50 mL of ether. The reaction was stirred at ice temperature for 30 m and at RT for 30 m, then 300 mL of sat. NaHCO₃ was added. The aqueous layer was removed and the organic layer washed with sat. NaHCO₃, brine and the solvent was evaporated to leave 11.95 g (89%) of red oil, 83: BP 29–30°C/0.25 mm; IR (neat) 2980, 2780, 1670, 1640 cm⁻¹; NMR (CDCl₃) δ 1.9 (2H, m), 2.2 (3H, s), 2.6 (4H, bt), 10.1 (1H, s).

2-Methylcyclopentenylmethanol (79)

To a solution of 0.95 g (8.6 mmol) of 83 in 10 mL of dry ether at -10°C was added dropwise a suspension of 153 mg (4.0 mmol) of lithium aluminum hydride in 5 mL of dry ether. The reaction was stirred for 10 m at -10°C then 2 mL of water and 3.5 mL of 10% H₂SO₄ was added. The aqueous layer was removed and the organic phase was washed with brine, and the solvent was evaporated. The residue was distilled to yield 0.82 g (86%) of a clear oil, 79: BP 55–57/0.55 mm; IR (neat) 3370, 1670, 1375 cm⁻¹; NMR (CDCl₃) δ 1.7 (3H, s), 1.7–2.0 (3H), 2.4 (4H, m), 4.2 (2H, s).

2-Methylcyclopentenylmethyl Mesitoate (78)

To an ice cold solution of 0.75 g (4.1 mmol) of mesitoyl chloride in 1.5 mL of ethanol free chloroform was added dropwise a solution of 0.45 g (4.0 mmol) of 79 and 1 mL of pyridine in 1 mL of CHCl_3 . The mixture was stirred at RT overnight and then 1 mL of water was added. The organic layer was removed and washed with water, 10% HCl, 5% NaHCO_3 , and the solvent was evaporated. The residue was distilled to give 0.82 g (80%) of yellow oil, 78: BP 110-112°C/0.15 mm; IR (neat) 1725, 1615 cm^{-1} ; NMR (CDCl_3) δ 1.7 (6H, bs), 2.3 (12H, s), 4.75 (2H, s), 6.65 (2H, s).

6-(2-Methylcyclopentenylmethyl)-3,6-dimethylcyclohex-2-en-1-one (84) and
5-(2-Methylcyclopentenylmethyl)-2,5-dimethylcyclohexanone (85)

To a mixture of 100 mg (14.3 mmol) of lithium in 10 mL of dry THF under dry N_2 was added a solution of 0.82 g (3.0 mmol) of 78 in 2 mL of THF. When the lithium had dissolved, a solution of 0.4 g (3.2 mmol) of 69 in 1 mL of THF was added. The reaction was stirred at RT for 15 h, then 10 mL of water was added and the mixture was extracted with ether. The ether extracts were washed with brine, and the solvent was evaporated. The crude product was submitted directly to preparative G.C. (10' x 3/8" 10% OV-17, 200°C) to afford 84 (4.1%): NMR (CDCl_3) δ 0.86 (3H, s), 1.65 (3H, s), 1.0-1.9 (6H), 2.0-2.4 (4H), 5.3 (1H, bs); and 85 (5.6%): IR (neat) 1705, 1375 cm^{-1} ; NMR (CDCl_3) δ 0.8-1.2 (6H, m), 1.65 (3H, bs), 1.8-2.5 (15H, m).

1-(3-Methylbut-2-enyl)-3,6-dimethylcyclohex-2-en-1-ol (76) and
1-(2-Methylbut-3-en-2-yl)-3,6-dimethylcyclohex-2-en-1-ol (87)

To a mixture of 0.15 g (6.0 mmol) of magnesium turnings in 10 mL of dry THF was added a solution of 0.59 g (4.0 mmol) of 55 and 0.62 g (5.0 mmol) of 69 in 15 mL of THF over 40 m. The reaction was stirred at RT for 1 h, then refluxed for 3 h. The reaction was cooled and 10 mL of sat. NH_4Cl was added. The aqueous portion was removed and the organic layer was washed with brine, and the solvent was evaporated to leave 0.80 g (100%) of yellow oil, 76 and 87: IR (neat) 3470, 1680 cm^{-1} ; NMR (CDCl_3) δ 1.05 (7.5H, m), 1.5-2.5 (12H), 4.8-6.2 (2.5H, m).

Alkoxy-Cope Rearrangement of 76 and 87

A suspension of 6 mg (1.5 mmol) of potassium hydride in mineral oil was washed with dry hexane, then 5 mL of dry THF and 396 mg (1.5 mmol) of 18-Crown-6 was added. To the stirred solution under dry N_2 was added a solution of 160 mg (0.82 mmol) of 76 and 87. The reaction was stirred at RT for 4 h and then 5 mL of water was added and the mixture extracted with ether. The combined ether extracts were washed with brine, and the solvent was evaporated to leave 141 mg of red oil. IR (neat) 3420, 1710, 1675, 1380 cm^{-1} ; NMR (CCl_4) δ 0.75-1.5 (7.8H), 1.5-2.5 (12.44H), 3.6 (0.44H), 4.9-6.0 (1.32H).

2,5-Dimethylcyclohexanone (94)

A mixture of 500 mg PtO_2 and 300 mL of abs. ethanol was stirred under a H_2 atmosphere until H_2 uptake ceased, then 10 g (0.081 mol) of 69 was added through a septum and the reaction stirred until 1880 mL

of H₂ had been taken up. The mixture was filtered through Celite and the solvent carefully evaporated. The residue was distilled to yield 7.1 g (69%) of a clear liquid, 94: BP 48.5–49.5°C/3.2 mm; IR (neat) 1705, 1375 cm⁻¹; NMR (CDCl₃) δ 1.0 (3H, d), 1.05 (3H, d), 1.2–2.5 (8H).

1,1-Dimethoxy-2,5-dimethylcyclohexane (95)

A solution of 6.85 g (0.054 mol) of 94, 56.5 g (0.54 mol) of trimethylorthoformate, 100 mg of p-toluenesulfonic acid and 40 mL of abs. methanol was stirred at RT for 40 h. A solution of NaOMe/MeOH was added to dissipation of the blue color. The solvent was evaporated and the residue was taken up in 100 mL of ether, washed with brine, and the solvent was evaporated. The residue was distilled to leave 8.0 g (86%) of a clear oil, 95: BP 58–60°C/4.3 mm; NMR (CDCl₃) δ 0.85 (6H, m), 1.1–2.1 (8H), 3.15 (6H, s).

1-Methoxy-2,5-dimethylcyclohexene (93) and

1-Methoxy-3,6-dimethylcyclohexene (96)

A mixture of 4.2 g (24.4 mmol) of 95 and 200 mg of finely ground (NH₄)H₂PO₄ was slowly heated in a flask carrying a still head to 200°C. A forerun consisting of methanol was collected and then the product, which was stored overnight over 4A molecular sieves. The liquid was decanted and distilled at water aspirator pressure to yield 2.81 g (83%) of clear liquid, 93 and 96: BP 60–65°C; IR (neat) 1680, 1650, 1180 cm⁻¹; NMR (CDCl₃) δ 1.0 (4.57H, m), 1.1–2.5 (7.9H), 3.46 (3H, s), 4.35 (0.53H, d, J=3Hz).

3-Methylbut-2-enol (97)

To an ice cold mixture of 2.4 g (0.062 mol) of lithium aluminum hydride and 250 mL of dry ether was added a solution of 2.7 g (0.02 mol) of aluminum chloride in 50 mL of dry ether. The reaction was warmed to RT and a solution of 6.0 g (0.06 mol) of 3,3-dimethylacrylic acid in 50 mL of ether was added dropwise. The reaction was stirred at RT for 5 h, then 100 mL of 10% of H₂SO₄ and 100 mL of water was added. The aqueous portion was saturated with NaCl(s) and extracted with ether. The ether extracts were washed with sat. NaHCO₃, brine and the solvent was evaporated. The residue was distilled to yield 3.17 g (61%) of a clear liquid, 97: BP 62-64°C/15 mm; IR (neat) 3400, 1680 cm⁻¹; NMR (CDCl₃) δ 1.7 (3H, s), 1.75 (3H, s), 2.1 (1H, s), 4.15 (2H, d), 5.4 (1H, t).

2-(2-Methylbut-3-en-2-yl)-2,5-dimethylcyclohexanone (98) and2-(2-Methylbut-3-en-2-yl)-3,6-dimethylcyclohexanone (99)

A mixture of 0.75 g (5.4 mmol) of 93 and 96, 0.5 g (5.9 mmol) of 97, 350 mg (1.1 mmol) of Hg(OAc)₂ and 130 mg (1.6 mmol) of NaOAc in 5 mL of dry benzene under dry N₂ was refluxed for 21 h, during which time 100 mg additions of Hg(OAc)₂ were made at 12, 17 and 19.5 h. The reaction was cooled, 300 mg K₂CO₃(s) was added and the mixture was stirred overnight. The mixture was filtered and the solvent was evaporated. The residue was taken up in 5 mL of dry toluene and refluxed under dry N₂ for 48 h. The reaction was cooled and the solvent was evaporated. The residue was chromatographed (CH₂Cl₂) to yield 320 mg (31%) of an oil, 98: rf 0.64 (19:1, CHCl₃:EtOH); IR (neat) 3080, 1700,

1660, 995 cm^{-1} ; NMR (CDCl_3) δ 0.98 (3H, d), 1.08 (6H, s), 1.13 (3H, s), 1.70 (4H, m), 2.0–2.4 (3H), 4.95 (1H, dd, $J=1.7, 19.5\text{Hz}$), 5.00 (1H, dd, $J=1.7, 11\text{Hz}$), 6.08 (1H, dd, $J=11, 19.5\text{Hz}$); MS m/e (relative intensity) 194 (M^+ , 6.8), 179 (3.8), 126 (100), 69 (53.1). In a previous run was obtained the minor isomer 99: rf 0.70 (19:1, CHCl_3 : EtOH); IR (neat) 3085, 1695, 845 cm^{-1} ; NMR (CDCl_3) δ 0.96 (3H, d), 1.01 (3H, d), 1.05 (3H, s), 1.11 (3H, s), 1.2–2.2 (4H), 2.2–2.6 (2H, m), 4.97 (1H, dd, $J=1.5, 17\text{Hz}$), 5.05 (1H, dd, $J=1.5, 11\text{Hz}$), 5.98 (1H, dd, $J=11, 17\text{Hz}$); MS m/e (relative intensity) 194 (M^+ , 5.8), 179 (21.9), 126 (38.8), 69 (100).

6-(2-Methylbut-3-en-2-yl)-3,6-dimethylcyclohex-2-en-1-one (102)

To a solution of 121 mg (1.2 mmol) of diisopropylamine in 6 mL of dry THF at -78°C under dry N_2 was added 0.54 mL (1.2 mmol) of 2.2 M nBuLi. A solution of 159 mg (0.82 mmol) of 98 in 1.5 mL of THF was added dropwise and the reaction stirred for 5 m at -78°C , then a solution of 194 mg (1.0 mmol) of phenylselenenylchloride in 2 mL of THF was added in one portion. The reaction was stirred at -78°C for 5 m, then at 0°C for 30 m. To the reaction was added 0.5 mL of water, 0.12 mL of glacial acetic acid and 0.52 mL of 30% H_2O_2 . The mixture was stirred at RT for 30 m, then refluxed for 1 h. The cooled mixture was poured into 20 mL of sat. NaHCO_3 and 20 mL of 1:1 ether:hexane. The organic layer was removed and the aqueous phase extracted with ether. The combined ether extracts and organic layer was washed with water, 0.1 N HCl, water, brine, and the solvent was evaporated. The residue was chromatographed (CH_2Cl_2) to give 39 mg of 98 and 46 mg (45%) of an oil, 102: IR (neat) 3080, 1665, 1635 cm^{-1} ; NMR (CCl_4) δ 1.02 (3H, s), 1.08 (6H, s), 1.5–2.1 (2H, m), 1.89 (3H, d, $J=1.5\text{Hz}$), 2.18 (2H, m),

4.86 (1H, dd, J=1.5,17Hz), 4.92 (1H, dd, J=1.5,10Hz), 5.66 (1H, q, J=1.5Hz), 6.04 (1H, dd, J=10,17Hz); MS m/e (relative intensity) 192 (M^+ , 12.4), 177 (4.6), 124 (100), 69 (28.8).

6-(2-Methylbut-3-en-2-yl)-3,6-dimethylcyclohex-2-en-1-ol (103)

To an ice cold solution of 25 mg (0.13 mmol) of 102 in 2 mL of dry ether was added dropwise a suspension of 5 mg (0.13 mmol) of lithium aluminum hydride in 5 mL of ether. The mixture was stirred at 0°C for 1 h, then 5 mL of water was added and the aqueous phase was saturated with NaCl(s). The organic layer was removed and the aqueous layer was extracted with ether. The combined ether extracts and organic layer was washed with brine, and the solvent was evaporated to leave 22 mg (87%) of a pale yellow oil, 103: IR (neat) 3420, 3085, 1635, 1630, 1005 cm^{-1} ; NMR (CCl_4) δ 0.72 (3H, s), 1.08 (3H, s), 1.10 (3H, s), 1.2-1.5 (2H), 1.68 (3H, d, J=1.5Hz), 1.9 (2H, m), 1.98 (1H, bs), 3.67 (1H, d, J=6.5Hz), 4.90 (1H, dd, J=1.5,17Hz), 4.95 (1H, dd, J=1.5,10Hz), 5.47 (1H, dq, J=1.5,6.5Hz), 6.21 (1H, dd, J=10,17Hz).

2,5-Dimethylcyclohexenyl 2-Methylcyclopentenylmethyl Ether (39) and

3,6-Dimethylcyclohexenyl 2-Methylcyclopentenylmethyl Ether (105)

A mixture of 0.75 g (5.4 mmol) of 93 and 96, 0.65 g (5.9 mmol) of 79, 350 mg of $\text{Hg}(\text{OAc})_2$, 130 mg of NaOAc and 5 mL of dry benzene was refluxed under dry N_2 for 22 h, during which time 100 mg additions of $\text{Hg}(\text{OAc})_2$ were made at 1, 3.5, 4.5, 6, 8.5, and 12 h. The mixture was cooled and 700 mg of K_2CO_3 was added, and the mixture was stirred for 1 h. The mixture was filtered and the solvent was evaporated to leave

1.23 g of brown oil. Chromatography (CH_2Cl_2) led to a fraction of 110 mg (9.2%) of an oil, 39 and 105: NMR (CDCl_3) δ 0.8-2.5 (21.37H), 3.2-3.8 (2H, m), 4.5 (0.63H, m).

2,3-Trans-2-(1-Methyl-2-methylenecyclopentyl)-3,6-dimethylcyclohexanone (108) and 2,3-Cis-2-(1-Methyl-2-methylenecyclopentyl)-3,6-dimethylcyclohexanone (109)

Reaction exactly as above for 39 and 105 to yield 1.34 g of brown oil, which was taken up in dry xylenes and refluxed under dry N_2 for 48 h. The reaction was cooled and the solvent was evaporated. The residue was chromatographed (CH_2Cl_2) to yield 174 mg (15%) of yellow oil, 108: rf 0.49 (19:1, CHCl_3 :EtOH); BP 80-85°C/0.2 mm; IR (neat) 3075, 1700, 1645 cm^{-1} ; NMR (CCl_4) δ 0.96 (3H, s), 0.98 (3H, d), 1.00 (3H, d), 1.3-1.9 (8H), 2.1-2.5 (5H), 4.72 (1H, t, J=2Hz), 4.91 (1H, t, J=2Hz); MS m/e (relative intensity) 220 (M^+ , 8.7), 205 (1.4), 95 (100); Exact mass calcd. for $\text{C}_{15}\text{H}_{24}\text{O}$: 220.183; Found: 220.184; and 54 mg (4.5%) of an oil, 109: rf 0.62 (19:1 CHCl_3 :EtOH); BP 75-80°C/0.35 mm; IR (neat) 3050, 1705, 1640 cm^{-1} ; NMR (CCl_4) δ 0.94 (3H, d), 0.96 (3H, d), 0.98 (3H, s), 1.1-1.4 (2H, m), 1.5-1.9 (5H), 1.9-2.15 (2H, m), 2.2-2.6 (4H), 4.67 (1H, t, J=2Hz), 4.81 (1H, t, J=2Hz); MS m/e (relative intensity) 220 (M^+ , 11.9), 205 (4.5), 95 (100).

Trans-6-(1-Methyl-2-methylenecyclopentyl)-2,5-dimethylcyclohexenyl Trimethylsilyl Ether (110)

To a solution of 111 mg (1.1 mmol) of diisopropylamine in 3 mL of dry THF at -78°C under dry N_2 was added 0.5 mL (1.1 mmol) of 2.2 M nBuLi.

To the stirred solution was added a solution of 51 mg (0.23 mmol) of 108 in 2 mL of THF. The reaction was stirred at -78°C for 40 m, then 54 mg (1.1 mmol) of trimethylsilyl chloride was added and the reaction stirred for an additional 30 m at -78°C . The reaction was poured into 10 mL of cold sat. NaHCO_3 and 10 mL of hexane. The organic layer was removed, dried and the solvent was evaporated. The residual oil was purified by TLC (CH_2Cl_2) to leave 41 mg (61%) of an oil, 110: rf 0.76 (19:1 CHCl_3 :EtOH); IR (neat) 3060, 1675, 1645 cm^{-1} ; NMR (CCl_4) δ 0.19 (9H, s), 0.90 (3H, d), 1.17 (3H, s), 1.58 (3H, s), 1.0-2.5 (12H), 4.63 (1H, t, $J=1.5\text{Hz}$), 4.88 (1H, t, $J=1.5\text{Hz}$).

Cis-6-(1-Methyl-2-methylenecyclopentyl)-2,5-dimethyl-
cyclohexenyl Trimethylsilyl Ether (111)

Prepared exactly as 110 to yield 31 mg (46%) of 111: rf 0.74 (19:1 CHCl_3 :EtOH); IR (neat) 3075, 1680, 1645 cm^{-1} ; NMR (CCl_4) δ 0.18 (9H, s), 0.93 (3H, d), 1.18 (3H, s), 1.58 (3H, s), 1.0-2.5 (12H), 4.63 (1H, t, $J=1.5\text{Hz}$), 4.88 (1H, t, $J=1.5\text{Hz}$).

6-Acetoxy-4-carboethoxy-5-methylbicyclo[3.2.0]hept-3-en-2-one (138) and
7-Acetoxy-4-carboethoxy-5-methylbicyclo[3.2.0]hept-3-en-2-one (139)

A solution of 2.0 g (11.9 mmol) of 112 and 5.1 g (59.4 mmol) of vinyl acetate in ca. 125 mL of hexane was irradiated with a Pyrex-filtered 450 W medium pressure mercury lamp with N_2 bubbling through the solution for 1.5 h. The solvent was evaporated and the residual oil was taken up in 8 mL of CCl_4 , to which a solution of 1.52 g (9.4 mmol) of bromine in 4 mL of CCl_4 was added dropwise. A water aspirator vacuum

was installed and the reaction was stirred for 1.2 h, after which 1.3 g (12.0 mmol) of triethylamine was added and the reaction was refluxed for 2 h. The mixture was filtered and the filtrate was washed with 10% HCl, sat. NaHCO₃, brine and the solvent was evaporated. The residue was distilled to yield 1.99 g (67%) of yellow oil, 138 and 139: BP 115–120°C/0.1 mm; IR (neat) 3000, 1750 cm⁻¹; NMR (CDCl₃) δ 1.38 (3H, t), 1.5 (3H, m) 2.1–3.1 (6H, m), 4.36 (2H, q), 4.6–5.5 (1H, m), 6.75–7.0 (1H, m).

5-Acetoxy-7-carboethoxy-6-methyltricyclo[5.4.0.0^{3,6}]undec-8-ene-2,10-dione (146) and 4-acetoxy-7-carboethoxy-6-methyltricyclo[5.4.0.0^{3,6}]undec-8-ene-2,10-dione (147)

A solution of 0.5 g (1.98 mmol) of 138 and 139 and 1.3 g (7.55 mmol) of 145 in 4 mL of dry benzene was sealed in an ampule and heated at 200°C for 24 h. The reaction was cooled, and the contents of the tube were taken up in 10 mL of benzene, 100 mg p-toluenesulfonic acid was added and the solution was refluxed in a flask fitted with a Dean-Stark trap charged with 4A molecular sieves in the sidearm for 10 h. The cooled solution was washed with brine and the solvent was evaporated. The residue was chromatographed first by column (2% acetone/CH₂Cl₂) and then by TLC (2% acetone/CH₂Cl₂) to yield 240 mg (38%) of an oil, 146 and 147: IR (neat) 3050, 1750, 1740, 1735, 1688, 1645 cm⁻¹; NMR (CCl₄) δ 1.1–1.8 (6H, m), 1.9–2.1 (3H, m), 2.0–3.0 (4H), 3.8 (1H, m), 4.2 (2H, m), 4.7–5.5 (1H, m), 5.95 (1H, dd, J=2.0,10Hz), 6.82 (1H, dd, J=1.5,10Hz); MS m/e (relative intensity) 320 (M⁺, 1.4), 277 (5.1), 235 (19.0).

5-Acetoxy-7-carboethoxy-6-methyltricyclo[5.4.0.0^{3,6}]undecan-2,10-
dione (148) and 4-acetoxy-7-carboethoxy-6-methyltricyclo-
[5.4.0.0^{3,6}]undecan-2,10-dione (149)

A mixture of 98 mg (0.306 mmol) of 146 and 147 and 10 mg of 10% Pd/C in 6 mL of abs. ethanol was stirred under 1 atm. of H₂ until 15 mL of H₂ had been absorbed. The mixture was filtered through Celite and the solvent was evaporated to leave 90 mg (91%) of a clear oil, 148 and 149: IR (neat) 1750, 1740, 1715, 1700 cm⁻¹; NMR (CDCl₃) δ 1.1-1.7 (7H, m), 2.0 (3H, m), 2.1-3.1 (6H), 3.5-4.0 (1H, m), 4.2 (2H, m), 4.7-5.5 (1H, m); MS m/e (relative intensity) 322 (M⁺, 1.7), 279 (15.3), 237 (60.2).

5-Acetoxy-7-carboethoxy-6-methyl-10,10-ethylenedioxytricyclo[5.4.0.0^{3,6}]-
undecan-2-one (150) and 4-acetoxy-7-carboethoxy-6-methyl-10,10-
ethylenedioxytricyclo[5.4.0.0^{3,6}]undecan-2-one (151)

A solution of 90 mg (0.279 mmol) 148 and 149, 19.2 mg (0.322 mmol) of ethylene glycol, 2 mg of p-toluenesulfonic acid and 10 mL of benzene was refluxed in a flask fitted with a Dean-Stark trap for 68.5 h. The cooled reaction was washed with sat. NaHCO₃, brine, and the solvent was evaporated. The residue was chromatographed (acetone/CH₂Cl₂ gradient) to leave 49 mg (44%) of a clear gum, 150 and 151: IR (CHCl₃ film) 1740, 1735, 1720 cm⁻¹; NMR (CDCl₃) δ 1.2-1.6 (8H, m), 2.0 (3H, s), 2.1-2.8 (6H, m), 3.5 (1H, bs), 3.9 (4H, m), 4.2 (2H, m), 5.0-5.4 (1H, m); MS m/e (relative intensity) 366 (M⁺, 3.6), 337 (2.3), 323 (2.7), 281 (6.7).

[Exo-4-Carboethoxy-5-methyl-6-pivaloxybicyclo[3.2.0]hept-3-ene-2-one (154), Exo-4-Carboethoxy-5-methyl-7-pivaloxybicyclo[3.2.0]hept-3-ene-2-one (156)], [Endo-4-Carboethoxy-5-methyl-6-pivaloxybicyclo[3.2.0]hept-3-ene-2-one (155), and Endo-4-Carboethoxy-5-methyl-7-pivaloxybicyclo[3.2.0]hept-3-ene-2-one (157)]

A solution of 1.94 g (11.54 mmol) of 112 and 4.6 g (36 mmol) of vinyl pivalate in ca. 125 mL of pentane was irradiated with a Pyrex-filtered 450 W medium pressure mercury lamp, with N₂ bubbling through the solution for 1.5 h, with the entire apparatus immersed in a dry ice-acetone bath. The solvent was evaporated and the residue was taken up in 8 mL of CCl₄ and a solution of 1.59 g (10 mmol) of bromine in 4 mL of CCl₄ was added dropwise. The reaction was stirred for 2 h, and then 2.2 g (21 mmol) of triethylamine was added and the reaction was stirred for 1 h. The mixture was filtered and the filtrate was washed with 0.2 N HCl, sat. NaHCO₃, brine and the solvent was evaporated. The residue was distilled (BP 112-120°C/0.04 mm) to leave 1.07 g of a yellow semisolid. Medium pressure liquid chromatography (3' x 2.5 cm, 10% EtOAc/cyclohexane, FR = 8.6 mL/m) upon 3.0 g of material so obtained led to 780 mg (26%) of 154 and 156: NMR (CCl₄) δ 1.0-1.5 (15H, m), 2.0-3.0 (3H, m), 4.3 (2H, q), 4.5-5.0 (1H, m), 6.7 (1H, d, J=2Hz); and 646 mg (21%) of 155 and 157: NMR (CCl₄) δ 1.0-1.7 (15H, m), 2.0-3.2 (3H, m), 4.25 (2H, m), 5.0-5.4 (1H, m), 6.8 (1H, d, J=14Hz).

Exo-cis-anti-cis-7-Carboethoxy-6-methyl-5-pivaloxy-
tricyclo[5.4.0.0^{3,6}]undec-8-ene-2,10-dione (157)

A solution of 150 mg (0.51 mmol) of 154 and 156 and 255 mg (1.48 mmol) of 145 in 3 mL of dry benzene was sealed in an ampule and heated at 200°C for 20 h. The reaction was cooled and the contents of the tube were taken up in 5 mL of benzene, 10 mg of p-toluenesulfonic acid was added and the reaction was refluxed in a flask fitted with a Dean-stark trap charged with 4A molecular sieves in the sidearm for 20 h. The cooled reaction was washed with brine and the solvent was evaporated. The residue was chromatographed (2% acetone/CH₂Cl₂) to afford 57.4 mg of semisolid. Recrystallization from ether/pet. ether yielded 13.4 mg (14%) of white plates, 157: MP 130.5-131.5°C; IR (CHCl₃ film) 3020, 1735, 1680 cm⁻¹; NMR (CDCl₃) δ 1.21 (9H, s), 1.28 (3H, t), 1.52 (3H, s), 2.3-2.6 (3H, m), 2.60 (1H, dd, J=7.0,17.5Hz), 3.05 (1H, dd, J=2.5,17.5Hz), 3.90 (1H, ddd, J=1.5,2.5,7.0Hz), 4.25 (2H, q), 5.39 (1H, ddd, J=1.5,7.0, 7.0Hz), 6.02 (1H, dd, J=1.0,10Hz), 6.88 (1H, dd, J=1.5,10Hz); MS m/e (relative intensity) 362 (M⁺, 10.5), 335 (2.8), 278 (20.8); Exact mass calcd. for C₂₀H₂₆O₆: 362.176; Found: 362.173.

Exo-cis-anti-cis-7-Carboethoxy-5-methyl-5-pivaloxy-
tricyclo[5.4.0.0^{3,6}]undecan-2,10-dione (160)

A mixture of 50 mg (0.38 mmol) of 157 and 6 mg of 5% Pd/C in 5 mL of abs. ethanol was stirred under 1 atm. of H₂ for 2 h. The mixture was filtered through Celite and the solvent was evaporated. The residue was chromatographed (2% acetone/CH₂Cl₂) to leave 48.3 mg (96%) of white solid, 160: MP 120.5-122°C (recrystallized from ether/pet. ether);

IR (CHCl₃ film) 1735 cm⁻¹; NMR (CDCl₃) δ 1.20 (9H, s), 1.36 (3H, s), 1.2-1.6 (4H), 2.1-3.0 (8H, m), 3.88 (1H, dt, J=2,8Hz), 4.30 (2H, q), 5.40 (1H, m).

Exo-cis-anti-cis-7-Carboethoxy-6-methyl-5-pivaloxy-10,10-ethylenedioxytricyclo[5.4.0.0^{3,6}]undecan-2-one (161)

A solution of 48 mg (0.132 mmol) of 160, 9.8 mg (0.16 mmol) of ethylene glycol, 2 crystals of p-toluenesulfonic acid and 20 mL of benzene was refluxed in a flask fitted with a Dean-Stark trap for 29 h. The cooled reaction was washed with sat. NaHCO₃, brine, and the solvent was evaporated. The residue was chromatographed (4% acetone/CH₂Cl₂) to leave 44.1 mg (82%) of white solid, 161: MP 111.5-113.0°C; IR (CHCl₃ film) 1735 cm⁻¹; NMR (CDCl₃) δ 1.18 (9H, s), 1.36 (3H, s), 1.2-2.0 (6H, m), 2.1-2.7 (6H, m), 3.5 (1H, dd, J=2,7Hz), 3.9 (4H, m), 4.24 (2H, q), 5.3 (1H, m); MS m/e (relative intensity) 410 (M⁺, 10), 379 (5.1), 365 (16.2), 281 (29.8).

Cis-4a-Carbomethoxy-7-ethoxy-4a,5,8,8a-tetrahydrocoumarin (163)

A solution of 0.5 g (3.25 mmol) of 116 and 0.637 g (6.5 mmol) of 2-ethoxybutadiene in 12 mL of dry benzene was sealed in an ampule and heated at 100°C for 20 h. The reaction was cooled, the ampule was opened and the solvent was evaporated to leave a yellow solid. Chromatography (CH₂Cl₂/ether gradient) gave 0.65 g (79%) of a white powder, 163: MP 105-106°C; IR (nujol) 3000, 1745, 1725, 1670 cm⁻¹; NMR (CDCl₃) δ 1.28 (3H, t), 2.18 (1H, m), 2.34 (1H, m), 2.74 (1H, m), 2.91 (1H, m), 3.73 (1H, m), 3.78 (3H, s), 4.63 (1H, m), 5.03 (1H, m), 6.05 (1H, d,

$J=9.5\text{Hz}$), 6.92 (1H, d, $J=9.5\text{Hz}$); MS m/e (relative intensity) 252 (M^+ , 7.9), 98 (47.2); Exact mass calcd. for $C_{13}H_{16}O_5$: 252.100 Found: 252.100.

Cis-4a-Carbomethoxy-7-oxo-4a,5,6,7,8,8a-hexahydrocoumarin (164)

To a solution of 102 mg (0.4 mmol) of 163 in 5 mL of acetone at ice temperature was added 10 mL of 10% HCl and the solution was stirred at ice temperature for 2 h, then 300 mg of $K_2CO_3(s)$ was added and the mixture was stirred for 30 m. The mixture was filtered, the solvent was evaporated and the residue was recrystallized from acetone/cyclohexane to furnish 69 mg (77%) of white needles, 164: MP 119°C (dec.); IR (nujol) 3050, 1740, 1710, 1700 cm^{-1} ; NMR ($CDCl_3$) δ 2.0-2.65 (4H), 2.75 (1H, dd, $J=3,16\text{Hz}$), 2.99 (1H, dd, $J=4,16\text{Hz}$), 3.91 (3H, s), 5.22 (1H, ddd, $J=1.5,3,4\text{Hz}$), 6.11 (1H, d, $J=9.5\text{Hz}$), 7.05 (1H, d, $J=9.5\text{Hz}$); MS m/e (relative intensity) 224 (M^+ , 3.4), 196 (16.9).

Cis-4a-Carbomethoxy-7,7-ethylenedioxy-
4a,5,6,7,8,8a-hexahydrocoumarin (166)

A solution of 0.63 g (4.1 mmol) of 116 of 0.81 g (8.2 mmol) of 2-ethoxybutadiene in 6 mL of dry benzene was sealed in an ampule and heated at 100°C for 20 h. The reaction was cooled, the tube was opened and the contents of the tube were taken up in 25 mL of benzene, 500 mg (8.0 mmol) of ethylene glycol and 3 crystals of p-toluenesulfonic acid were added, and the resultant solution was refluxed in a flask fitted with a Dean-Stark trap charged with 4A molecular sieves in the sidearm for 2 h. The reaction was cooled and washed with sat. $NaHCO_3$, brine and the solvent was evaporated. The residue was recrystallized from

CH₂Cl₂/hexane to yield 555 mg (50%) of yellow prisms, 166: MP 131-133.5°C; IR (CHCl₃ film) 3025, 1730 cm⁻¹; NMR (CDCl₃) δ 1.65 (2H, m), 1.99 (1H, dd, J=10,14Hz), 2.26 (1H, dd, J=5,14Hz), 2.1 (2H, m), 3.8 (3H, s), 4.0 (4H, s), 5.15 (1H, ddd, J=1.5,5,10Hz), 6.15 (1H, d, J=10Hz), 6.75 (1H, dd, J=1.5,10Hz); MS m/e (relative intensity) 268 (M⁺, 0.9), 240 (2.4), 154 (24.0).

Cis-4a-Carbomethoxy-3-methyl-7,7-ethylenedioxy-
2,3,4a,5,6,7,8,8a-octahydrocoumarin (167)

To a mixture of 800 mg (4.17 mmol) of CuI in 25 mL of dry ether at 0°C under dry N₂ was added 6.5 mL of 1.8 M CH₃Li. To the homogeneous solution was added dropwise a solution of 800 mg (3.0 mmol) of 166 in 20 mL of dry THF. The reaction was stirred at 0°C for 20 m and then 50 mL of NH₃/sat. NH₄Cl (pH = 8.0) buffer was added. The aqueous portion was removed and the organic phase was washed with sat. Na₂S₂O₃ and the solvent was evaporated to leave 680 mg of a heavy oil, 167: IR (neat) 1740 cm⁻¹; NMR (CDCl₃) δ 1.05 (3H, d), 1.2-2.6 (9H), 3.78 (3H, s), 3.96 (4H, bs), 4.98 (1H, dd, J=6,6Hz); MS m/e (relative intensity) 284 (M⁺, 0.7), 253 (5.0).

Cis-4a-Carbomethoxy-3-methyl-7,7-ethylenedioxy-
4a,5,6,7,8,8a-hexahydrocoumarin (118)

To a solution of 420 mg (4.16 mmol) of diisopropylamine in 10 mL of dry THF under dry N₂ at -78°C was added 2.58 mL of 1.6 M nBuLi and then a solution of 1.0 g (3.4 mmol) of 167 in 15 mL of dry THF was added dropwise. The reaction was stirred at -78°C for 2 h and then a solution

of 0.79 g (4.16 mmol) of phenylselenenyl chloride and 744 mg (4.16 mmol) of hexamethylphosphoramide in 10 mL of dry THF was added rapidly. The reaction was stirred at -78°C for 2 h, warmed to RT and 25 mL of sat. NH_4Cl and 25 mL of ether were added. The aqueous portion was removed and the organic phase was washed with 0.1 N HCl, sat. NaHCO_3 , water, brine and the solvent was evaporated. The residue was taken up in 50 mL of THF and 0.25 mL of glacial acetic acid and 1 mL of 30% H_2O_2 was added and the reaction was stirred at RT for 1 h. The reaction was poured into 25 mL of sat. NaHCO_3 and 25 mL of ether. The aqueous portion was removed and the organic phase was washed with brine and the solvent was evaporated. The residue was chromatographed ($\text{CH}_2\text{Cl}_2 \rightarrow 10\%$ ether/ CH_2Cl_2) to yield 0.766 g (79%) of a red oil, 118: IR 1735, 1640 cm^{-1} ; NMR (CDCl_3) δ 1.1 (2H, m), 1.65 (2H, m), 1.9-2.4 (5H, m), 3.84 (3H, s), 4.04 (4H, s), 5.1 (1H, dd, $J=6,8\text{Hz}$), 6.02 (1H, bs).

Cis-anti-cis-8-Carbomethoxy-7-methyl-11,11-ethylenedioxy-
2-oxatricyclo[6.4.0.0^{4,7}]dodec-5-en-3-one (173)

A solution of 0.65 g (2.3 mmol) of 118 in ca. 125 mL of dry ether was irradiated through a Vycor filter with a 450 W medium pressure mercury lamp with a stream of acetylene bubbling through the solution for 1 h. The solvent was evaporated and the residue was chromatographed (5% ether/ CH_2Cl_2) to yield 361 mg (50.9%) of yellow oil, 173: IR (neat) 1725 cm^{-1} ; NMR (CDCl_3) δ 1.27 (3H, s), 0.8-2.5 (6H), 3.27 (1H, t, $J=1.0\text{Hz}$), 3.78 (3H, s), 4.0 (4H, m), 4.95 (1H, ddd, $J=0.5,4,4\text{Hz}$), 6.24 (1H, dd, $J=1.0,3.0\text{Hz}$), 6.35 (1H, dd, $J=1.0,3.0\text{Hz}$); MS m/e (relative intensity) 308 (M^+ , 1.1), 235 (3.2), 99 (100); Exact mass calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_6$: 308.126; Found: 308.128.

Spiro[1-methyl-4-oxabicyclo[4.2.0]oct-7-en-5-ol-
2,1'-4,4-ethylenedioxcyclohexan-2-ol] (174)

To a solution of 63 mg (0.2 mmol) of 173 in 2.5 mL of dry toluene under dry N₂ was added 1 mL of 1 M diisobutylaluminum hydride. The reaction was stirred at -78°C for 30 m, and then 3 mL of 1:2 acetic acid:water was added, the reaction warmed to RT and 5 mL of brine was added. The mixture was extracted with chloroform and the combined extracts were washed with sat. NaHCO₃, brine and the solvent was evaporated to leave 49 mg (81%) of an oil, 174: IR 3450, 1100 cm⁻¹; NMR (CDCl₃) δ 1.30 (3H, s), 1.0-2.5 (8H), 2.62 (1H, dd, J=0.5,2Hz), 3.5 (1H, d, J=9Hz), 3.95 (4H, s), 4.12 (1H, d, J=9Hz), 4.2 (1H, m), 5.22 (1H, d, J=2Hz), 6.10 (1H, d, J=3Hz), 6.50 (1H, dd, J=0.5,3Hz).

Spiro[1-methyl-4-oxabicyclo[4.2.0]oct-7-en-5-ol-
2,1'-4-oxocyclohexan-2-ol] (175)

A solution of 65 mg (0.23 mmol) of 174 in 3 mL of 97% formic acid was stirred for 1.5 h, and then 5 mL of water was added and the solution was extracted with ether. The combined extracts were washed with sat. NaHCO₃, brine and the solvent was evaporated. The residue was chromatographed to give 16 mg (29%) of a yellow solid, 175: NMR (CDCl₃) δ 1.2 (3H, m), 1.36 (3H, s), 1.8-2.4 (3H, m), 2.7 (1H, dd, J=1.0,2.5 Hz), 2.80 (1H, ddd, J=1.5,7,16Hz), 3.12 (1H, dd, J=10,16Hz), 3.5 (1H, d, J=9Hz), 4.12 (1H, d, J=9Hz), 4.18 (1H, dd, J=7,10Hz), 5.27 (1H, d, J=3Hz), 6.19 (1H, d, J=2.5Hz), 6.48 (1H, dd, J=0.5,3Hz).

Spiro[1-methyl-8-formyloxy-4-oxabicyclo[3.2.1]oct-6-ene-
2,1'-cyclohex-2-en-4-one] (176)

A solution of 49 mg (0.19 mmol) of 174 in 2 mL of anhydrous HCO_2H was stirred at 70°C for 45 m. To the cooled reaction was added 5 mL of brine and the mixture was extracted with chloroform. The combined extract were washed with sat. NaHCO_3 , brine and the solvent was evaporated to leave 46 mg (97%) of an oil, 176: IR (neat) 1780, 1725, 1685 cm^{-1} ; NMR (CDCl_3) δ 1.12 (3H, s), 1.2-1.6 (2H, m), 2.0-3.0 (2H, m), 3.60 (1H, d, $J=12\text{Hz}$), 3.82 (1H, d, $J=12\text{Hz}$), 4.20 (1H, dd, $J=3,9\text{Hz}$), 4.62 (1H, d, $J=9\text{Hz}$), 6.03 (1H, d, $J=10\text{Hz}$), 6.16 (1H, dd, $J=3,6\text{Hz}$), 6.36 (1H, d, $J=6\text{Hz}$), 6.45 (1H, d, $J=10\text{Hz}$); MS m/e (relative intensity) 248 (M^+ , 0.6), 205 (16.5), 203 (2.1).

Cis-anti-cis-8-Hydroxymethyl-7-methyl-11,11-ethylenedioxy-
2-oxatricyclo[6.4.0.0^{4,7}]dodec-5-en-3-ol (177)

To a solution of 50 mg (0.16 mmol) of 173 in 2 mL of dry toluene at -78°C under dry N_2 was added 0.75 mL of 1 M diisobutylaluminum hydride. The reaction was stirred at -78°C for 30 m, and then 2 mL of dry methanol was cautiously added. The reaction was allowed to come to RT and stirred for an additional 15 m. The resulting gelatinous precipitate was removed by filtration and the filtrate was evaporated to leave 33 mg (73%) of a clear oil, 177: IR (neat) 3440, 1100 cm^{-1} ; NMR (CDCl_3) δ 1.0-2.2 (10H), 2.70 (1H, d, $J=7\text{Hz}$), 3.4-3.8 (2H, m), 4.00 (4H, s), 5.0-5.2 (1H, m), 5.30 (1H, d, $J=7\text{Hz}$), 6.35 (2H, s).

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