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Synthetic approaches toward 12,13-epoxytrichothecenes

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SYNTHETIC APPROACHES TOWARD 12,13-EPOXYTRICHOTHECENES

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Synthetic approaches toward 12,13-epoxytrichothecenes

by

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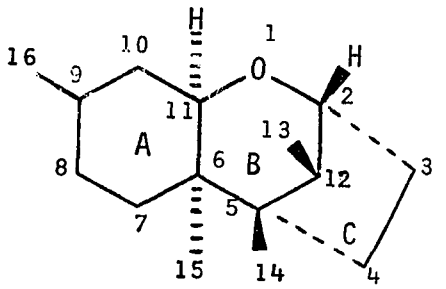
INTRODUCTION

The challenges encountered in the synthesis of complex organic molecules are much like those encountered in piecing together a jig-saw puzzle. As one attempts to complete a puzzle, many combinations of pieces must be tried until the correct piece fits into place. Also with organic synthesis, one attempts to piece together the carbon framework to achieve a "correct fit". Functionality and stereochemistry as well become pieces of that puzzle. In one sense, organic synthesis is even more difficult than a jig-saw puzzle. The inability to find the correct "piece" of the synthetic puzzle at one point may require one to back up and remove several "pieces" that had already been assembled. This backtracking is necessary to find new "pieces" that will allow completion of the puzzle.

The synthesis of the epoxytrichothecene skeleton has indeed been a difficult puzzle to assemble. This dissertation recounts the many "pieces" that have been assembled and the many "pieces" that have not fit in the working of this puzzle.

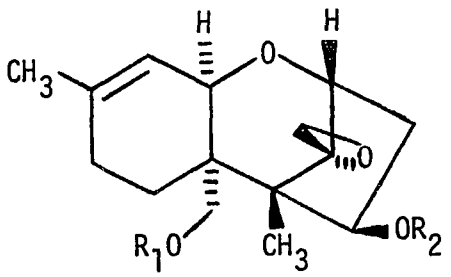
HISTORICAL

The trichothecanes are a class of closely related sesquiterpenoids produced by various species of imperfect fungi (1). Trichothecane (1), the sesquiterpene skeleton, illustrates the stereochemistry and the correct numbering system for this family of natural products.



1

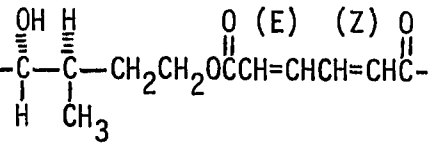
All the naturally occurring trichothecanes possess an olefinic bond between carbons 9 and 10, as well as an epoxide at carbons 12 and 13. Thus, these compounds are classified as 12,13-epoxytrichothecenes. A representative sampling of the epoxytrichothecenes is presented below.

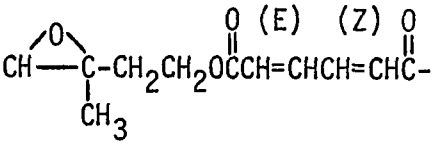


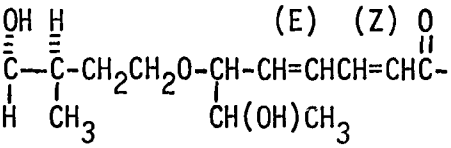
2

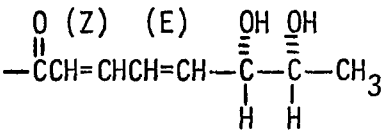
a $R_1=R_2=H$, verrucarol

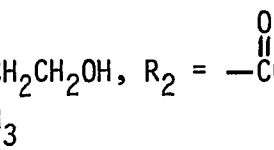
b $R_1=R_2=Ac$, diacetylverrucarol (2)

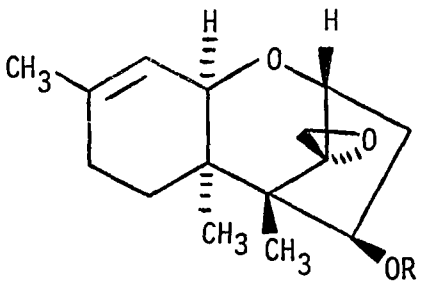
c $R_1, R_2 =$  verrucarin A (3,4)

d $R_1, R_2 =$  verrucarin B (3,5)

e $R_1, R_2 =$  roridin A (3,6)

f $R_1 = H, R_2 =$  trichoverrol A (7)

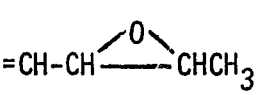
g $R_1 =$  , $R_2 =$ trichoverrin A (7)



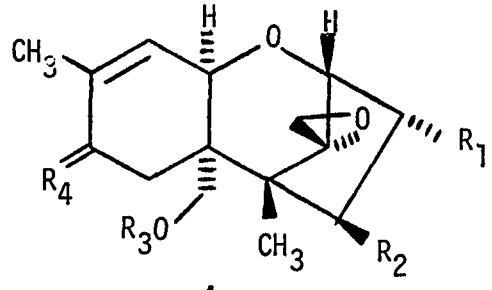
3

a R=H trichodermol (roridin C) (3)

b R=Ac trichodermin (8)

c R=  trichodermadiene (7,9)

(Z) (E) (R) (R)



4

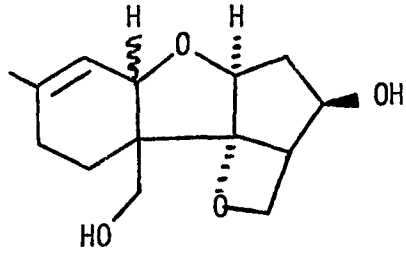
a R_1=OH, R_2=OAc, R_3=Ac, R_4=H,H — anguidin (10)

b R_1=OAc, R_2=H, R_3=Ac, R_4=H,H — calonectrin (11)

c R_1=H, R_2= —OCCH=CHCH$_3$, R_3=Ac, R_4=O — trichothecin (12)

The discovery of the first trichothecenes dates back to 1946 when, in the extensive post World War II search for new antibiotics, Brian and McGowan reported the isolation of Glutinosin (13). This was later found to be a mixture of verrucarins A and B: (2c&d) (14). Trichothecin was the first member of this class to be isolated in pure form in 1948 (12b).

Structural elucidation of the trichothecenes lagged far behind isolation studies. Gutzwiller and Tamm in 1963 proposed structure 5 for verrucarol (15). Verrucarol is not actually produced by any fungus; rather, it is the product obtained from the basic hydrolysis of the

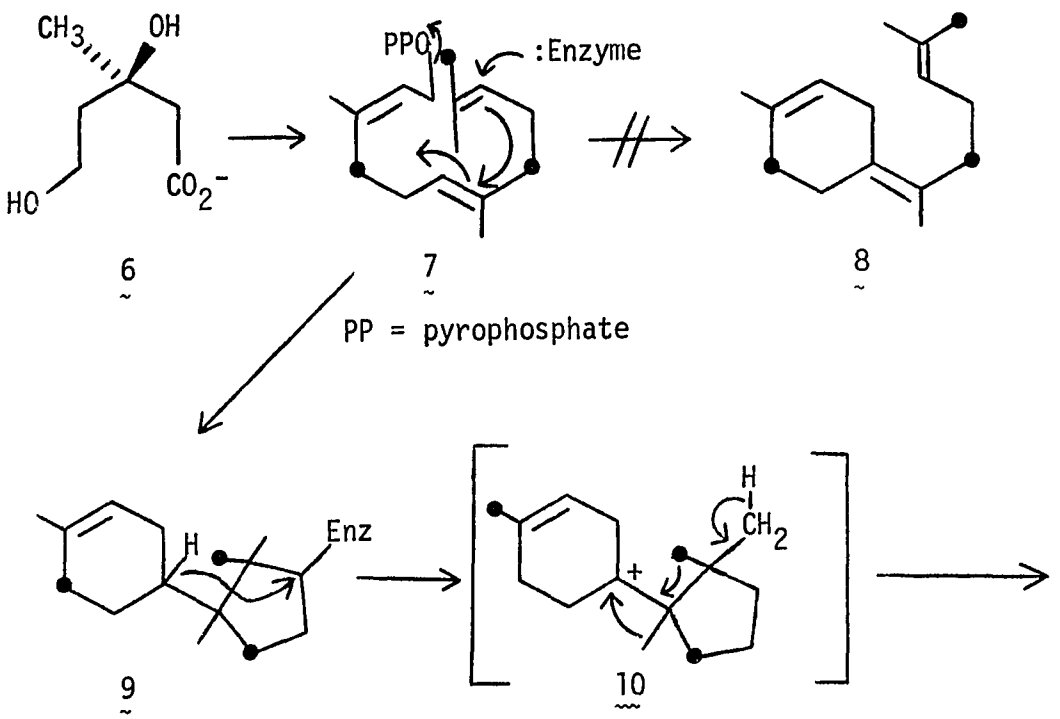


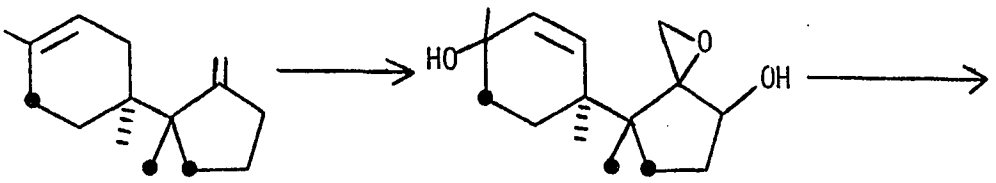
5

macrocyclic verrucarins and roridins (1a). Only after x-ray analysis of the p-bromobenzoate of trichodermol (3a) was the correct trichothecene skeleton established (16). The structures of all the trichothecenes have since been proven by interconversion to known trichothecene derivatives which were in turn related to the structure of trichodermol.

Gutzwiller and Tamm were not totally in error, however. Structure 5 corresponds to the apotrichothecene skeleton which is produced via acid catalyzed rearrangement of the trichothecene system (17). This rearrangement is just one of a great many that the trichothecenes undergo under a variety of conditions (1a).

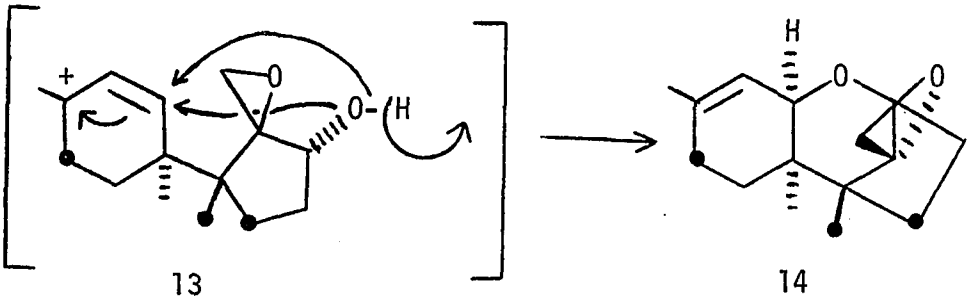
Studies into the biogenesis of the trichothecene skeleton are numerous and several pathways have been put forward (1e, 7, 18-21). The presently accepted biosynthetic route is shown below (1b,e).





trichodiene
11

trichodiol
12



13

14

Feeding studies with labeled geranyl pyrophosphate, farnesyl pyrophosphate (7) and trichodiene (11) resulted in the incorporation of the labeled carbons as indicated (18b,c,f; 19). It was originally postulated that γ-bisabolene (8) was involved in the biosynthetic pathway (10a, 20). However, more recent studies have shown low incorporation and extensive degradation of labeled α- and γ-bisabolene into cultures of Trichothecium roseum (19, 21), thus discounting the likelihood of such an intermediate.

Much less is known about the biogenesis of the macrocyclic trichothecenes (1a,c). However, the recent isolation of the trichodermadienes, trichodermadiols, trichoverrols, and trichoverrin by Jarvis and coworkers suggest basic intermediates (7). Additionally, Jarvis et al. have obtained some evidence that these compounds are biologically converted to the macrocyclic compounds.

The great interest in the epoxytrichothecenes stems from the numerous and varied biological activities of this family of compounds. It was as a result of the antibiotic activity that Glutinosin was first isolated (vide supra). This subject has been reviewed extensively (1a,b) and will only be highlighted here.

To date, verrucarin A (2c) is the only trichothecene known to possess antibacterial activity (3a). However, all trichothecenes demonstrate fungistatic properties, many being effective at low concentrations (1a). Limited research concerning antiviral activities has shown trichothecin (4c) to be an inhibitor of plant viral infections (22). Likewise, verrucarin A was found effective against Herpes simplex virus strain (HSV) (23).

All of the trichothecenes are potent toxins. Increasing awareness of mycotoxicoses has led to the probable involvement of several trichothecenes in actual field cases of mycotoxin diseases affecting cattle, horses, poultry and swine which had been fed moldy feed (24). The lethal dose (LD_{50}) values have been determined for oral, intraperitoneal, intravenous and subcutaneous administration of many of the naturally occurring trichothecenes (1a, 3a, 10d, 25). These studies indicate that the verrucarins and roridins are among the most toxic compounds known which do not contain nitrogen. Also, very dilute solutions of verrucarins and roridins, when applied to the skin of laboratory animals and man, caused severe local irritation, inflammation and in some cases lesions and eventual loss of skin (10d, 25a, 26).

By far the most significant aspect of the biological properties exhibited by the trichothecenes is their cytostatic activity. Harri and coworkers studied various verrucarins and roridins for cytostatic effects on mouse tumor cells (P-815) (3a). All the compounds tested proved to be effective; and verrucarin A (2c), with a 50% inhibition of tumor cell growth at 0.6 ng/ml, is one of the most potent cytostatic agents known. Verrucarin A has also exhibited *in vivo* cytostatic activity against a variety of laboratory sarcomas, carcinomas and tumors (3a, 27).

Anguidin (4a) also displays cytostatic characteristics. Loeffler *et al.* reported that anguidin prevents mitosis of certain strains of cells and that it could be used against blood diseases and tumors (25b). Stähelin and coworkers have also reported that anguidin has a moderate to fairly strong inhibitory effect on tumor growth in mice and rats (28). Several naturally occurring trichothecenes and some of their alcohol derivatives were tested by Strong *et al.* (1a, 29). They found no inhibition of L cells (normal mouse fibroblasts) by any of the compounds at the concentrations tested. However, KB (human epidermal carcinoma) and L1210 (leukemia) cells were markedly inhibited by several compounds (*e.g.*, anguidin).

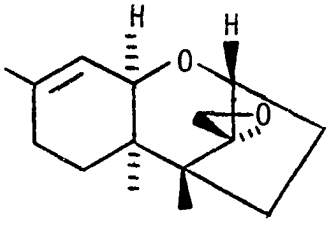
The exact mechanism of action of the trichothecenes on a molecular basis has been studied extensively (30, 31). Ueno and workers in 1968 reported the inhibition of protein synthesis by trichothecenes in cell free protein synthesizing systems and cultured cells (30a). Presently, it is known that certain trichothecenes inhibit polypeptide chain

initiation steps whereas others interfere with the elongation steps of eukaryotic protein synthesis (30b,c,d). DNA replication is also inhibited by certain trichothecenes. This inhibition is presumably due to the inhibition of the synthesis of necessary enzymes (31).

Relatively little work has been done to establish structure-activity relationships (1a, 32). It is apparent that free sesquiterpene alcohols are not as active as are esterified compounds (1a). The 12,13-epoxide is also intricately involved in biological activity (32), since removal of the epoxide by reduction with lithium aluminum hydride leads to inactive materials. Further, derivatives in which the epoxide remained but which had ring C altered so as to permit nucleophilic attack on the rear side of the epoxide were inactive. Additional molecular features are also important, notably the 9,10-olefinic functionality. Jarvis et al. have recently reported peculiar results (9). Epoxidation of the 9,10-double bond results in marked increases in antitumor activities (P388 mouse leukemia) for the macrocyclic verrucarins and roridins, while similar epoxidation in the simple trichothecenes results in a great diminution of activity. Grove and Mortimer have also demonstrated that the unsaturation of the macrocyclic compounds aids considerably in enhancing cytostatic activity (32). Such relationships between structure and activity will become clearer as more derivatives and analogs are prepared and tested (33).

The biological activities in conjunction with the structural complexities of the epoxytrichothecenes have combined to make these compounds extremely attractive targets for synthetic organic chemists.

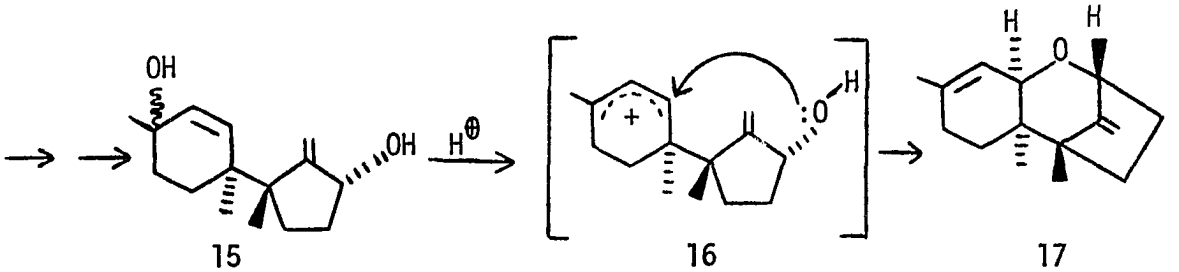
The synthesis of verrucarol (2a), in particular, is of interest as it would provide an entry into synthetic schemes directed toward the macrocyclic verrucarins. The cytostatic properties of anguidin (4a) have also made it a very attractive synthetic target. To date, the structural complexities of verrucarol and anguidin have thwarted all attempts at successful syntheses. However, successful total syntheses have been reported for some of the simpler epoxytrichothecenes; these include the basic epoxytrichothecene skeleton (±)-12,13-epoxy-Δ^9-trichothecene (14) (34, 35), (±)-trichodermol (3a) (36, 37) and some aromatic A-ring analogs (38).



14

Two general synthetic routes have been developed for preparing the tricyclic skeleton of the trichothecenes. One scheme is modeled along the biogenetic pathway (Scheme I) (35, 37, 39, 40). Other researchers

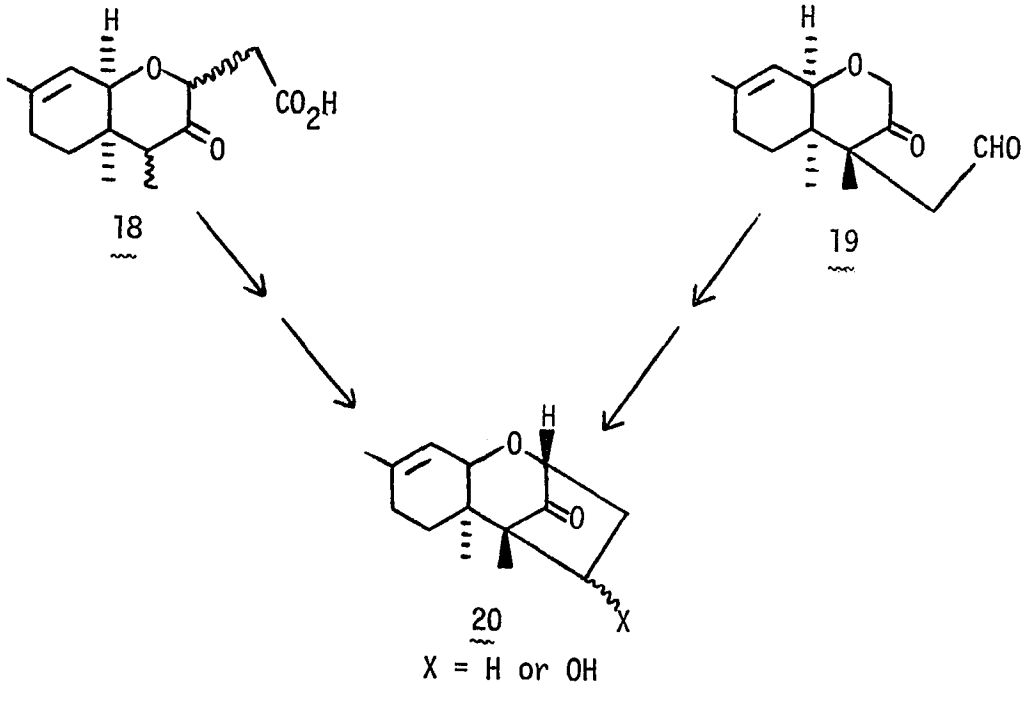
Scheme I



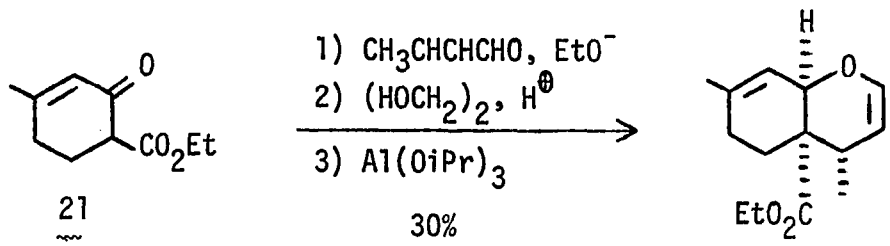
15 16 17

have prepared the tricyclic system utilizing variously substituted β-keto ethers (Scheme II) (34, 35, 41, 42).

Scheme II

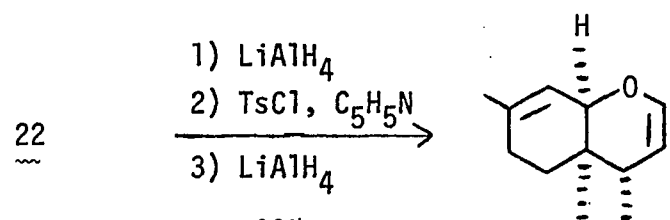


Fujimoto et al. employed a β-keto ether as a key intermediate in the first reported synthesis of (±)-12,13-epoxy-Δ^9-trichothecene (14) (34). The β-keto ester 21 was quickly converted to the dihydropyran 22. Remarkably, Meerwein-Ponndorf reduction of the intermediate enone acetal afforded 22 directly. Analysis of the proton NMR revealed that the ring fusion was exclusively cis. Furthermore, the C-4 methyl was exclusively cis to the carboethoxy group. Although the



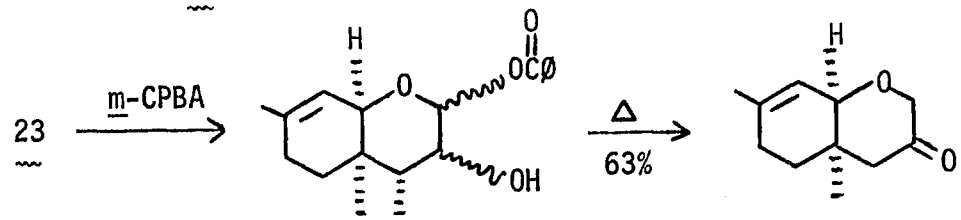
21 22

carboethoxy functionality appears to be primed for conversion to the C-15 hydroxymethyl of verrucarol, Fujimoto et al. chose at this point to reduce the ester of 22 to a methyl group. No comment was made concerning the rationale behind this transformation.



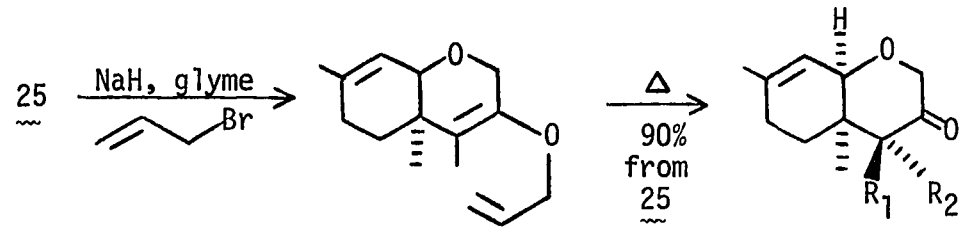
22 23

Treatment of 23 with m-chloroperbenzoic acid resulted in selective epoxidation of the enol ether. The intermediate epoxide underwent nucleophilic attack in situ to produce a mixture of diastereomeric benzoates 24. Ester pyrolysis subsequently afforded the β-keto ether 25.



23 24 25

The introduction of the trichothecene C-ring was accomplished via a five step sequence. Unexpectedly, alkylation of 25 resulted in exclusive formation of the O-alkylated enol ether 26. However, the allyl enol ether underwent a Claissen rearrangement to produce a mixture of diastereomers (27a:27b; 2:1). The desired compound 27a

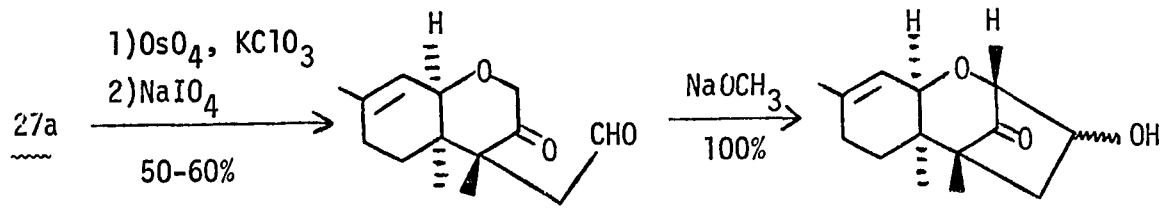


26

27a $R_1=CH_3$, $R_2= -CH_2CH=CH_2$

27b $R_1=CH_2CH=CH_2$, $R_2=CH_3$

was then converted via standard reactions to the aldehyde 28. Base catalyzed intramolecular aldol condensation produced the tricyclic skeleton quantitatively.

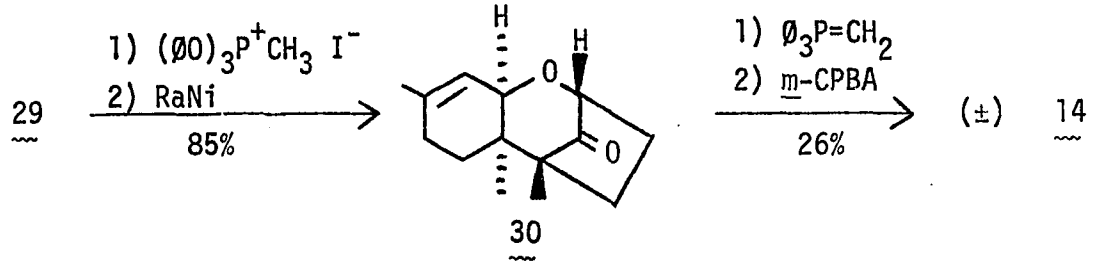


28

29

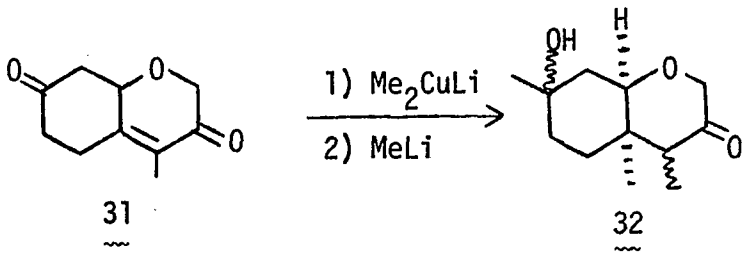
The alcohol 29 was then reduced via an intermediate iodide to yield ketone 30. A Wittig reaction and epoxidation produced the desired epoxytrichothecene (±) 14 in low yield. Notably, treatment of 30 with dimethyloxosulfonium methylide afforded the 12,13-epoxide epimeric to

14. The overall yield of 14 was less than 0.5% from β-keto ester 21.



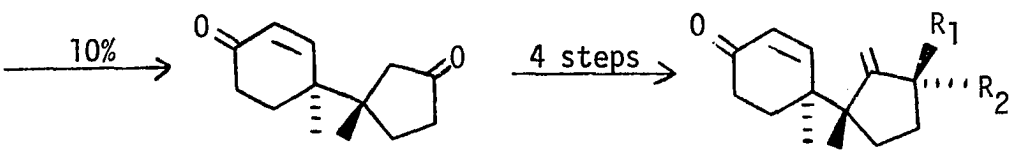
Goldsmith et al. (43) had previously reported the synthesis of a compound which appears to be a suitable precursor to the β-keto ether (25) employed by Fujimoto and coworkers. The reaction scheme is of note for its elegant use of an enolate as a means of protecting a carbonyl unit.

Conjugate addition of lithium dimethylcuprate to the diketone 31 introduced the C-15 methyl of the epoxytrichothecenes. The enolate so generated was then reacted with excess methyl lithium to produce, upon workup, the tertiary alcohol 32.



It is now known that dehydration of tertiary alcohols in similar systems will yield predominantly the endocyclic 9,10-olefin (trichothecene nomenclature) (42). Therefore, it would seem that the Fujimoto et al. intermediate 25 could be prepared via this route.

A second complete synthesis of (±) 14 has also been reported by Masuoka and Kamikawa (35). This work employed the biomimetic scheme to produce the trichothecene skeleton. These workers chose as starting material the diketone 33 which is available from the photochemical reaction of 4-methyl-cyclohex-3-en-1-one, ethylene ketal with 3-methyl-cyclopent-2-en-1-one and subsequent acid catalyzed rearrangement. 33 was converted in a four step sequence to the diastereomeric allylic acetates 34 and 35. Basic hydrolysis of the acetates produced alcohol

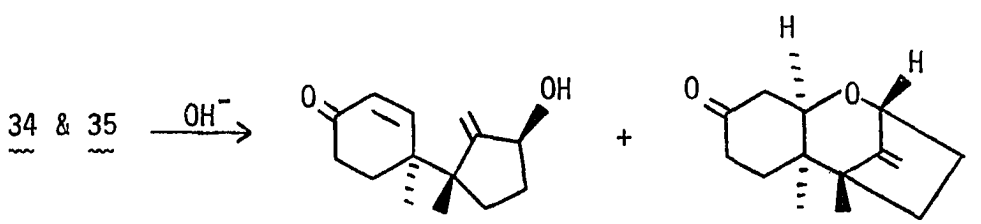


33

34 R_1=OAc R_2=H

35 R_1=H R_2=OAc

36 and a minor amount of the tricyclic 37. Model studies had already indicated that only the alcohol leading to the cis-fused ring system was capable of cyclization (44). Thus, the product ratio of 60% to 12% roughly reflected the ratio of the diastereomers 34:35.



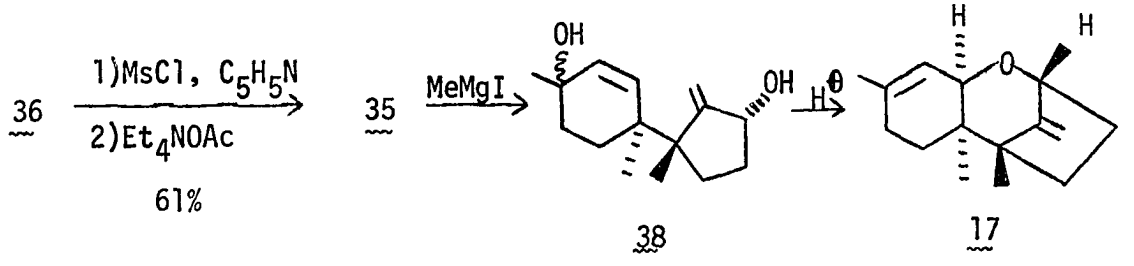
36

60%

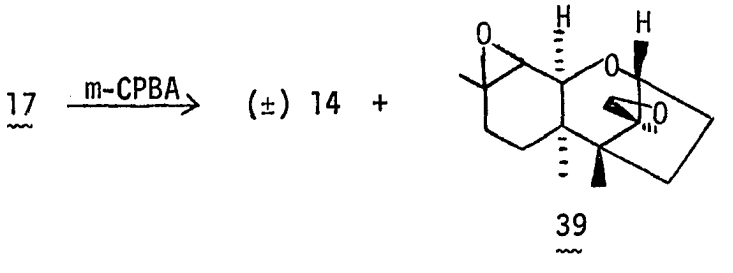
37

12%

Although 37 appears ripe for transformation to the desired epoxytrichothecene, no further mention is made with respect to such a reaction sequence. Rather, the authors epimerized the allylic alcohol position of 36 using conventional methods. The allylic acetate 35 so obtained was subsequently treated with methyl Grignard to afford diol 38. The diol 38, when treated with acid, produced the tricyclic diene 17.

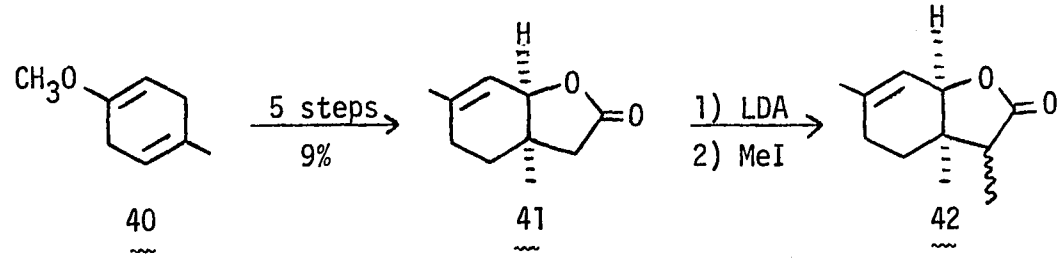


Masuoka and Kamikawa found that epoxidation of 17 then led to a 1:1 mixture of (±) 14 and the epoxide 39. This lack of regiocontrol in the epoxidation had not been reported by Fujimoto et al., although they reported only a 30% conversion of diene 38 to (±) 14. The synthesis of Masuoka and Kamikawa, although shorter and perhaps more elegant, proceeded in an overall yield almost identical to that obtained by Fujimoto and coworkers.



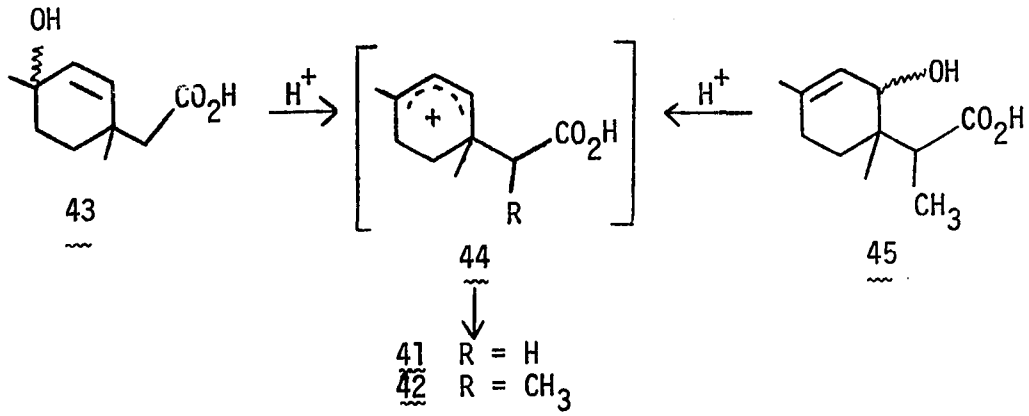
The synthesis of trichodermol (3a) could be considered as being one level of difficulty above the synthesis of (±) 14. The greater difficulty arises from the introduction of a C-4 hydroxyl group. To date, two routes to trichodermol have appeared.

The first preparation of trichodermol in 1973 was also the first synthesis of the trichothecene skeleton (36). Colvin et al. started with diene 40 which was then converted to the cis-fused γ-lactone 41 in five steps. Subsequent methylation afforded lactone 42. Welch and Wong have since reported an improved procedure for obtaining 42 (45). This reaction sequence proceeded in 56% yield and produced the γ-lactone in optically active form.

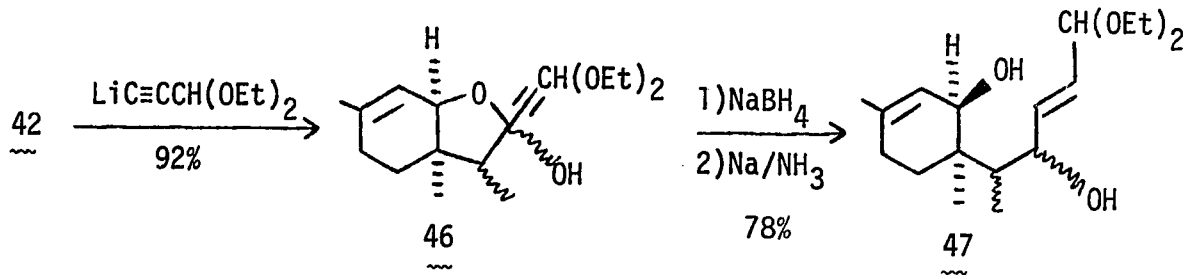


40 41 42

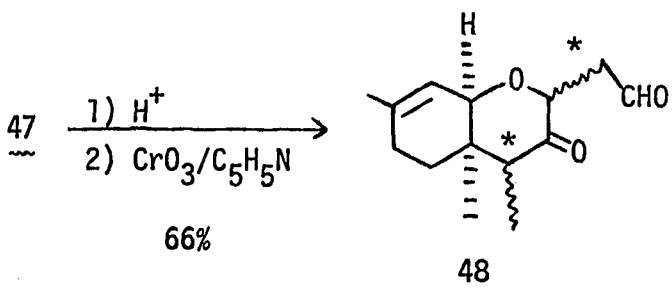
Each group of investigators prepared the cis-fused lactone via an allylic carbonium ion 44 generated from either the allylic alcohol 43 (Colvin, et al.) or the allylic alcohol 45 (Welch and Wong). The steric constraints imposed on the intramolecular trapping of the carbocation insured the cis-ring fusion.



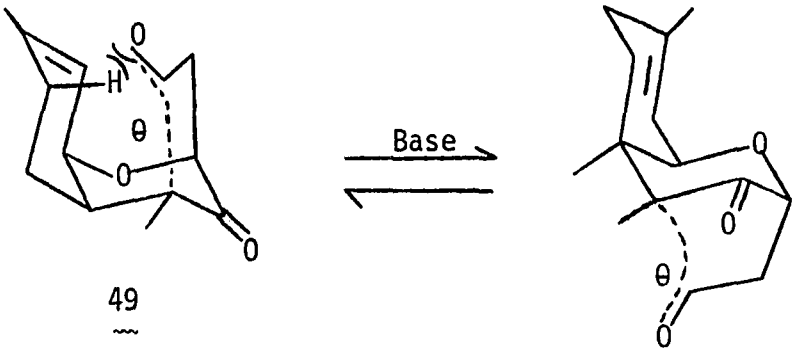
Colvin and coworkers found that treatment of 42 with the lithium salt of 3,3-diethoxypropyne produced the lactol 46 in high yield. Whereupon, sodium borohydride reduction to the diol and reduction with sodium in ammonia afforded the trans-olefin 47.



Subsequent mild acid hydrolysis effected both deprotection of the aldehyde and *in situ* addition of the allylic alcohol to the α,β-unsaturated aldehyde. Selective oxidation afforded the keto aldehyde 48. After



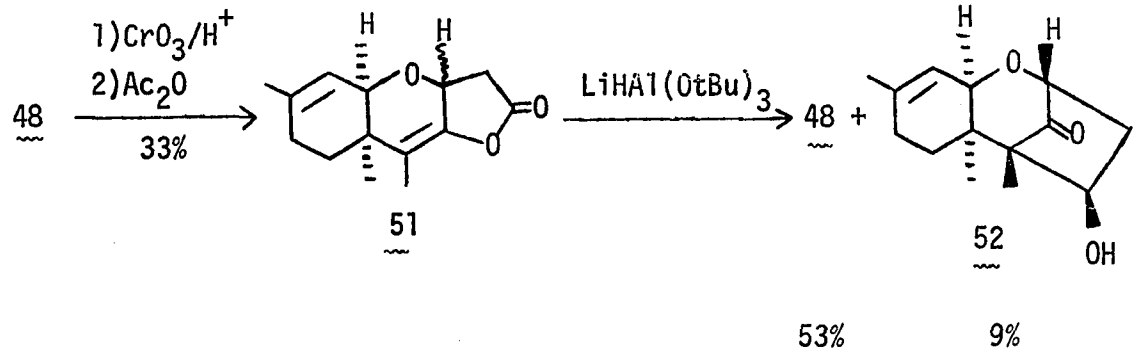
preparation of 48, Colvin et al. believed three simple transformations (aldol condensation, olefination and epoxidation) would produce trichodermol. It was unnecessary at this point to determine the precise stereochemistry at either of the epimerizable positions (*) of 48, since equilibrating conditions of an aldol reaction would alter this stereochemistry. Because of steric constraints, Colvin et al. reasoned that only two of the four possible diastereomers might be expected to undergo internal aldolization. Further analysis of the two transition states (49 and 50) indicated that cyclization of 49 would be energetically less favorable because of steric interactions involving the A-ring. Thus, under equilibrating conditions, aldol condensation was expected to proceed through 50 and yield the stereochemistry required for tricho-



49 50

dermol. As reasonable as this analysis would seem, "extensive experimentation" (36) failed to induce intramolecular aldol condensation. (Over fifty sets of experimental conditions gave no indication of any cyclized product!)

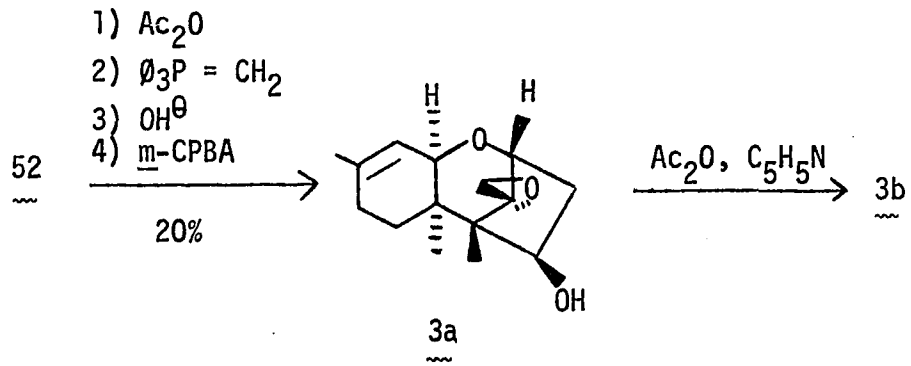
The authors overcame this major setback by oxidation of 48 to the keto acid which upon treatment with acetic anhydride produced a diastereomeric mixture of enol lactones 51. Reduction of enol lactone 51



51 52

53% 9%

with lithium tri-tert-butoxyaluminum hydride afforded a mixture of keto aldehyde 48 and 9% of the much sought after tricyclic alcohol 52. Alcohol protection, olefination, deprotection and epoxidation afforded the desired (±) trichodermol (3a). Trichodermin (3b) was also prepared via standard acetylation procedures.

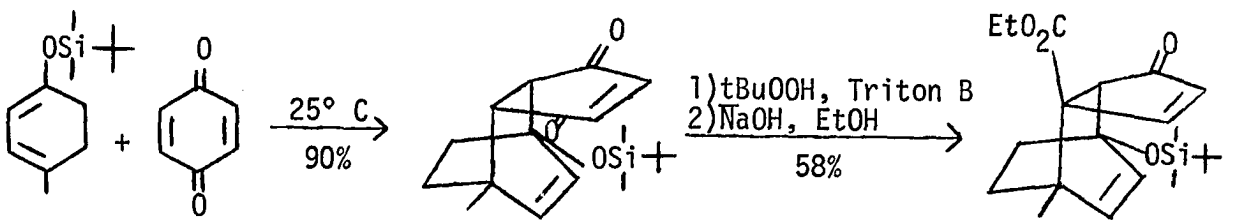


52 3a 3b

This synthetic scheme, especially the cyclization via reduction of enol lactone 51, is indeed conceptually elegant. However, when one considers the miniscule yield (∿0.025%), Colvin et al. achieved at best a Pyrrhic victory in their synthesis of trichodermol.

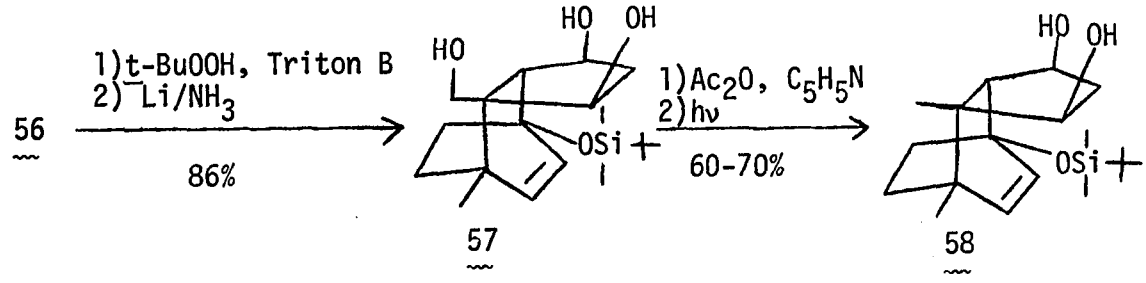
The other synthesis of trichodermol, by Still and Tsai (37), does not suffer from the abysmal yields encountered by Colvin and coworkers This scheme is notable not only for its improved yields but also for an exceptionally clever approach to a key intermediate via an anionic fragmentation.

Still and Tsai obtained diketone 55 from the Diels-Alder reaction of the cyclohexadienyl silyl ether 53 and the quinone 54. Epoxidation and subsequent Herz-Favorski ring contraction proceeded regiospecifically to give the cyclopentanonecarboxylic ester 56.

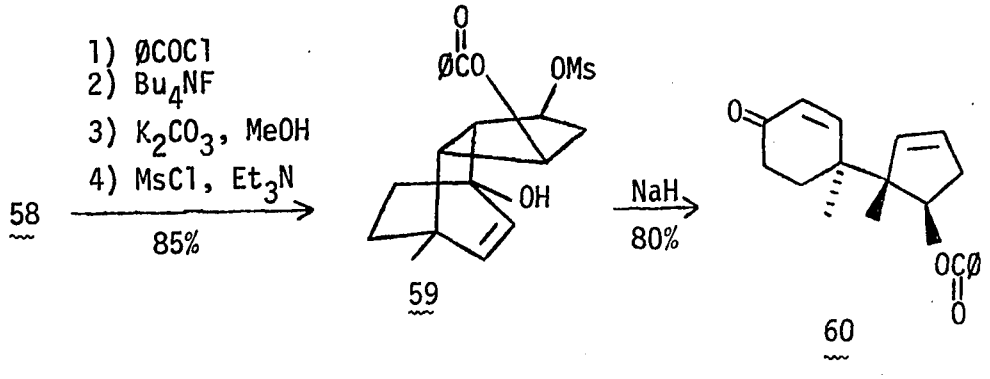


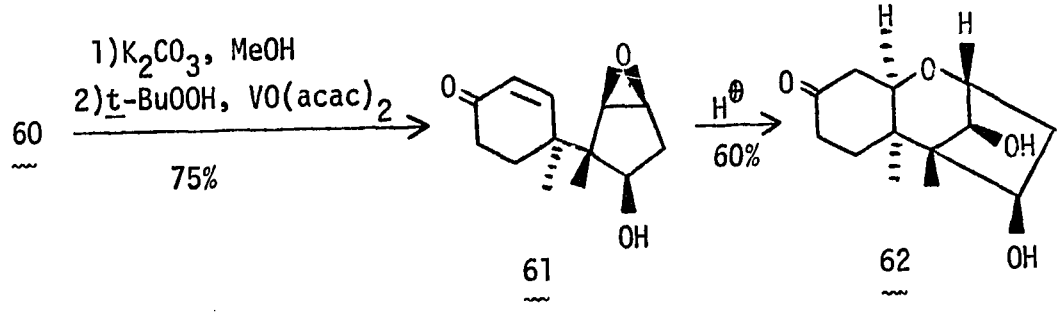
53 54 55 56

Selective epoxidation and dissolving metal reduction stereospecifically introduced the C-4 hydroxyl (trichothecene nomenclature). The resulting triol 57 was monoacetylated and a photochemical reduction (deoxygenated HMPA, H_2O, 450-W medium pressure Hanovia, quartz) removed the unwanted acetate.

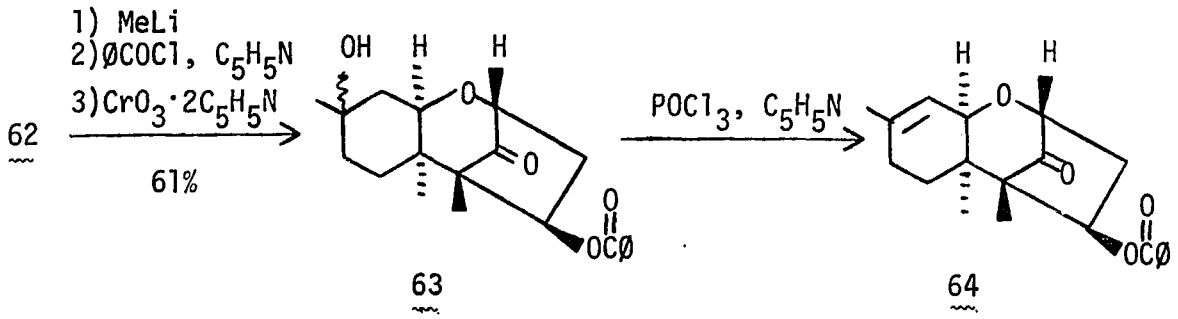


Diol 58 was converted to the mesylate 59 in four steps. Anionic fragmentation was then used to unravel compound 59 to the key intermediate 60 which was quickly converted to the tricyclic alcohol 62. Debenzoylation and hydroxyl directed epoxidation afforded the β-oxide 61. Subsequent acid catalyzed glycol formation proceeded with inversion at C-2 (trichothecene nomenclature) to yield a polyol which under the acidic conditions cyclized to the tricyclic diol 62.



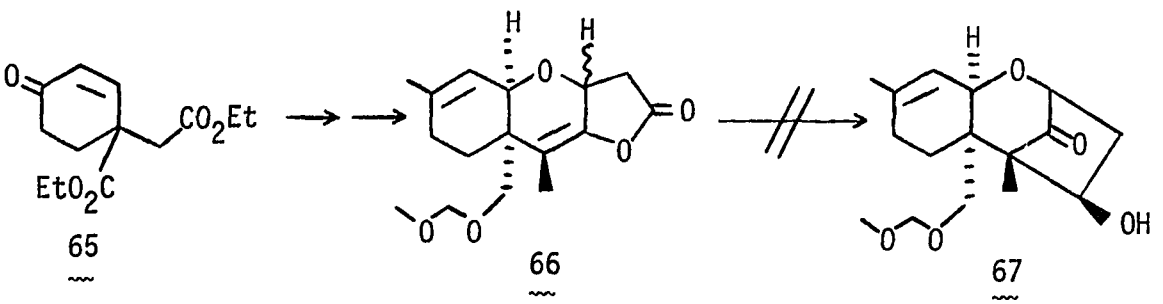


Final elaboration of 62 to trichodermol was straightforward. Methylation at the C-9 position produced a tertiary alcohol which was monobenzoylated and oxidized to yield 63. Dehydration of the tertiary alcohol of 63 produced olefin 64 as the major isomer as a 7:1 mixture of olefins. Compound 64 was transformed to trichodermol (3a) exactly as

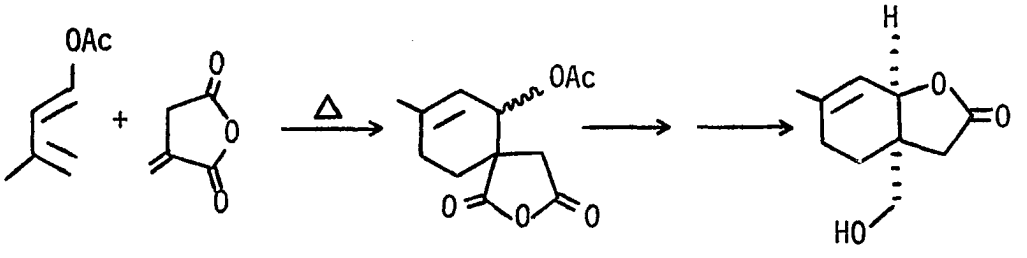


Colvin et al. had described for the analagous acetate (vide supra). The overall yield of trichodermol was a respectable 0.65%.

Synthetic approaches toward verrucarol (2a) have met with minimal success. Colvin and coworkers attempted to extend their previous work in this area. Although they successfully prepared the enol lactone 66, an exhaustive search of reaction conditions failed to produce even the slightest amount of aldol condensation product 67 (41).

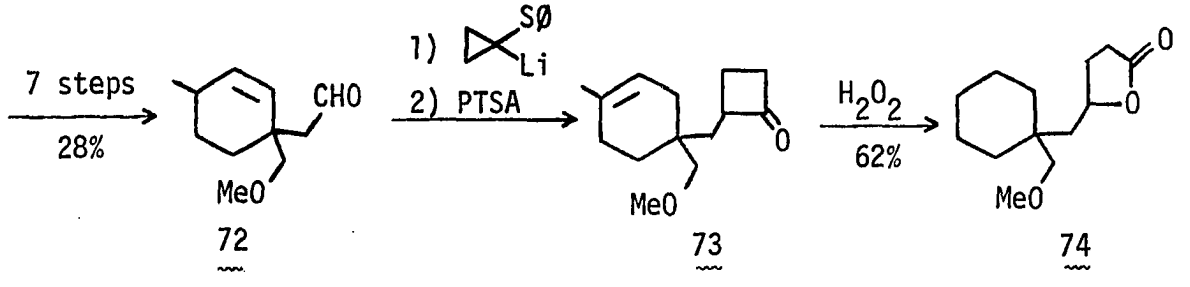


Prior to the report of Colvin et al., two other research groups communicated their synthetic approaches toward verrucarol. Snider and Amin prepared δ-lactone 71 using a Diels-Alder approach (46). This lactone was an intermediate of Colvin and coworkers in their preparation of the enol lactone 66. Similarly, Trost and Rigby prepared the keto-ester 76

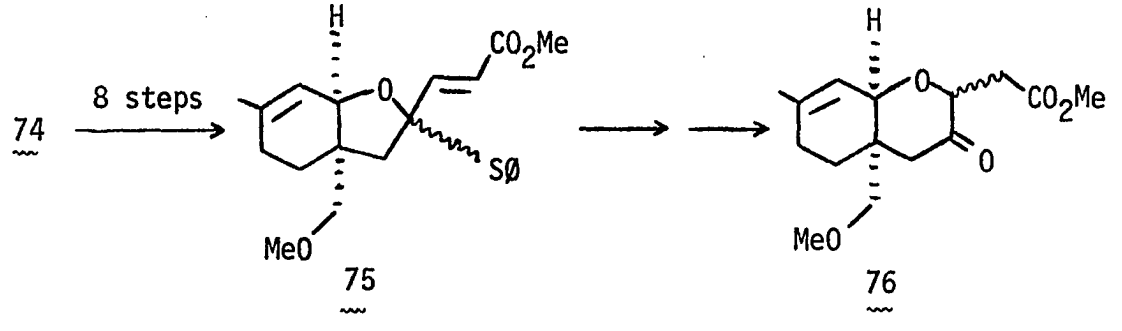


68 69 70 71

in an interesting, yet lengthy, reaction sequence (42). Their intention was to convert 76 to verrucarol employing the Colvin et al. strategy that had proven successful in the synthesis of trichodermol. Unfortunately, Colvin et al. have now demonstrated the apparent uselessness of such intermediates as 71 and 76.

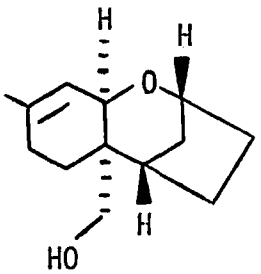


72 73 74



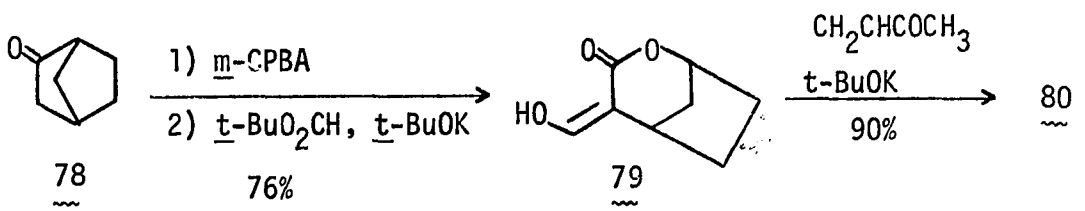
75 76

To date, introduction of the C-15 hydroxyl has presented a formidable challenge to synthetic chemists. Just recently, the first successful synthesis of a trichothecene analog possessing the C-15 hydroxyl (trichothecene nomenclature) was reported (39). However, this synthesis of Roush and D'Ambra is seriously lacking since the product 77 lacks the C-13 and C-14 methyl groups and the C-4 hydroxyl of the trichothecenes. Also, there are no functional handles that would permit facile introduction of these features.

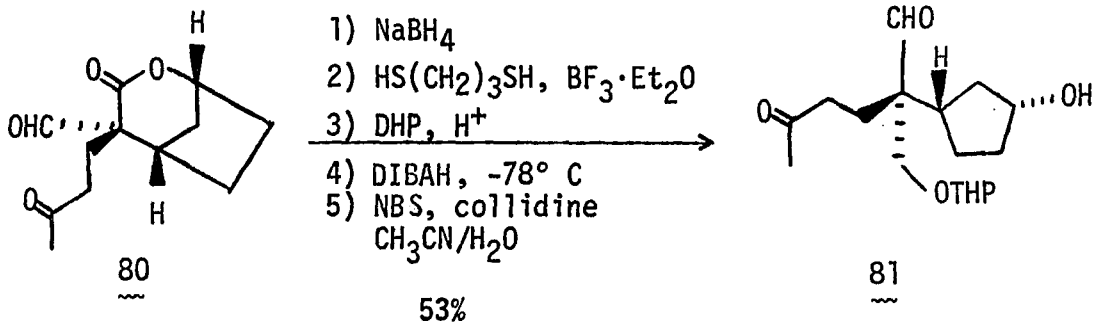


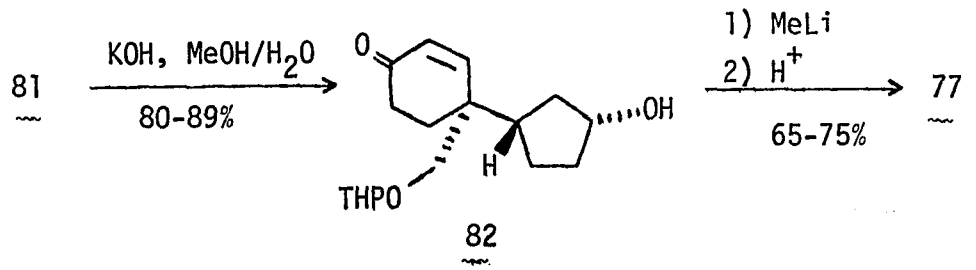
77

Roush and D'Ambra started with norcamphor, 78, which afforded lactone 79 upon Baeyer-Villiger oxidation and formylation. Michael reaction of 79 with methyl vinyl ketone produced adduct 80. Conventional transformations yielded the keto aldehyde 81 in five steps. Internal aldol condensation was then employed to afford enone 82 in good yield. Subsequent ring closure of 82 to 77 was accomplished by treatment of the enone with methyl lithium followed by aqueous acid.

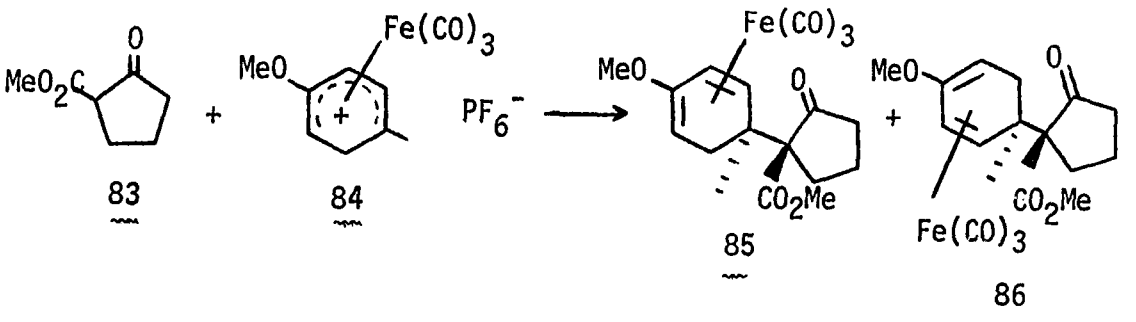


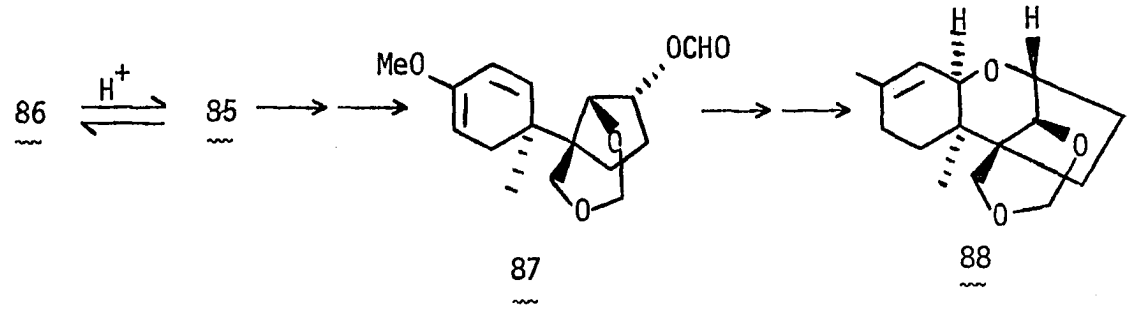
78 79 80



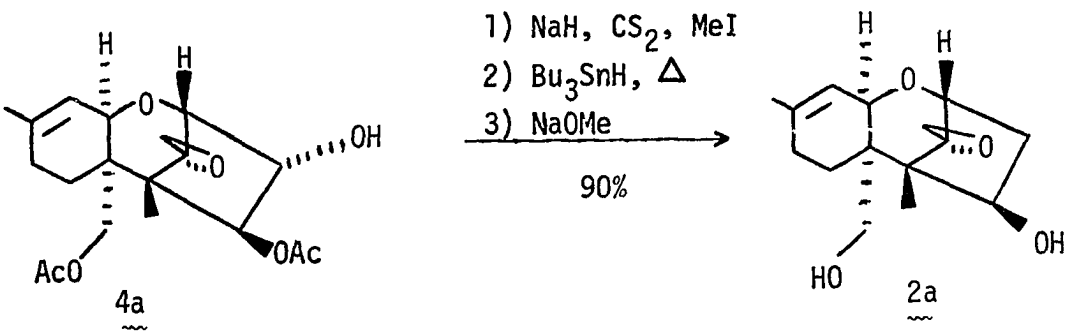


Recent communications have also reported the synthesis of an interesting trichothecene analog 88 via tricarbonylcyclohexadienylium iron complexes (40). It is likely, at least in principle, that trichodermol could be prepared via this route with only slight modifications in reactants or reaction sequences. Again, the C-15 hydroxyl of verrucarol appears to be unattainable with this route.





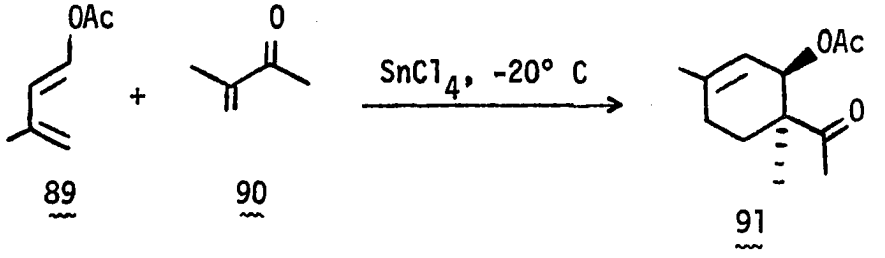
Although a total synthesis of verrucarol has not been reported, Tulshian and Fraser-Reid have recently communicated a simple high yield conversion of anguidin (4a) to verrucarol (2a) (47). Thus, any synthesis of anguidin would also constitute a formal synthesis of verrucarol.

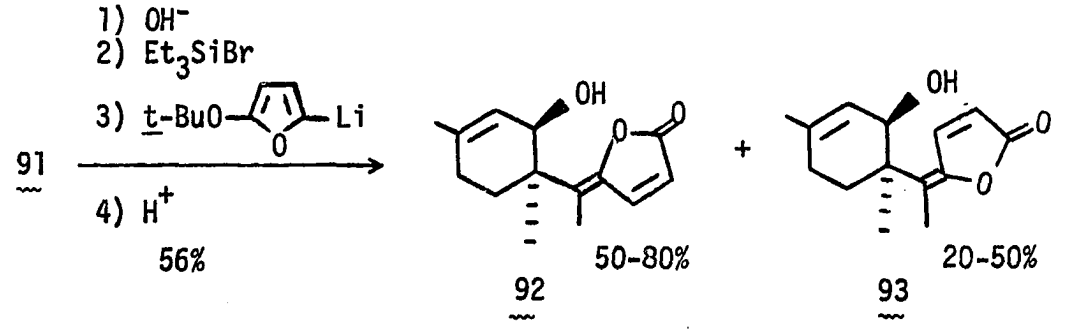


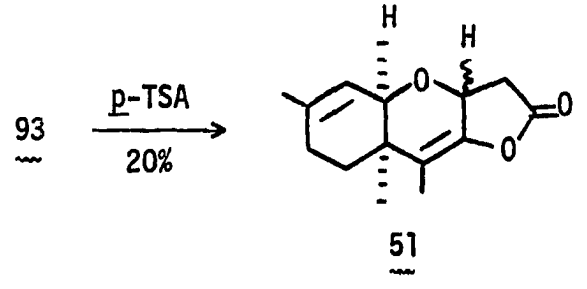
At this point, it is appropriate to review the results of work conducted within my research group. Dr. Hirohiko Sugimoto and Dr. Bruce Roth, both under the direction of Dr. George A. Kraus, developed synthetic schemes directed toward the trichothecenes. This research coincided with my own efforts in this area.

Kraus and Sugimoto utilized a novel preparation of γ-alkylidene butenolides to synthesize the enol lactone intermediate 51 of Colvin et al. (48). Ketone 91 was prepared via an acid catalyzed Diels-Alder reaction. Ketone 91 was reacted with lithium t-butoxyfuran to yield a

mixture of γ-alkylidene butenolides isomeric about the γ,δ-double bond. Acid treatment of butenolide 93 afforded the enol lactone 51.



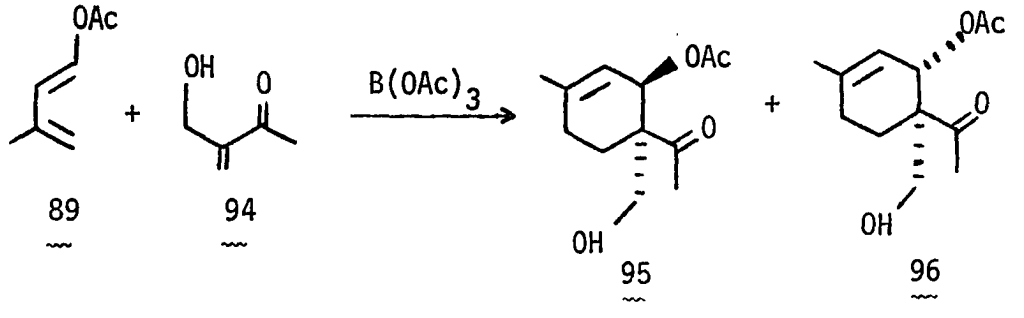




Whereas Colvin et al. synthesized the enol lactone 51 in twelve steps, Kraus and Sugimoto prepared 51 in five steps. This approach represented not only a significant improvement in the synthesis of the enol lactone but also a formal total synthesis of trichodermol (3a). While this work was in progress, Colvin et al. reported the failure of the analogous

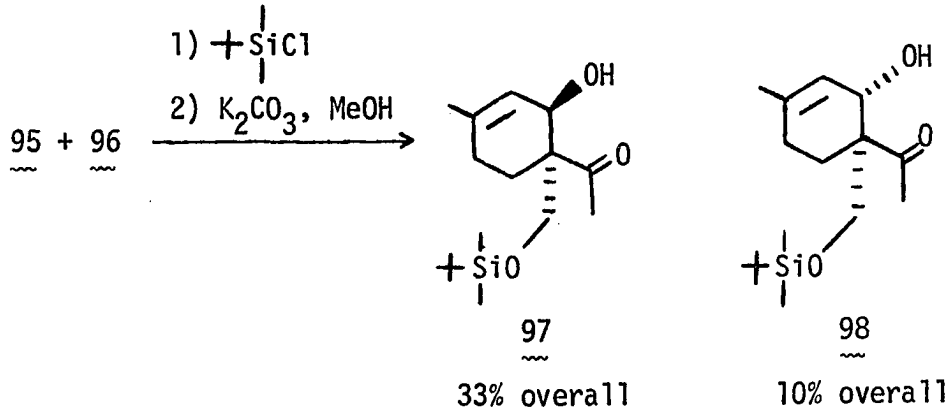
precursor (66) to yield verrucarol (2a). This discovery prompted the abandonment of the above scheme in favor of an alternate route.

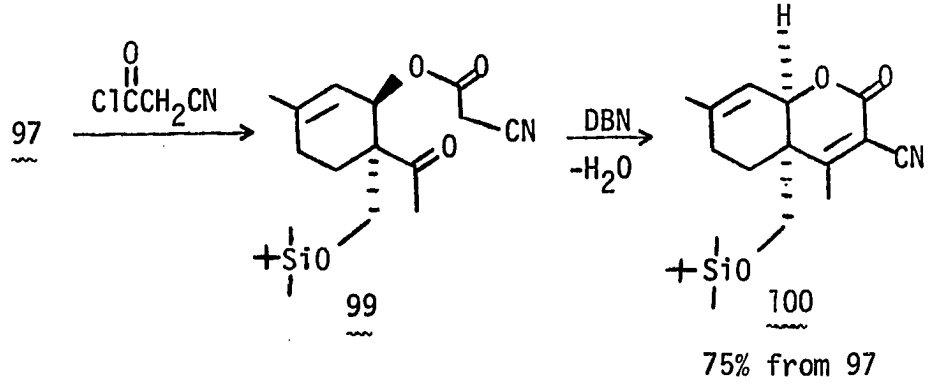
Kraus and Roth have since prepared the trichothecene skeleton possessing both the C-15 hydroxyl and C-ring functionality that will allow elaboration to produce verrucarol and anguidin (49). The Lewis acid promoted Diels-Alder reaction between 1-acetoxy-3-methylbutadiene (89) and 3-(hydroxymethyl)-3-buten-2-one (94) afforded a mixture of diastereomeric acetoxy ketones (95:96; 3.5:1). Whereas 91 was the exclusive product obtained from the tin tetrachloride catalyzed Diels-Alder reaction of 89 and 90, boron triacetate was found to be the Lewis acid catalyst of choice for obtaining optimal yields of 95.



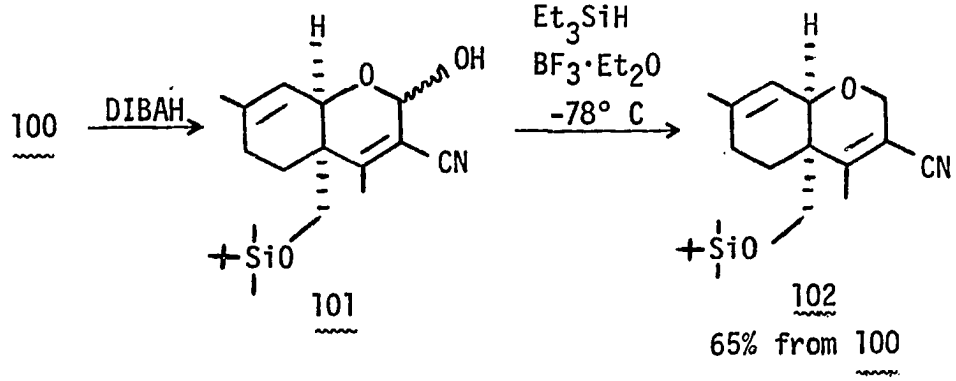
89 94 95 96

The mixture of diastereomers, 95 and 96, was silylated and saponified to yield a mixture of silyloxy ketones 97 and 98. At this point, 97 was easily separated and reacted with cyanoacetyl chloride to yield the cyano ester 99. Treatment of 99 with base produced the lactone 100 in good yield.

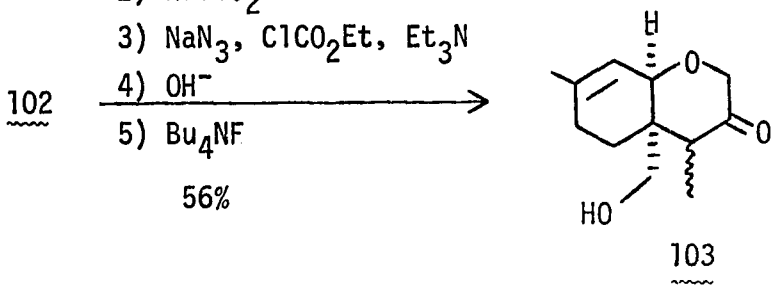




One equivalent of diisobutylaluminum hydride reduced the cyano lactone 100 to the cyano lactol 101, which afforded the unsaturated nitrile 102 upon reduction with triethylsilane and boron trifluoride etherate.

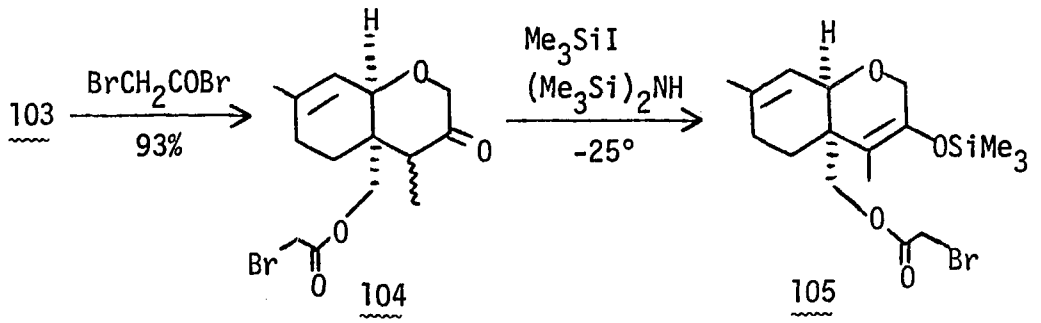


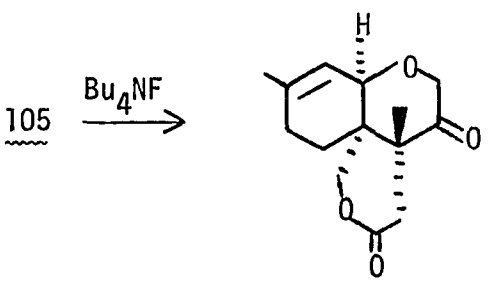
The nitrile 102 was subsequently converted in five steps to the keto alcohol 103. This crucial intermediate was obtained in twelve steps in 10.4% overall yield (49a).



103

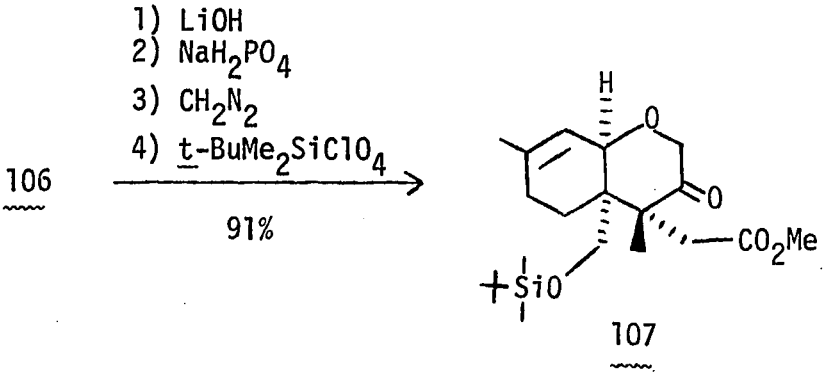
Elaboration of 103 to the trichothecene skeleton (49b,c) involved reaction with bromoacetyl bromide to yield 104. The silyl enol ether 105 was then generated regiospecifically. The enolate produced upon treatment of 105 with fluoride ion underwent intramolecular alkylation to afford the tricyclic lactone 106.





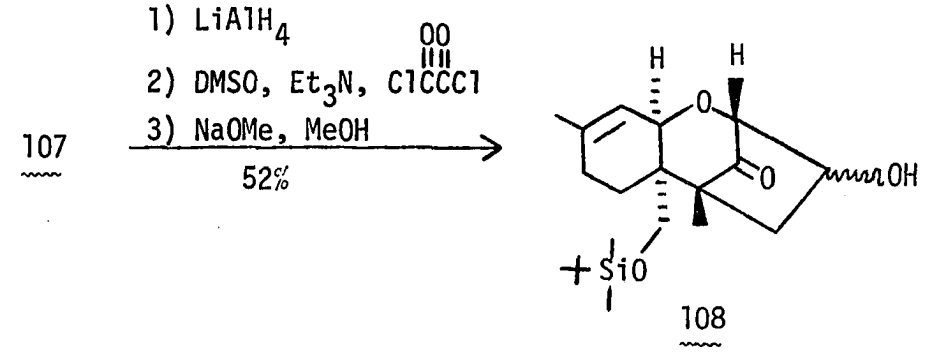
106
47% from 104

Lactone 106 was opened to the hydroxy acid and treated *in situ* with diazomethane. The hydroxyl so generated was then protected as a silyl ether. To avoid relactonization, reactive silyl perchlorates were required for this protection reaction.

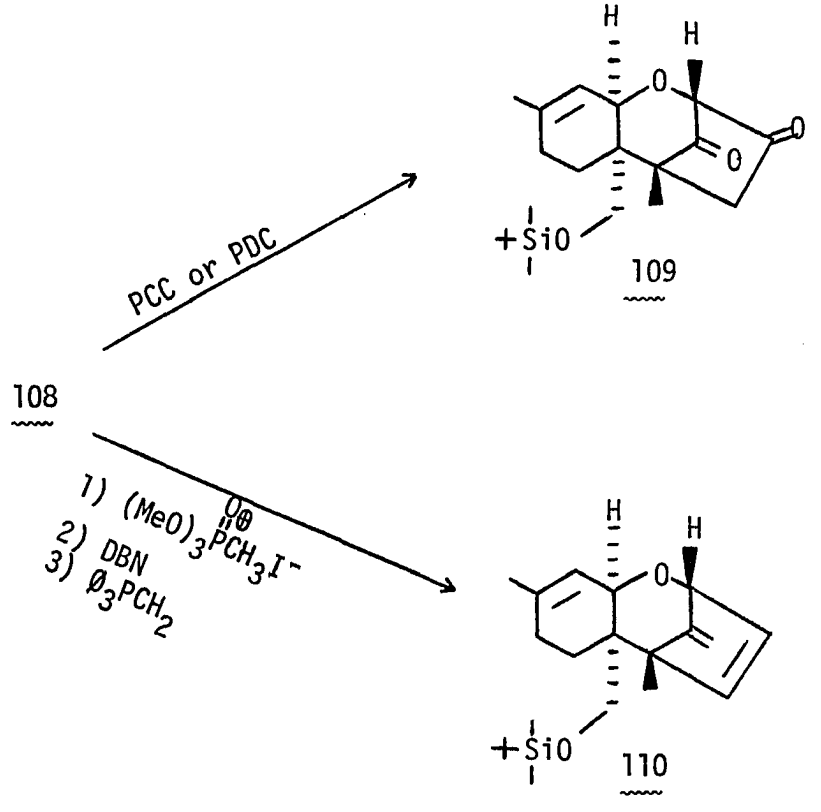


The overall transformation of keto alcohol 103 to keto ester 107 is notable for the elegant manner in which the stereochemistry at carbon 5 (trichothecene nomenclature) was unambiguously established. Attention was next directed at cyclization of keto ester 107 to produce the C-ring of the trichothecene skeleton.

Attempts at direct cyclization of the keto ester 107 proved unsuccessful. However, the keto ester could be reduced to a diol and reoxidized to a keto aldehyde which cyclized to tricyclic keto alcohol 108 in sodium methoxide. The ease (30 min at reflux MeOH, NaOMe) with which the cyclization occurred is in sharp contrast to aldol reactions on the other side of the ketone (*vide supra*).

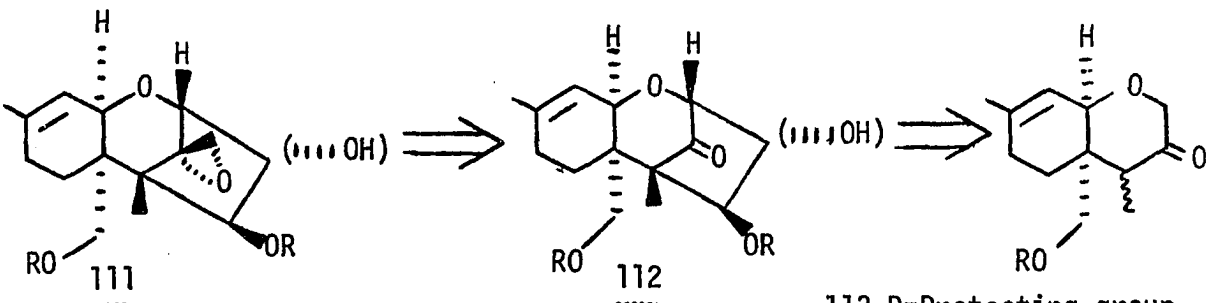


The keto alcohol 108 was then transformed to both diketone 109 and triene 110. These three tricyclic compounds should prove to be especially valuable intermediates for the synthesis of highly oxygenated epoxytrichothecenes (e.g., verrucarol and anguidin).



RESULTS AND DISCUSSION

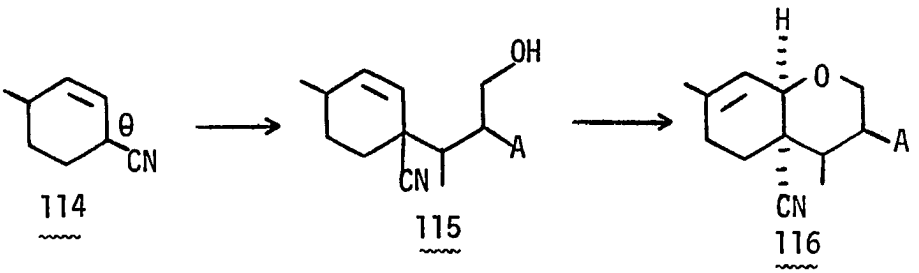
Retrosynthetic analysis of the epoxytrichothecene skeleton led us to believe keto alcohol 103 would be a key synthon in the overall synthetic scheme directed toward verrucarol and anguidin. Introduction of the two carbon unit of the C ring appeared close at hand via any number of annulation procedures. Also, it had already been established that the 12,13-epoxide could be generated from the ketone 113 once the C ring was formed (vide supra). Thus, our first goal in the synthesis of the trichothecenes was to develop a route to the AB ring system of verrucarol (keto alcohol 103).



A Michael Addition Approach to the AB Ring System

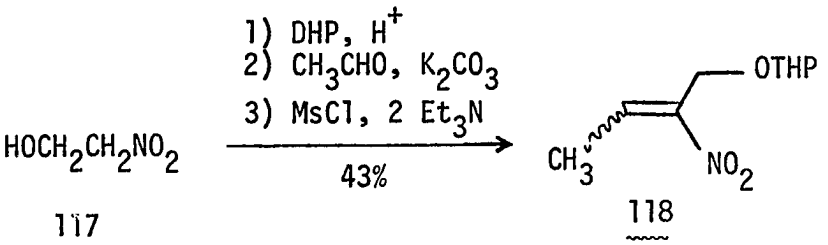
Our initial synthetic strategy directed toward the AB ring system is outlined in Scheme III. Key steps involved a Michael addition of an unsaturated nitrile and an intramolecular etherification. The etherification reaction must afford a cis ring junction. Additionally, the unspecified group A must serve as both an activator for Michael addition and a convenient precursor for a carbonyl group.

Scheme III



114 115 116

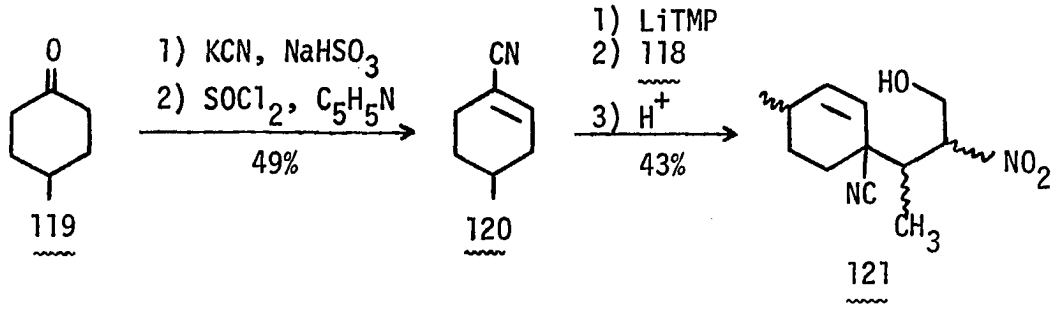
Previous work in our laboratory indicated that Michael addition reactions of cyclic unsaturated nitriles with good Michael acceptors afforded variable yields of desired products (50). In accord with the requirements for group A, we chose nitro olefin 118. After serving as an activator for the Michael addition, the nitro group would be converted to the desired carbonyl unit (e.g., $TiCl_3$). Compound 118 was conveniently prepared from β-nitroethanol 117. Although the nitro olefin could be stored at 0°C, optimal results were achieved with freshly prepared material.



117 118

The desired nitrile 120 was easily obtained by dehydration of the cyanohydrin of 4-methycyclohexanone. The allylic anion was then generated with lithium 2,2,6,6-tetramethylpiperidide at -78°C in tetrahydrofuran. Subsequent addition of nitro olefin 118 afforded a

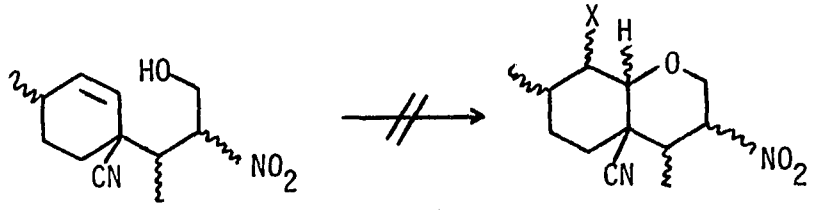
good yield of Michael adduct. By treating the crude reaction mixture with aqueous acid, the protecting group was removed to yield the nitro alcohol 121.



119 120 121

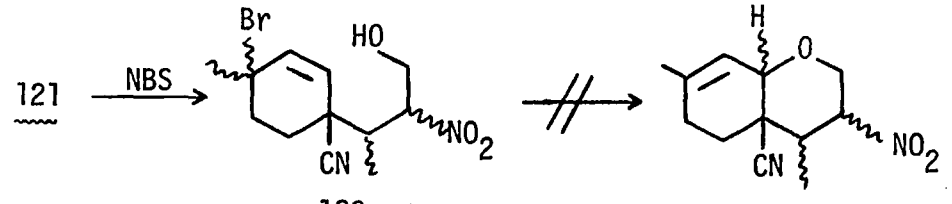
Compound 121 was clearly a mixture of diastereomers. However, stereochemistry was unimportant at this point since each isomer could be converted to the desired product. No products arising from γ-Michael addition of the nitrile were observed. This result was fully anticipated in light of similar reactions studied in our laboratory (50,51). Additionally, no elimination of the tetrahydropyranyloxy group could be detected. Other products resulted from polymerization of the nitro olefin.

Reaction conditions were then required for transformation of the Michael adduct 121 to a cis-fused ether. The olefinic alcohol 121 seemed perfectly designed for the selenoetherification method developed by Nicolaou et al. (52). However, even after extensive reaction times with phenylselenyl chloride, the alcohol was recovered unchanged. Attempted oxymercuration with mercuric trifluoroacetate similarly led to recovery of starting materials (53).



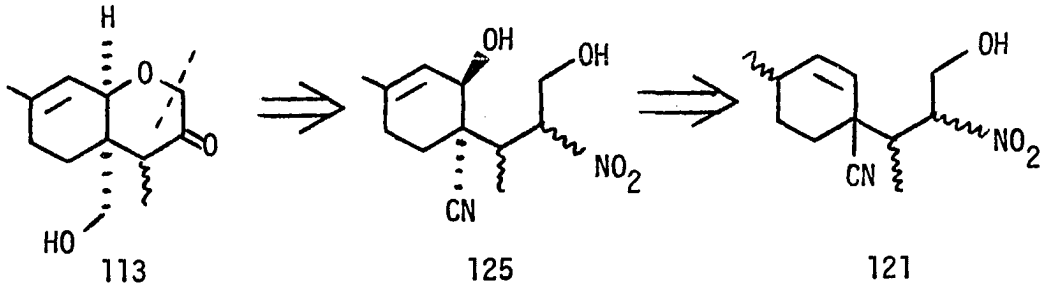
121 122

Since the inductive effect of the nitrile could be deactivating the olefin toward electrophilic reactions, hydrolysis of the nitrile was considered. All attempts to convert the nitrile to an acid (aqueous HCl; ROH, $Ba(OH)_2$) led to recovery of starting materials. Efforts to generate the aldehyde (DIBAH) afforded no recognizable products. Alternatively, 121 could be brominated with N-bromosuccinimide (NBS) to produce the allylic bromide, again as a mixture of diastereomers. Neither base induced cyclization (DBN) nor silver nitrate mediated cyclization afforded any identifiable products.



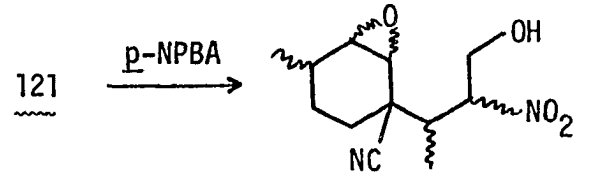
123 124

In view of the failure of olefinic alcohol 121 to cyclize, a modification of our initial plan was required. Further analysis led us to believe that the desired AB ring system could be developed from ether formation involving diol 125. Such a reaction scheme would avoid a mixture of *cis* and *trans* ring fusions. It also appeared that diol 125 could be prepared from olefinic alcohol 121.



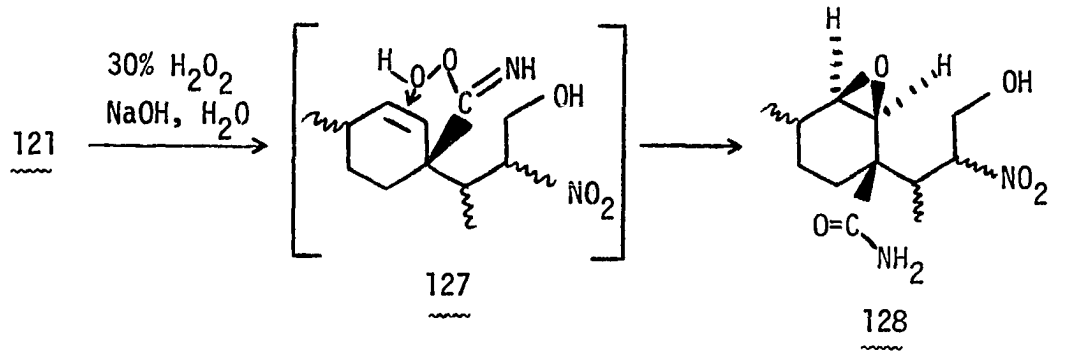
113 125 121

The first step in converting the olefin functionality of 121 into an allylic alcohol was the introduction of the oxygen. This was accomplished via epoxidation of the double bond with p-nitroperbenzoic acid (p-NPBA). Notably, m-chloroperbenzoic acid (m-CPBA) produced none of the desired epoxide even after extensive reaction periods. This gave further evidence of the deactivation of the double bond through the inductive effect of the nitrile.



126

Although epoxidation of 121 with p-NPBA was not stereoselective, we planned to later employ the method of Payne et al. (54) wherein the nitrile would be utilized to introduce the epoxide stereoselectively (i.e., 121 → 128). Such a procedure would provide a "handle" for the stereoselective generation of the cis-fused AB ring system. However, epoxide 126 was a suitable model for use in determining procedures for the generation of the allylic alcohol 125.



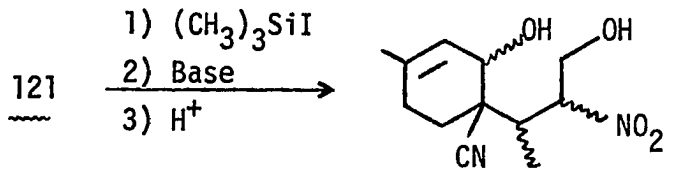
Preparation of Allylic Alcohols from Epoxides

Using Iodotrimethylsilane (55)

After making the diastereomeric epoxide 126, we required a regioselective conversion to produce the allylic alcohol 125. We initially attempted to form the bromohydrin from the epoxide (48% HBr solution) (56) in the hope that subsequent dehydrohalogenation would produce the desired allylic alcohol. However, the results provided no grounds for optimism and we sought another method. Although the transformation might have been accomplished using lithium dialkylamides or dialkylaluminum amides (57), the strongly basic conditions were not compatible with the nitro and alcohol functionalities in the molecule. Sodium phenylselenide had also been used to convert epoxides to allylic alcohols under milder conditions (58). However, such a reaction with epoxide 125 would lead to nonselective attack of the selenide on the epoxide.

Isolated examples of reactions of epoxides with halosilanes had been communicated (59). The products of these reactions were reported as either halohydrins or halosilyl ethers. More recent studies also indicated that iodotrimethylsilane was effective in cleaving ethers (60).

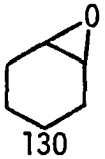
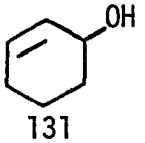
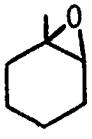
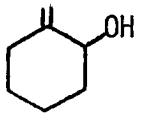
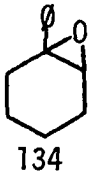
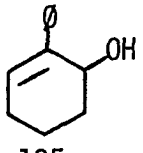
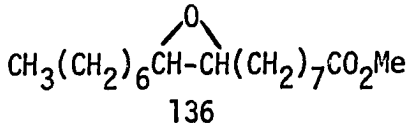
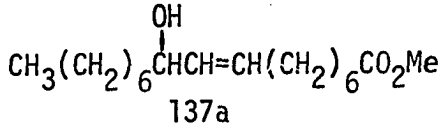
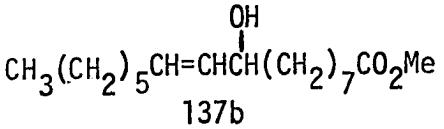
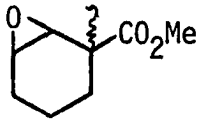
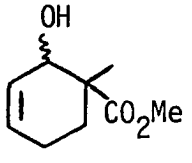
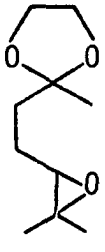
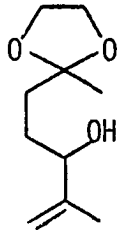
We reasoned that if epoxide 125 was treated with iodotrimethylsilane and the iodide was eliminated with base, the allylic alcohol 129 would be the probable product because of the inductive effect of the nitrile.



129

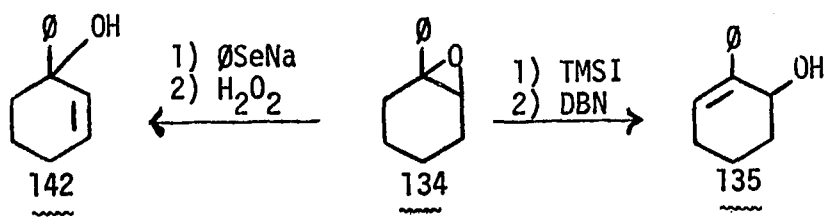
To determine reaction parameters and to test the validity of our postulated reaction sequence, several representative epoxides were prepared and reacted with iodotrimethylsilane. The general reaction procedure involved addition of iodotrimethylsilane to a solution of epoxide and base in an appropriate solvent. The initial epoxide opening to produce the intermediate halosilyl ether was rapid at 0°C, as evidenced by thin layer chromatography. However, the dehydrohalogenation step was not complete until the reaction temperature was raised to reflux for 12 to 48 hours. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) proved to be the most effective dehydrohalogenating agent. In agreement with the results of previous workers (59), the epoxide opening could be done in a variety of aprotic solvents. However, dehydrohalogenation afforded the best yields in acetonitrile. The results of our studies are compiled in Table I. In all cases, trisubstituted epoxides reacted to form secondary alcohols exclusively. Significantly, 1-phenylcyclohexene oxide gave better yields of allylic alcohol when the order of addition of reagents was altered. Standard reaction conditions produced

Table I. Conversion of epoxides to allylic alcohols

Epoxide	% Yield of Product	Allylic Alcohol
 130	79%	 131
 132	69%	 133
 134	68%	 135
 136	75%	 137a and  137b
 138	70%	 139
 140	50%	 141

significant amounts (∿30%) of 2-phenylcyclohexanone. Presumably this side reaction involved a hydride shift. The improved yield of 135 resulted when iodotrimethylsilane was added to epoxide 134 in benzene. The solvent was switched to acetonitrile, DBN was added and the mixture heated as usual. The improved yield reflected a minimization of the undesired side reaction.

As demonstrated in Table I, the reaction conditions are compatible with the presence of esters and cyclic ketals. Since Jung et al. showed that these groups react with iodotrimethylsilane (61), this selectivity is notable. Overall, the mild conditions and operational simplicity of this method offer major advantages over the use of dialkylamides. This procedure serves to compliment the organoselenium chemistry of Sharpless and Lauer (58) in that trisubstituted epoxides afford secondary alcohols (i.e., 134 → 135). It must be mentioned that while our work was being prepared for publication, Murata et al. published a procedure similar to ours employing trimethylsilyl trifluoromethanesulfonate and DBN (62). The use of iodotrimethylsilane, however, offers advantages of lower cost and greater availability.



142 134 135

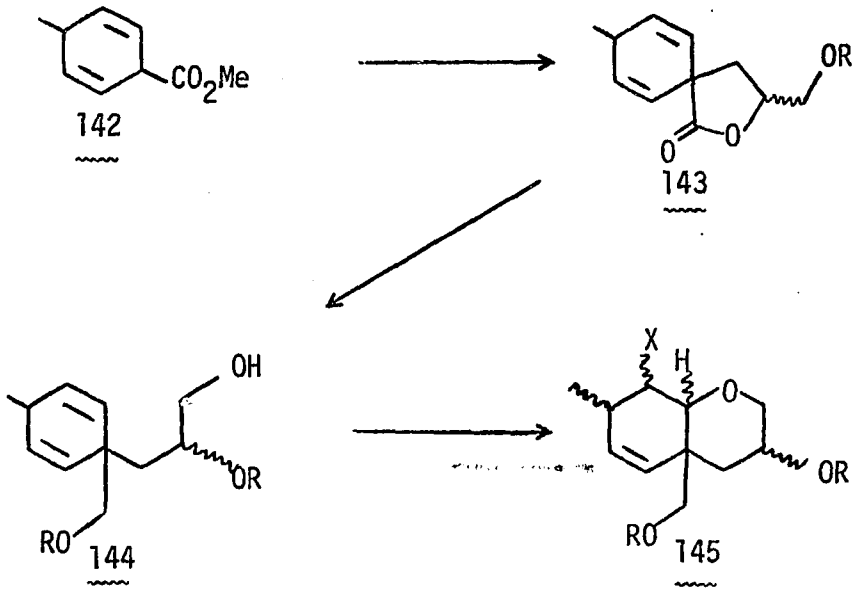
One of the model compounds was of considerable interest. Epoxide 138 is very similar to 121. Notably, the epoxide ring opening and subsequent elimination afforded regioselectively allylic alcohol 139 as a mixture of diastereomers. At no time was there any indication of the products arising from cleavage of the epoxide at the carbon β to the ester. Apparently, the inductive effect of the carbomethoxy was sufficient to exert total regiocontrol over cleavage of the epoxide. This result was very encouraging and led us to anticipate similar regioselectivity in the reaction of iodotrimethylsilane and epoxy nitrile 126. Quite unexpectedly, reacting 126 with iodotrimethylsilane and DBN resulted in total decomposition with no identifiable materials recovered. The functionality of 121 apparently did not tolerate the silyl iodide and the amine.

An Approach Toward the AB Ring System Via Spiro Lactones

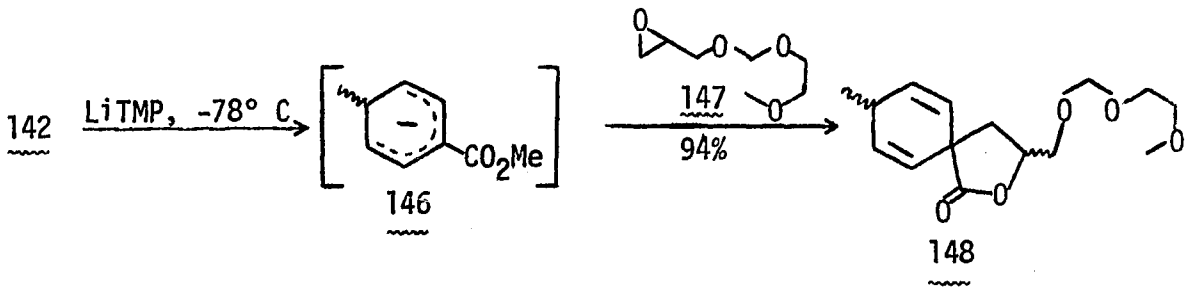
Despite the unfortunate results, we proceeded undaunted since another synthetic scheme seemed to show significant promise. This synthetic plan is depicted in Scheme IV.

Since the nitrile functionality appeared to exhibit considerable deactivating effects upon the olefin in 121, and the nitrile was also reluctant to hydrolyze, we sought another starting material. The anion of the α,β-unsaturated ester analogous to nitrile 120 was unstable. However, the dienic ester 142 afforded a stable anion.

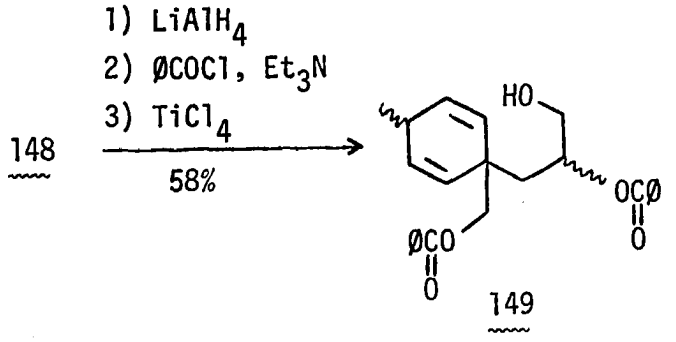
Scheme IV



This diene was readily accessible via Birch reduction of p-toluic acid and subsequent esterification (MeOH, $BF_3 \cdot Et_2O$, reflux). At this point, we also chose to abandon the use of nitro olefins. We opted for reaction of the anion of 142 with various epoxides. This led to the isolation of spiro lactones in excellent yields. The most effective route involved reaction of 142 with the glycidol derivative 147.



Lithium aluminum hydride reduction of the lactone 148 produced a diol which was benzoylated using standard reaction conditions. The MEM protecting group was then selectively hydrolyzed ($TiCl_4$) to afford the dibenzoate alcohol 149.



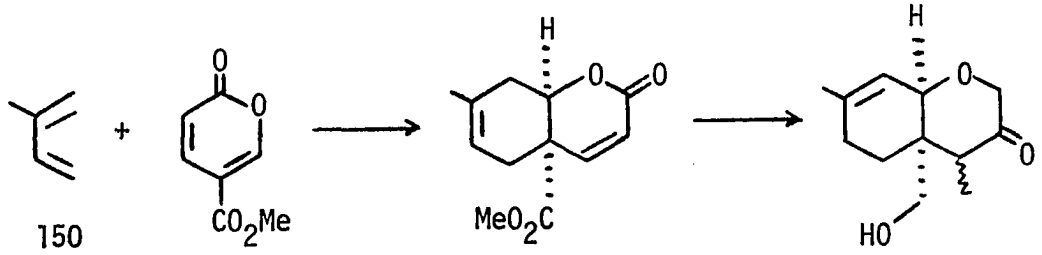
Alcohol 149 appeared to possess distinct advantages over hydroxy nitrile 121. Foremost, the troublesome nitrile was no longer present. Secondly, the symmetry of 149 ensured that reaction of either double bond would lead to desired product. Unfortunately, attempted cyclization of 149 with phenylselenyl chloride or mercuric trifluoroacetate led only to recovery of starting material.

Analysis of the attempted ring closures with respect to Baldwin's "rules" (63) gave no explanation as to why the attempted etherification reactions of 121 and 149 failed. According to the "rules", cyclization of both compounds should be "favored" processes.

A Diels-Alder Route to the AB Ring System (64)

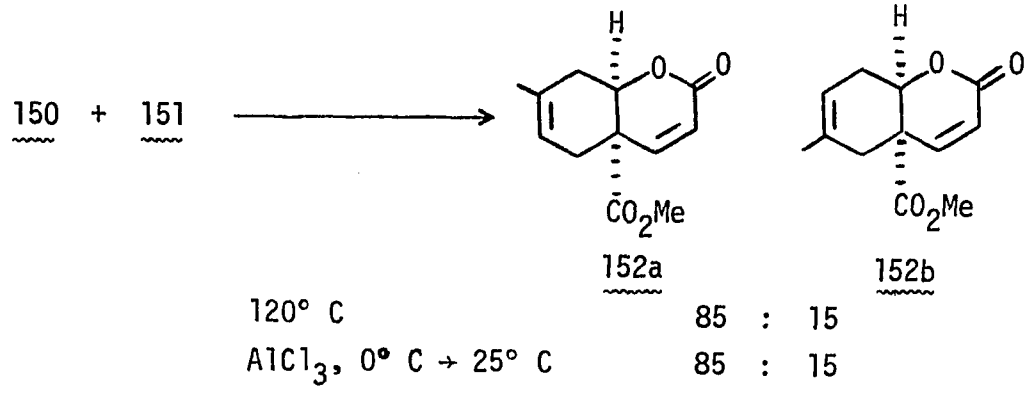
In view of the problems encountered in forming the AB ring system by intramolecular etherification, a new strategy was devised which unambiguously defined the stereochemistry of the ring junction and also permitted rapid access to a functionalized B ring. This plan is outlined in Scheme V.

Scheme V



150 151 152a 103

Although the Diels-Alder reaction of isoprene with methyl coumalate (151) had been reported (65), no assessment of the regiochemical purity of the products had been made. We felt reasonably certain that the major regioisomer would prove to be the desired lactone 152a and not lactone 152b. Analysis of 300 MHz proton NMR (66) and decoupling experiments indicated that the products were obtained in a ratio of 85:15, with the expected isomer predominating.

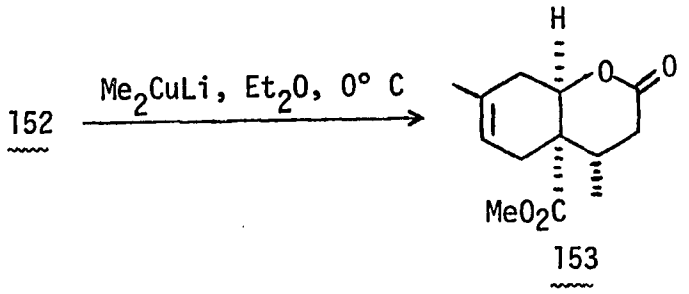


We attempted to improve upon the observed regioselectivity by employing Lewis acid catalysis for the Diels-Alder reaction (67). However, analysis indicated the same ratio of 152a:152b. Since the aluminum chloride only served to promote considerable polymerization of the isoprene, this method was abandoned.

No attempt was made to separate the regioisomers at this point. Instead, all further transformations directed toward keto alcohol 103 were conducted on the mixture of isomers. For simplicity, only the desired isomer is depicted in all ensuing structures and diagrams.

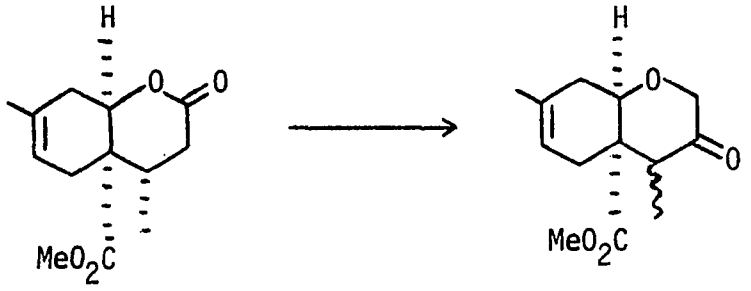
The Diels-Alder reaction also afforded significant amounts of products that arose from a Diels-Alder reaction involving methyl coumalate (151) as the diene and isoprene as the dienophile (65). There was no significant difference in the relative amounts of these unwanted products produced when thermal and acid catalyzed reaction mixtures were compared. A tedious chromatographic procedure was required to obtain lactone 152 totally pure.

Reaction of dimethylcopper lithium with the unsaturated lactone 152 produced the desired conjugate addition product 153. Quite fortuitously, when mixtures of 152 and the unwanted Diels-Alder by-products were reacted with dimethylcopper lithium, the only product isolated was 153. The overall yield of lactone 153 from methyl coumalate (151) was unaffected by the presence of the undesired material. This result greatly facilitated the preparation of large amounts of lactone 153, since the tedious purification of lactone 152 was no longer necessary. A 400 MHz proton NMR of the cuprate addition product again indicated the same 85:15 ratio of methyl regioisomers (68).



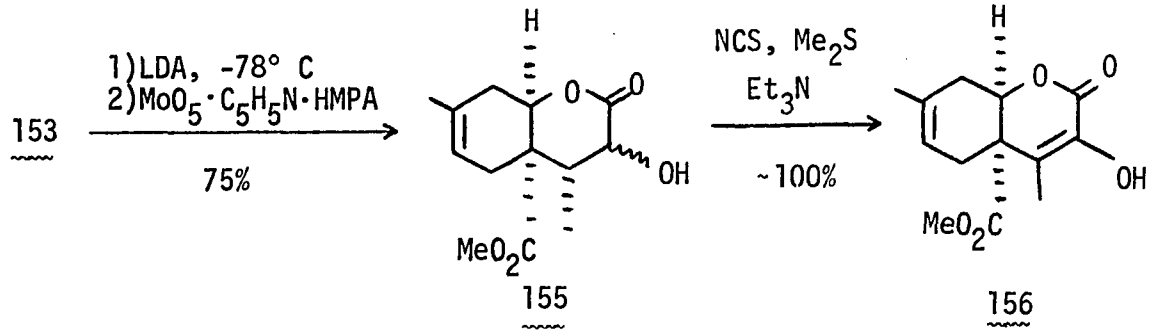
153

Conversion of lactone ester 153 to the desired keto alcohol 103 required three basic transformations. Obviously, the double bond had to be transposed and the ester had to be reduced to an alcohol. Since the third conversion appeared to present the greatest challenge, we tackled this problem first. What we required was a means of converting lactone 153 into a cyclic β-keto ether 154. We ultimately developed a convenient route that involved as the key step reduction of a lactol to a cyclic ether.



153 154

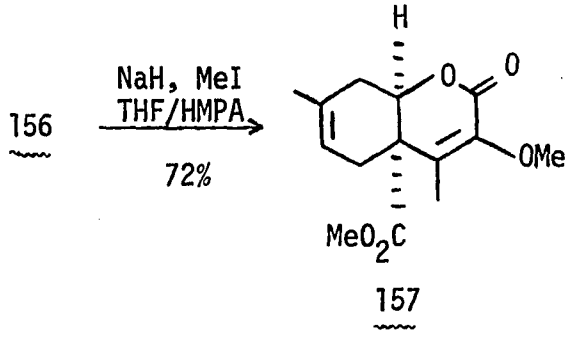
The first step of the sequence was the hydroxylation of lactone 153 according to the method of Vedejs et al. (69). This reaction served to introduce the oxygen functionality which eventually produced the ketone of 154. Oxidation of the α-hydroxy lactone 155 with N-chlorosuccinimide, dimethyl sulfide and triethylamine (70) afforded the enolic lactone 156 in high yield. A variety of oxidation procedures (Jones', pyridinium chlorochromate and pyridinium dichromate) gave a variety of products and inferior results. Notably, the oxidation product 156 was exclusively in the enolic form as evidenced by IR and proton NMR spectra.



153 155 156

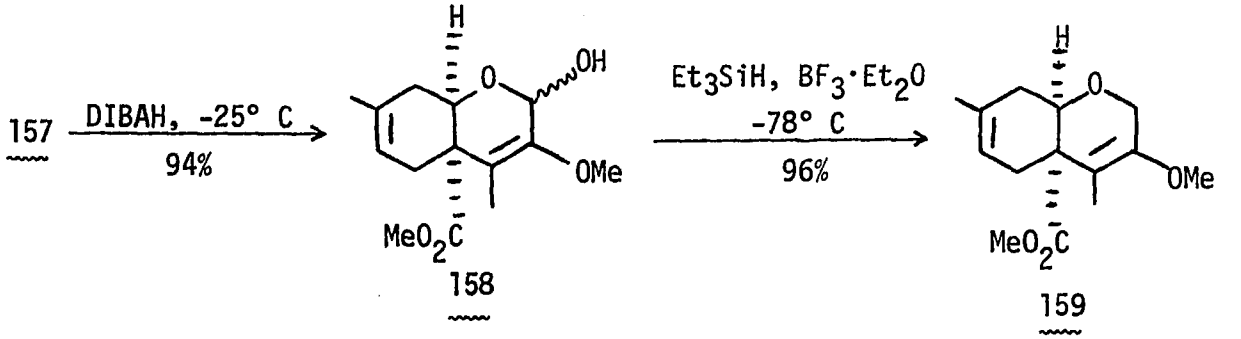
Exclusive O-methylation of 156 with sodium hydride and methyl iodide in a solution of tetrahydrofuran and hexamethylphosphoramide produced the

enol ether lactone 157. At this point, the carbonyl of the β-keto ether 154 had been introduced in a protected form.

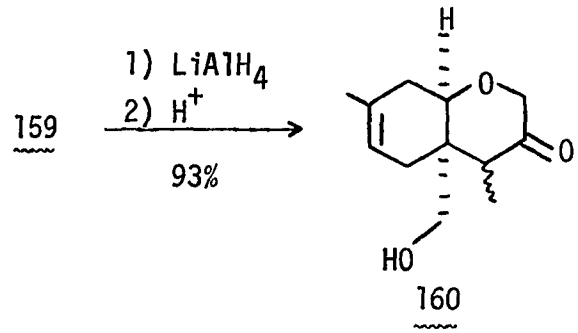


157

We then employed a two step sequence developed in our laboratory for the reduction of lactones to cyclic ethers (71). First, the lactone 157 was reduced with diisobutylaluminum hydride (DIBAH) to yield lactol 158. This lactol, as evidenced by all the spectral data, existed solely as the cyclic hemiacetal. The lactol 158 was successfully reduced to the cyclic ether 159 using triethylsilane and boron trifluoride etherate. This reaction is well precedented in the reductive deoxygenation chemistry of organosilanes (72). This two step reduction sequence has since proven to be a versatile synthetic tool in our laboratory (71). The use of organosilanes to reduce hemiacetals and mixed acetals has also been utilized effectively in more recent work directed toward verrucarol (vide infra).

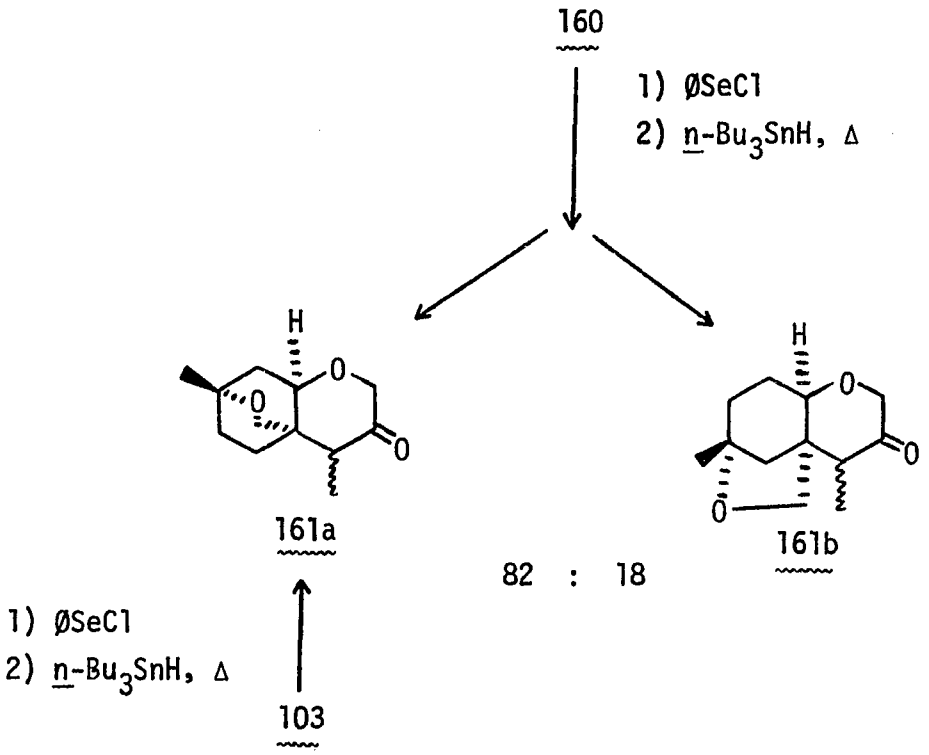


We next took advantage of the enol ether protecting group to reduce the ester of 159 to an alcohol. Lithium aluminum hydride reduction of 159 afforded, after acid hydrolysis, keto alcohol 160. In this manner, 160 was obtained in 7.9% overall yield from methyl coumalate (155).

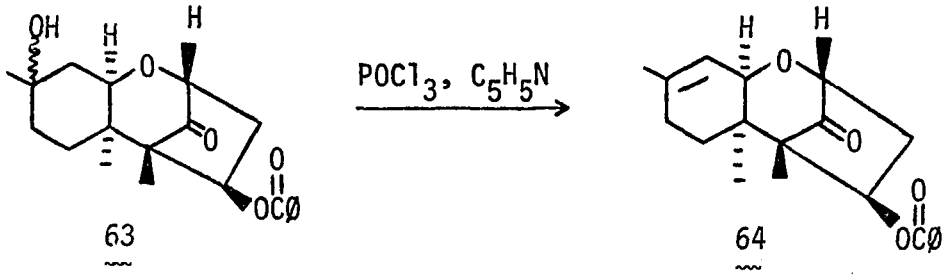


160

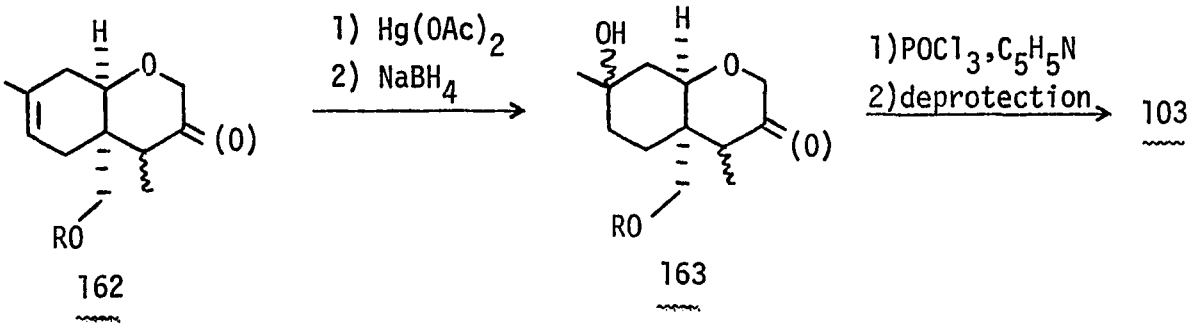
As an additional proof of structure, β-keto ether 160 was converted into ether 161 by cyclization with phenylselenyl chloride and reductive deselenylation (52). Ether 161a was identical in all respects (IR, proton NMR, capillary column gas chromatography) with material prepared from isomeric keto alcohol 103, in which the C-9 methyl (trichothecene nomenclature) had been unambiguously introduced by the synthetic approach (49a). Capillary column gas chromatography also confirmed our earlier analysis concerning regioselectivity of the initial Diels-Alder reaction. The ratio 161a:161b was identical to the ratios obtained from proton NMR analysis of the Diels-Alder products (156) and the conjugate addition products (157).



Having prepared β-keto ether 160, all that was left to accomplish in the synthesis of keto alcohol 103 was the isomerization of the trisubstituted olefin in the A ring. However, while our work was in progress, Still and Tsai reported their synthesis of trichodermol (37). In that communication, they reported the conversion of tertiary alcohol 63 to the desired olefin 64 (vide supra). We felt confident that protection of 160 and subsequent oxymercuration would produce the isomerized olefin 103 after dehydration according to the Still and Tsai procedure.



63 64



162 163

The isomerization was never attempted because development of our triethylsilane methodology evolved into another synthetic scheme directed toward keto alcohol 103. This new scheme would avoid the necessity of double bond isomerization.

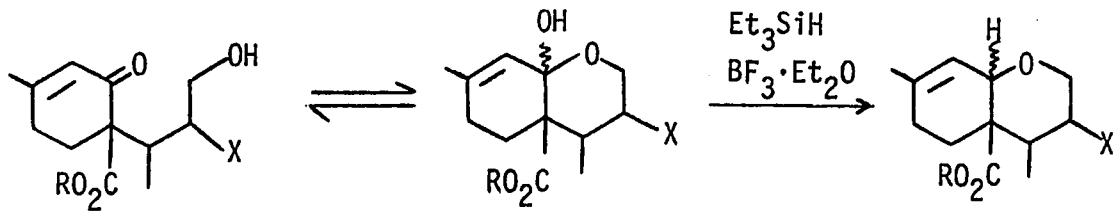
An Improved Route to Keto Alcohol 103

Several factors led us to seek an improved route to keto alcohol 103. The Diels-Alder reaction could not be carried out on an exceedingly large scale because of a lack of necessary apparatus. Also, the production of unwanted material in the Diels-Alder reaction was inefficient. Finally, we were unable to overcome difficulties associated with reliable production of the molybdenum reagent. This problem

was also noted by Vedejs et al. in their original report on this reagent (69).

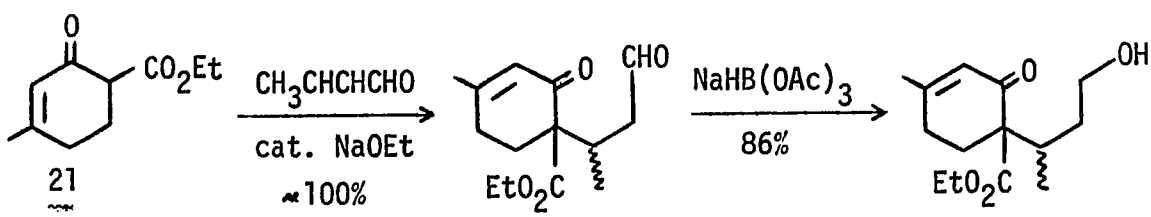
Our development of methodology for the reduction of hemiacetals and hemiketals led us to investigate a reaction scheme reminiscent of our early plans to produce the AB ring system. The key step of this strategy is illustrated in Scheme IV.

Scheme IV



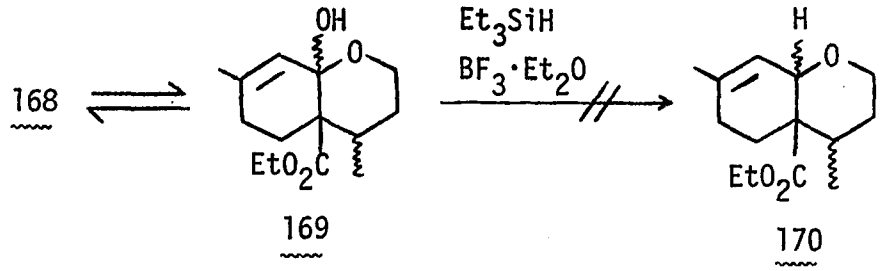
164 165 166

We prepared a model system starting with enone ester 21 (prepared from ethyl acetoacetate and methyl vinyl ketone). The Michael addition of 21 with crotonaldehyde afforded the enone aldehyde 167 in high yield. This aldehyde was then selectively reduced using sodium triacetoxyborohydride (73).



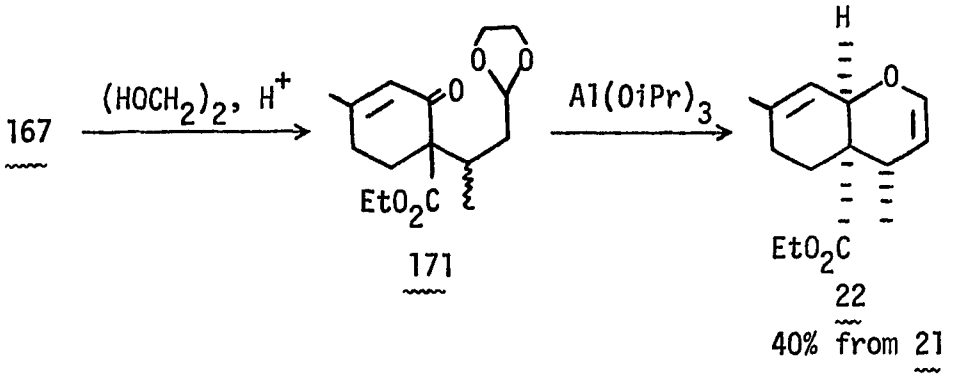
21 167 168

It was anticipated that the reduction product 168 would exist partially as the cyclic hemiacetal 169. Treatment of 168 with triethylsilane and boron trifluoride etherate was then expected to yield the fused AB ring system 170.

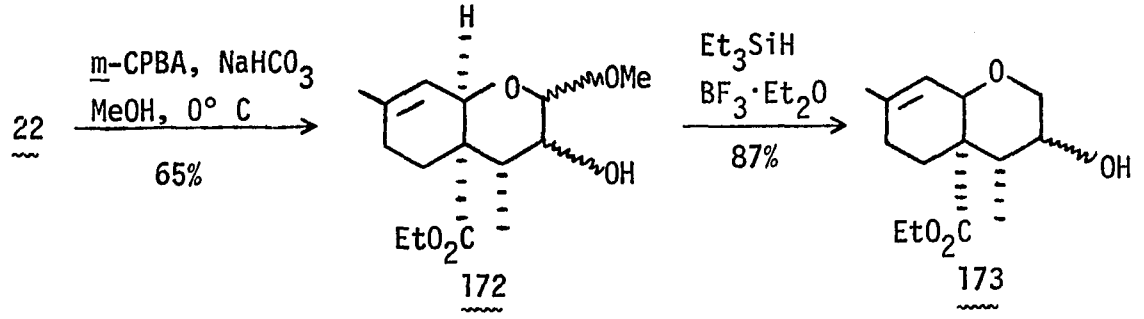


The stereochemistry of the ring fusion in 170 was a major question. This question remains unanswered because the enone alcohol 168 was inert to the organosilane reaction conditions. Apparently, the enone 168 does not form the hemiketal 169 and thus no reaction occurs. In fact, enone 168 resisted several ketalization procedures (e.g., ROH, H^+; $(MeO)_3CH$, NH_4NO_3; Me_3SiOMe, Me_3SiOTf).

Our plans of forming the AB ring system via intramolecular etherification again met with failure. We saw the possibility of using the triethylsilane reduction to advantage in yet another reaction scheme. By the method of Fujimoto et al., we prepared the cis-fused dihydropyran 22 via Meerwein-Ponndorf reduction of the enone acetal 171 (34). Unlike our Diels-Alder route, the cis-fused AB ring system when prepared by this reduction procedure could be produced in large quantities.

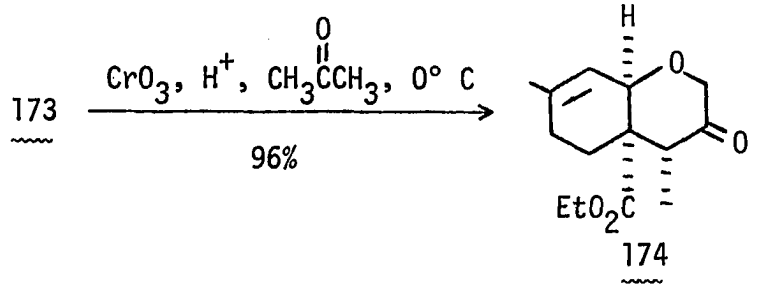


Epoxidation of enol ether 22 with m-chloroperbenzoic acid in the presence of sodium bicarbonate and with methanol as solvent afforded the mixed acetal alcohol 172 in good yield. Compound 172 was clearly a mixture of diastereomers. Reduction of the acetal 172 with triethylsilane and boron trifluoride etherate generated the desired β-hydroxy ether 173 in excellent yield. Notably, the alcohol of 172 required no protection and did not hinder the reaction.



Jones oxidation of the alcohol 173 produced keto ester 174 in essentially quantitative yield. In order to obtain the long sought

keto alcohol 103, we required a selective reduction of keto ester 174. This selective reduction became the focus of our efforts.



174

Selective Reduction Via Enolate Protection (74)

Many procedures are available for the reduction of a ketone or aldehyde in the presence of an ester or lactone (75). In order to achieve the complementary selectivity, a sequence involving protection, reduction and deprotection must be employed. In addition to the obvious operational inconvenience, olefin isomerization and other acid catalyzed rearrangements can occur during protection and deprotection. The structure of keto ester 174 suggested the possibility of using selective enolate formation as a means of protecting the ketone. The concept of using selective enolate formation in combination with hydride reduction was first introduced by Barton et al. for the reduction of steroidal ketones (76). Kieczykowski and Schlessinger (77), as well as Goldsmith et al. (43) have also used this concept. However, aside from these isolated applications, no study of this reduction strategy had been reported. We thus undertook an investigation of the scope and

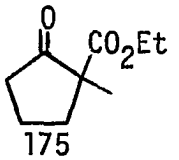
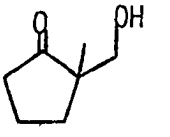
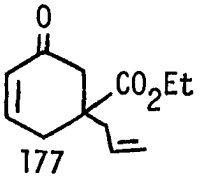
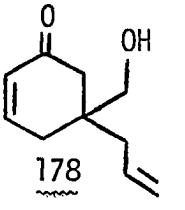
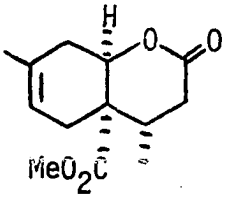
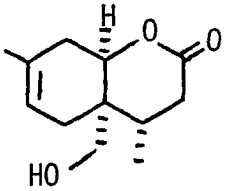
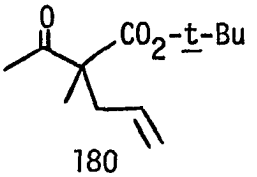
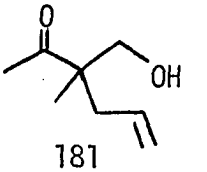
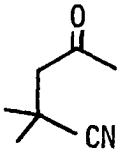
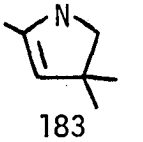
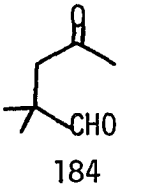
limitations of this enolate protection strategy before we attempted a reaction with the real system (i.e., keto ester 174).

A variety of ketones were prepared and subjected to deprotonation and reduction conditions. Ketone deprotonation was effected with either lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide. These reagents are nonnucleophilic and capable of completely deprotonating ketones at low temperatures. The reducing agents we employed were lithium aluminum hydride (LAH) and diisobutylaluminum hydride (DiBAH). We also selected for study model compounds that possessed a variety of functional groups. Our results are presented in Table II.

The experimental procedure we developed was exceptionally simple. The enolate was generated by slow addition of the ketone (1M in tetrahydrofuran) to a -78°C solution of the selected base. After enolate formation, the reducing agent was introduced. When the reduction was complete, as indicated by thin layer chromatography, the reaction was quenched by pouring the mixture into an aqueous acid solution.

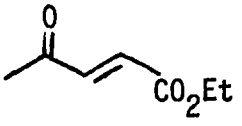
This method proved useful for the unambiguous synthesis of certain aldols (e.g., 176 and 181). Hirano and Wakabayashi had previously studied the acid catalyzed aldol condensation between ketones and formaldehyde (78). The reaction of 2-methylcyclopentanone and formaldehyde afforded a mixture of products via the acid catalyzed route. The major product was identical by proton NMR and IR with compound 176 definitively prepared via our enolate protection scheme.

Table II. Selective reduction via enolate protection

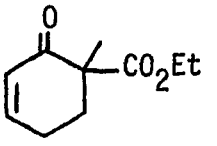
Reactant	Reducing Agent/Time	Yield	
 175	LAH/1h	76%	 176
 177	LAH/.5h	62%	 178
 153	LAH/.5h	65%	 179
 180	LAH/.5h	81%	 181
 182	LAH/.5h	67%	 183
182	DIBAH/2h	46%	 184

Reduction of the keto nitrile 182 afforded either a keto aldehyde 184 or a cyclic imine 183, depending upon the choice of reducing agents. Thus, it appears that this strategy is compatible with a variety of reducing agents and reducable functionalities.

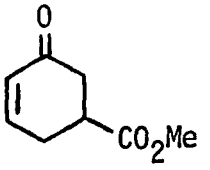
In contrast to the successful results in Table II, compounds 185 through 188 failed to yield appreciable amounts of the desired reduction products. Thin layer chromatography of the enolate solutions of these compounds indicated that, prior to addition of the hydride reducing agent, new products had already begun to form. Thus, failure of the reduction was because of enolate instability.



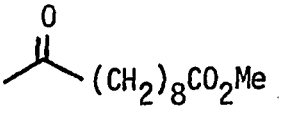
185



186



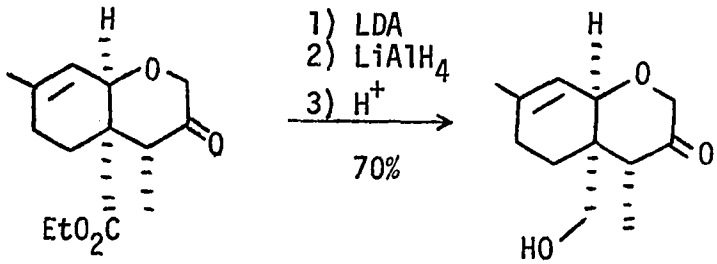
187



188

The failure of keto esters 187 and 188 to afford desired reduction products was significant. These dicarbonyls were the only two compounds tested in which the carbon α to the ester functionality possessed protons. Thus, ester enolate formation in competition with ketone enolate formation was possible. This competition between enolates may

have been a factor that led to the failure of 187 and 188 to react as anticipated. Nevertheless, this study illustrated that an enolate protection and reduction sequence was a viable strategy for the selective reduction of an ester in the presence of a ketone.



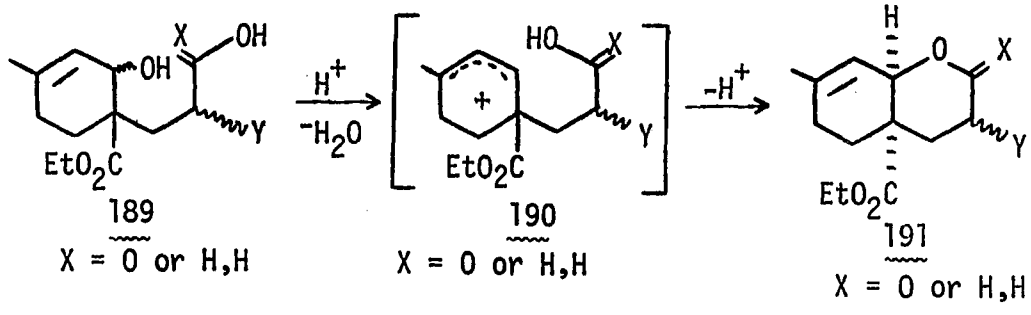
174 175

Having established a general reaction procedure, keto ester 174 was subjected to enolate formation and lithium aluminum hydride reduction. This reaction sequence produced the cis-fused AB ring system. The overall yield for the seven step sequence from enone ester 21 was 15%. The route also had the advantage that all reactions could be done easily and safely on large scale. Thus, keto ester 174 and keto alcohol 103 were available in multigram quantities necessary for further study directed toward introduction of the C ring of the trichothecenes.

Intramolecular Trapping of Allylic Carbonium Ions

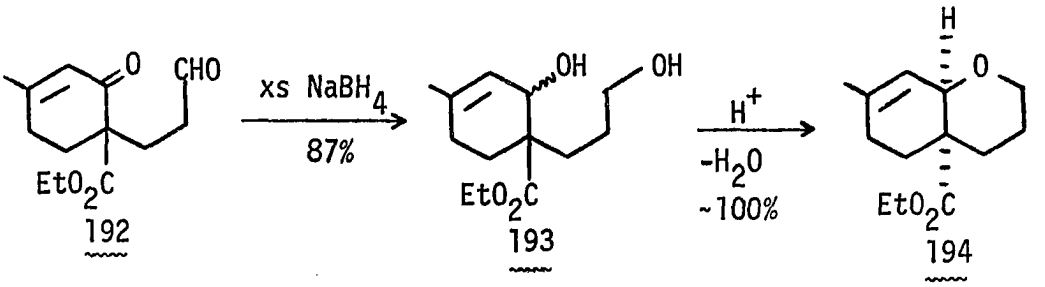
During the course of research directed toward the AB ring system, one synthetic scheme showed considerable promise. This route involved allylic carbonium ion formation and subsequent intramolecular trapping. This strategy is outlined in Scheme VII.

Scheme VII

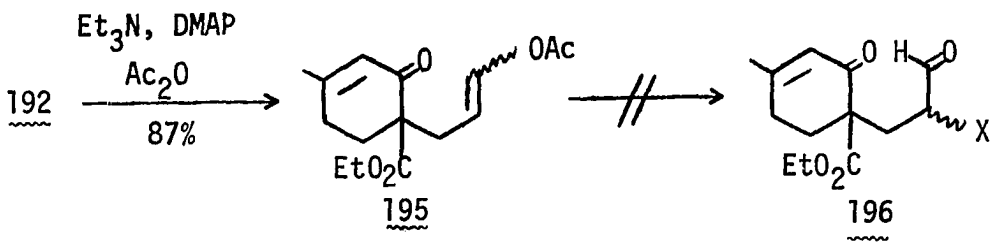


Colvin et al. (36,41) and Welch and Wong (45) had investigated the generation of allylic carbonium ions and subsequent γ-lactone formation in their routes directed toward the trichothecenes. The γ-lactone formation had ensured the cis stereochemistry of the ultimate AB ring fusion. Further, Masuoka and Kamikawa (35) and Still and Tsai (37) had employed biomimetic allylic carbonium intermediates in their syntheses of the trichothecenes (vide supra). We decided to investigate the possibilities of generating keto alcohol 103 using the intermediacy of allylic carbonium ions.

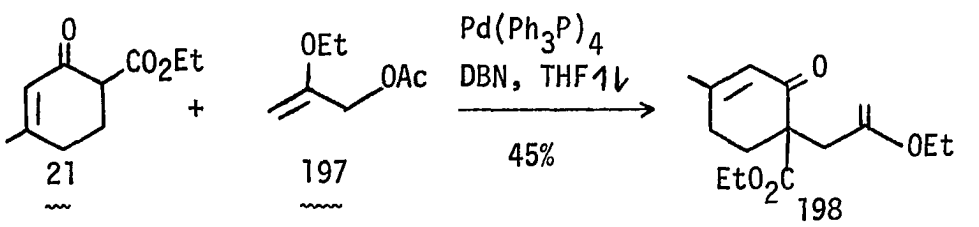
As a model system, we selected keto aldehyde 192. Reduction of 192 with excess sodium borohydride afforded diol 193 as a mixture of diastereomers. After examining several reaction conditions, we found that the allylic carbonium ion could be generated most efficiently by stirring diol 193 in methylene chloride with a catalytic amount of sulfuric acid. Under these conditions, the intramolecular etherification proceeded quickly and cleanly to yield one isomer exclusively, as determined by capillary column gas chromatography. Analysis of the proton NMR spectrum indicated that ether 194 was the cis-fused product.

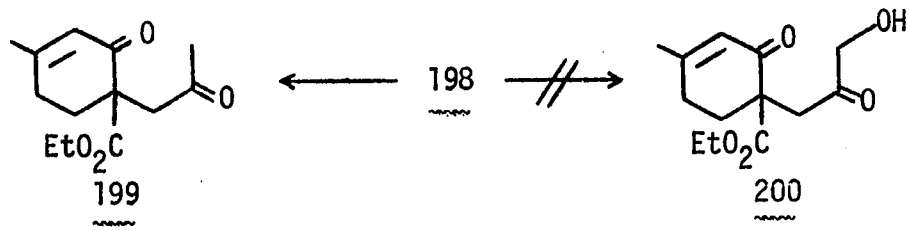


Encouraged by the results of the etherification reaction, we elected to construct a system that would possess the necessary B ring functionality. Enone aldehyde 192 was converted to enol acetate 195 (79); however, we were unable to convert this compound to a useful intermediate.



We next adopted the palladium chemistry developed by Trost and coworkers (80). Enol ether 198 was rapidly synthesized. Unfortunately, compound 198 was extremely susceptible to hydrolysis and all attempts at generating an α-hydroxy ketone 200 produced only the hydrolyzed product 199. Although diketone 199 was potentially useful, we chose to investigate other routes that would be more direct.



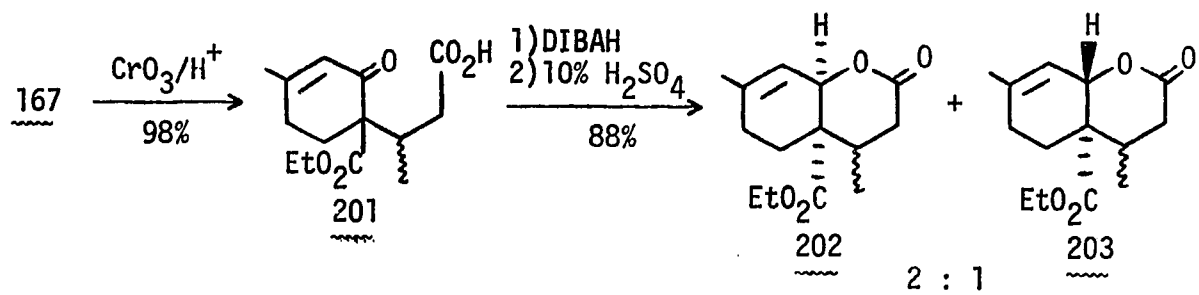


198

199

200

Keto acid 201 was prepared to investigate the feasibility of producing a cis-fused bicyclic lactone via an allylic carbonium ion intermediate. Subsequent reduction of the enone produced an allylic alcohol which lactonized upon acidic workup. Unlike the etherification reaction, lactone formation produced a mixture of cis- and trans-ring fused products (cis:trans; 2:1).



167

98%

201

1) DIBAH
2) 10% H_2SO_4

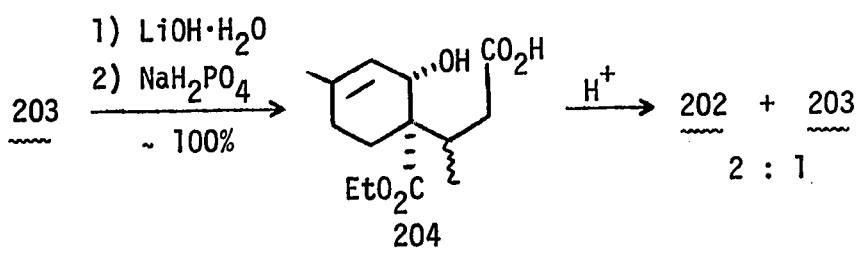
88%

202

2 : 1

203

To confirm that an intermediate allylic cation was involved in the lactonization, the trans-isomer 203 was hydrolyzed to the hydroxy acid 204 (LiOH; NaH_2PO_4) (81). Acid treatment of the hydroxy acid produced the same product ratio observed in the initial lactonization.



203

1) $LiOH \cdot H_2O$
2) NaH_2PO_4

~ 100%

204

H^+

202 + 203

2 : 1

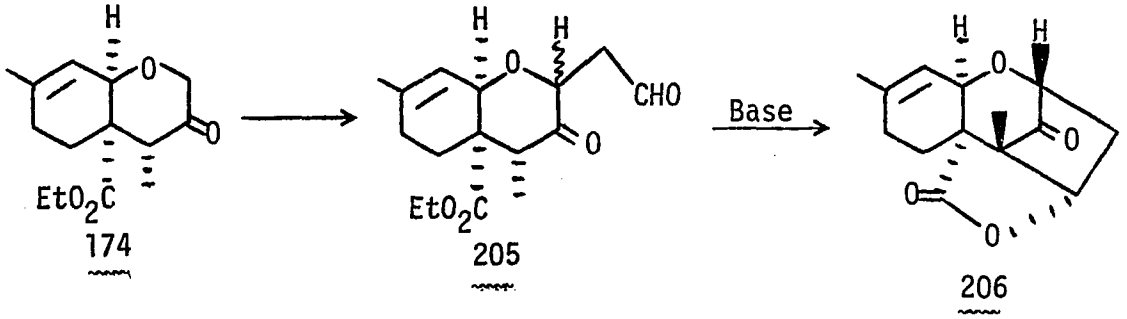
Since we had previously developed methodology for converting lactones to β-keto ethers, the preparation of lactone 202 represented an alternate route for the synthesis of keto alcohol 103. However, because of the successful development of our other route (vide supra), and because it would be inconvenient to continually recycle the undesired trans-lactone 203, we abandoned this route. It appears that future research in the area of allylic carbonium cyclizations ultimately may provide the most rapid synthesis of keto alcohol 103.

Approaches Toward the Trichothecene C Ring

Having surmounted the challenges presented by the synthesis of the AB ring system, we attacked the problem of introducing the trichothecene C ring. Although we had developed a practical route to keto alcohol 103, analysis of potential synthetic routes led us to believe further utilization of keto ester 174 possessed advantages over the use of keto alcohol 103 (82). For this reason, we advanced in our synthetic studies employing keto ester 174.

Our initial strategy is highlighted in Scheme VIII. We envisioned the introduction of an acetaldehyde unit onto keto ester 174 to afford the intermediate 205. Intramolecular aldol cyclization would then generate the trichothecene skeleton.

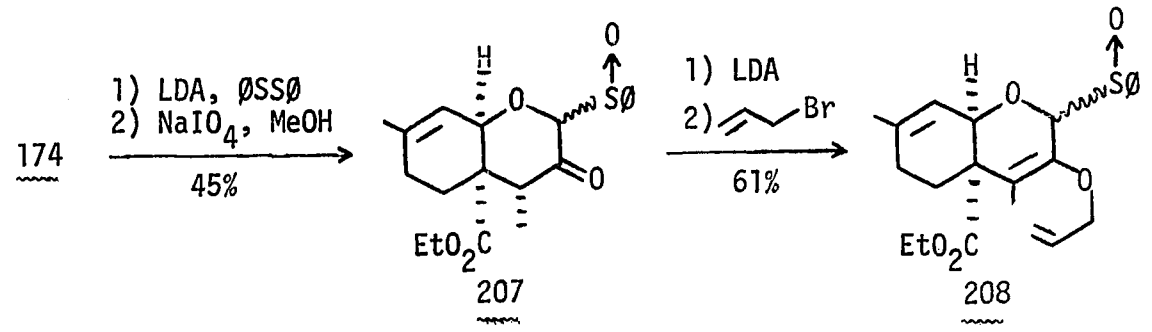
Scheme VIII



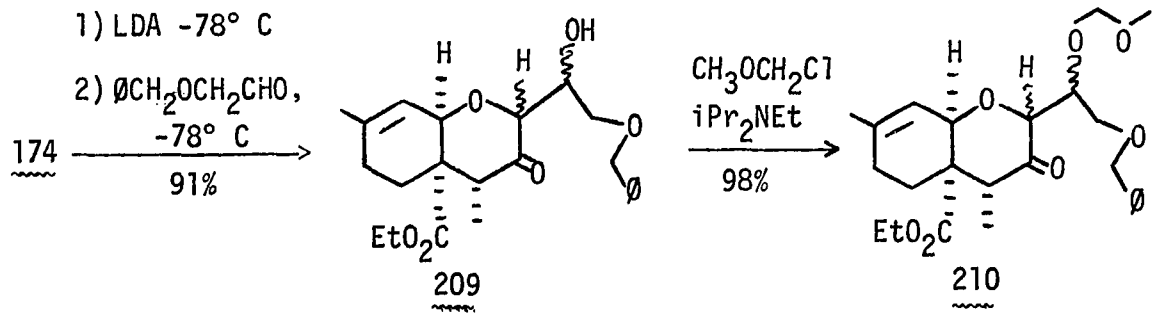
We were aware of the failure of Colvin et al. to induce aldol cyclizations (41) in systems similar to keto aldehyde 205. In generating the crowded quatenary center at C-5, retro-aldol reactions occurred to regenerate the less sterically hindered starting materials. We felt that this problem would be avoided by employing keto aldehyde 205. The close proximity of the carboethoxy group would lead to the trapping of the desired aldol product via lactone formation (206). The lactone would then be used as a protecting functionality until the ketone of 206 was transformed by a Wittig reaction. At that point, the retro-aldol reaction could no longer occur. Lactone formation would also have the added benefit of controlling the stereochemistry of the C-4 oxygen functionality.

We planned to construct keto aldehyde 205 via an alkylation procedure. In view of the work of Fujimoto et al. (34), we realized keto ester 174 would likely generate O-alkylated products. We attempted to promote C-alkylation by modifying 174. Sulfenylation of keto ester 174 (83) and subsequent selective oxidation (84) produced the β-keto

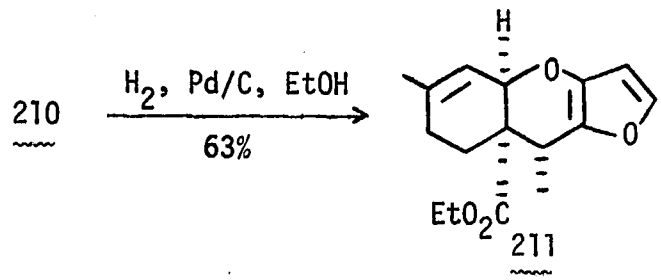
sulfoxide 207. Unfortunately, alkylation of 207 yielded only the O-alkylated product 208. It appeared that alkylation would not yield the products we required, and we were forced to consider alternate pathways.



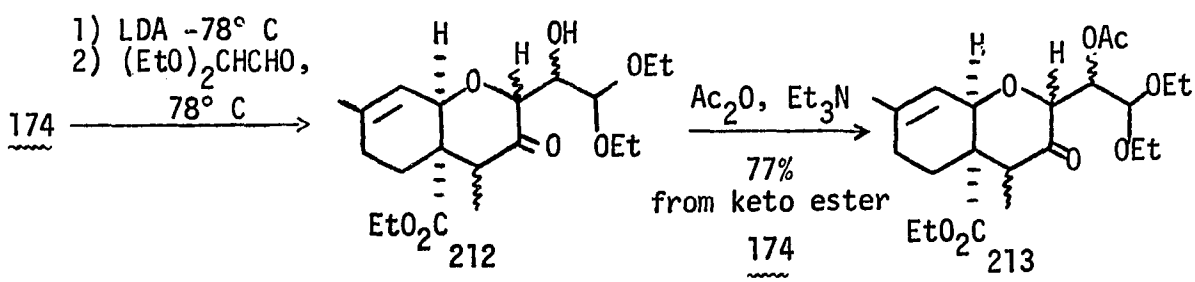
An aldol reaction with keto ester 174 appeared especially attractive. Such a scheme would introduce the C-3 hydroxyl of anguidin (4a). The kinetic enolate of keto ester 174 did indeed react with aldehydes to afford aldol products in high yield. After analysis of the functional requirements of the two carbon aldehyde unit, benzyloxyacetaldehyde was chosen for the aldol condensation. Aldol reaction and subsequent protection of the condensation product 209 afforded keto ester 210 very efficiently. We then investigated the conversion of the benzyl ether unit into the desired aldehyde.



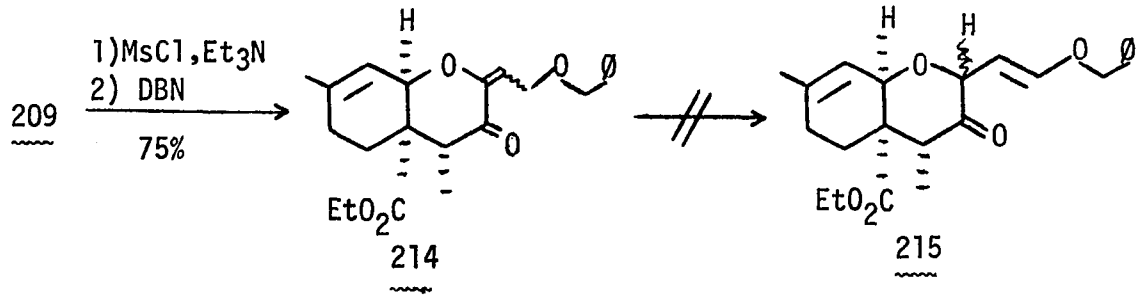
Unexpectedly, hydrogenolysis of the benzyl ether 210 did not produce the deprotected primary alcohol. It appeared that the alcohol readily cyclized to afford the tricylic furan 211. Furan 211 was the only product isolated.



In attempts to avoid generating the primary alcohol and the resulting furan formation, variously functionalized acetaldehydes were condensed with keto ester 174. Aldol condensations with ethyl glyoxylate produced only polymeric mixtures; but, 2,2-diethoxyacetaldehyde yielded the desired aldol product 212 which was protected as the acetate 213. However, attempts to hydrolyze the acetals 212 and 213 directly to α-oxygenated aldehydes produced no identifiable products.



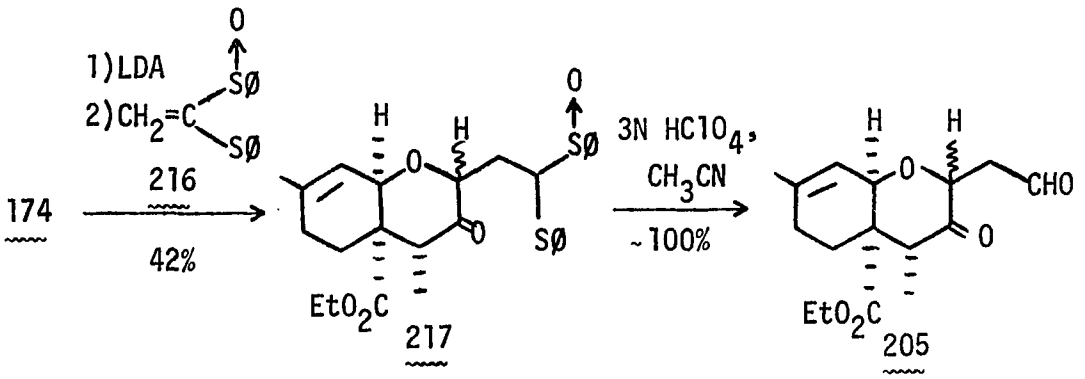
Redirecting our attentions to the original benzyloxyacetaldehyde aldol product 209, we reasoned that removal of the C-3 hydroxyl would preclude any furan formation. Thus, the alcohol was eliminated affording α,β-unsaturated ketone 214. In an attempt to generate keto aldehyde 205 directly, enone 214 was treated with strong base (LDA, t-BuOK). It was anticipated that deconjugation of the double bond would produce benzyl enol ether 215 which could be hydrolyzed to the keto aldehyde 205. However, deconjugation procedures led only to the destruction of enone 214.



The α,β-unsaturated ketone 214 was also subjected to reduction procedures known to produce conjugate reduction of enones [L-Selectride (85); $NaBH_4$, pyridine (86)]. Unfortunately, enone 214 afforded mixtures of 1,2- and 1,4-reduction products.

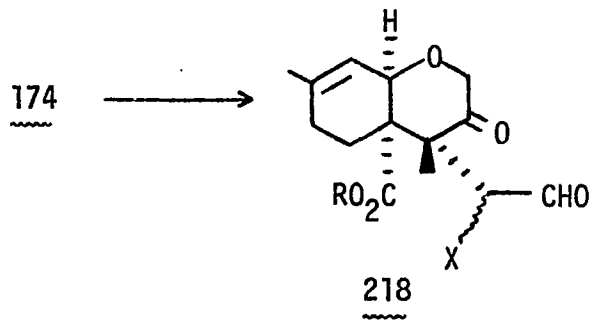
The difficulties encountered in preparing keto aldehyde 205 via aldol procedures prompted us to investigate new avenues of approach to this key intermediate. Previously, Herrmann et al. had developed methodology for generating 1,4-dicarbonyls via Michael additions of carbonyl enolates onto ketene thioacetal monoxides (87). The enolate of keto ester 174 was reacted with ketene thioacetal monoxide 216 to afford

a good yield of the Michael adduct. The crude thioacetal was then hydrolyzed to produce the crucial intermediate 205.



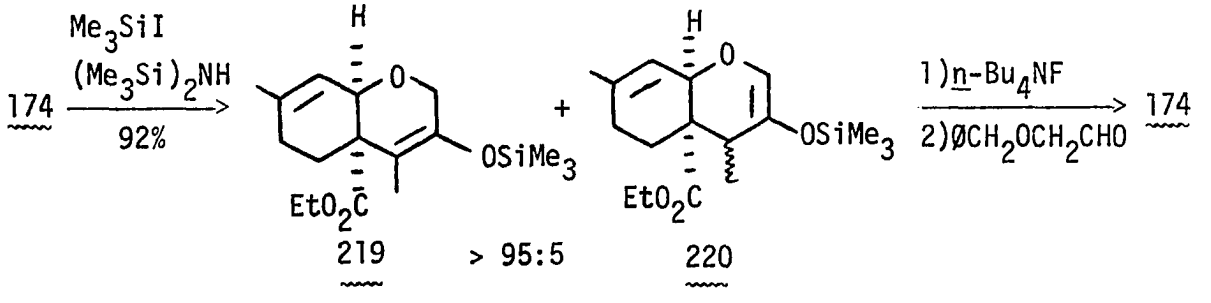
Initial investigations into the base-induced aldol cyclization and lactonization of keto aldehyde 205 resulted in recovery of starting material. Under more rigorous conditions, compound 205 was destroyed. These results were not totally unexpected in light of the results of Colvin et al.

In contrast to the reluctance of keto aldehyde 205 to undergo an intramolecular aldol reaction, the work of Fujimoto et al. demonstrated that aldol condensations to form the C ring could be accomplished with relative ease between centers 2 and 3 (34). Therefore, we studied the conversion of keto ester 174 into an intermediate of generalized structure 218.



Our immediate goal became the stereospecific generation of the quaternary center at C-5. The concave nature of the cis-fused ring system led us to believe that the quaternary center would be generated with the correct relative stereochemistry. Thus, the success of this strategy hinged upon the ability to generate the more highly substituted enolate of keto ester 174.

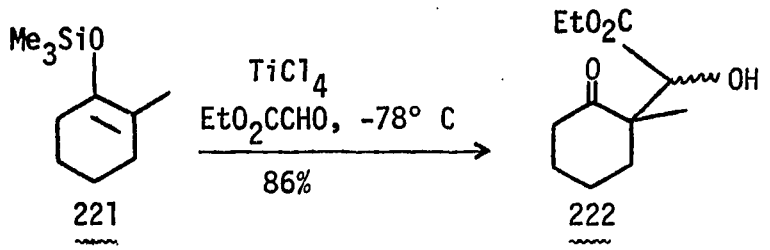
Initial attempts to generate the thermodynamic enolate of keto ester 174 resulted in reaction at the least substituted position. We were able to surmount the obstacle of selective enolate formation utilizing the versatile procedure of Miller and McKean for generating silyl enol ethers (88). Treatment of keto ester 174 with iodotrimethylsilane and hexamethyldisilazane resulted in the formation of the desired silyl enol ether 219 in greater than 95% regioselectivity (gas chromatography). However, generation of the tetra-n-butylammonium enolate (89) and addition of benzyloxyacetaldehyde resulted only in recovery of keto ester 174.



In recent years, silyl enol ethers have become versatile synthetic intermediates. A wide variety of methodologies has been developed for the application of these silyl compounds. Although regiospecific enolate

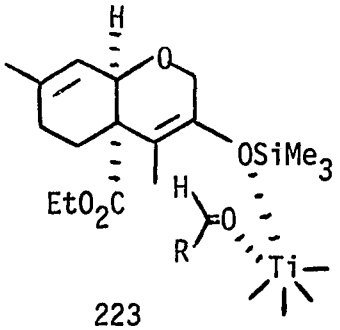
formation failed to produce the desired results, we believed that silyl enol ether 219 was still a valuable intermediate in the approaches toward keto aldehyde 218 and the trichothecenes.

We adopted methodology developed by Mukaiyama and coworkers (90). They found that silyl enol ethers and aldehydes, when reacted in the presence of titanium tetrachloride, afforded aldol products in high yield. Furthermore, the silyl enol ethers of unsymmetrical carbonyls reacted regiospecifically. We prepared aldol product 222 as a model system to test the feasibility of using ethyl glyoxylate as the aldehyde unit.



221 222

Encouraged by the successful preparation of 222, we attempted reaction with the real system (219). Analysis of the transition states involved in the condensation reaction led us to believe that, of the two possible diastereomeric lactones, the desired configuration 225 would predominate. We reasoned that the transition state wherein the less bulky hydrogen was forced under the ring would be lower in energy and therefore be favored. Lactone 225 would then be ready for cyclization to form the C ring.



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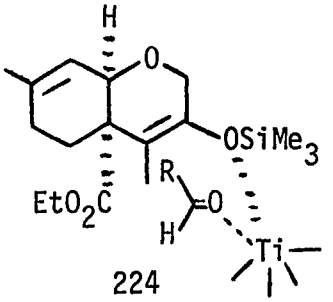

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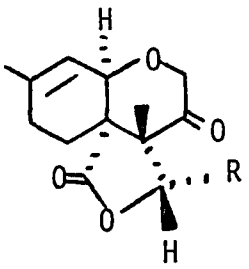

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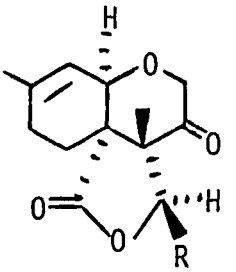
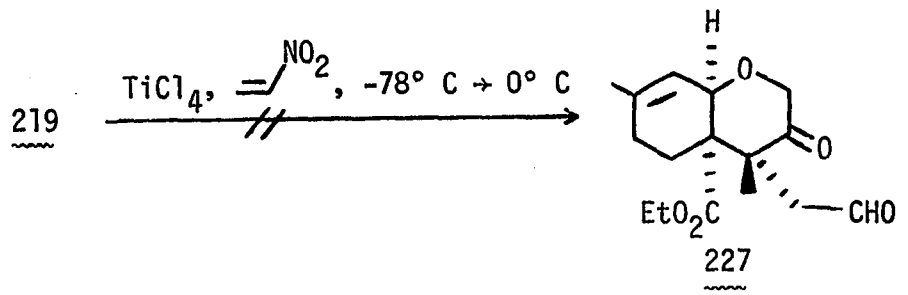


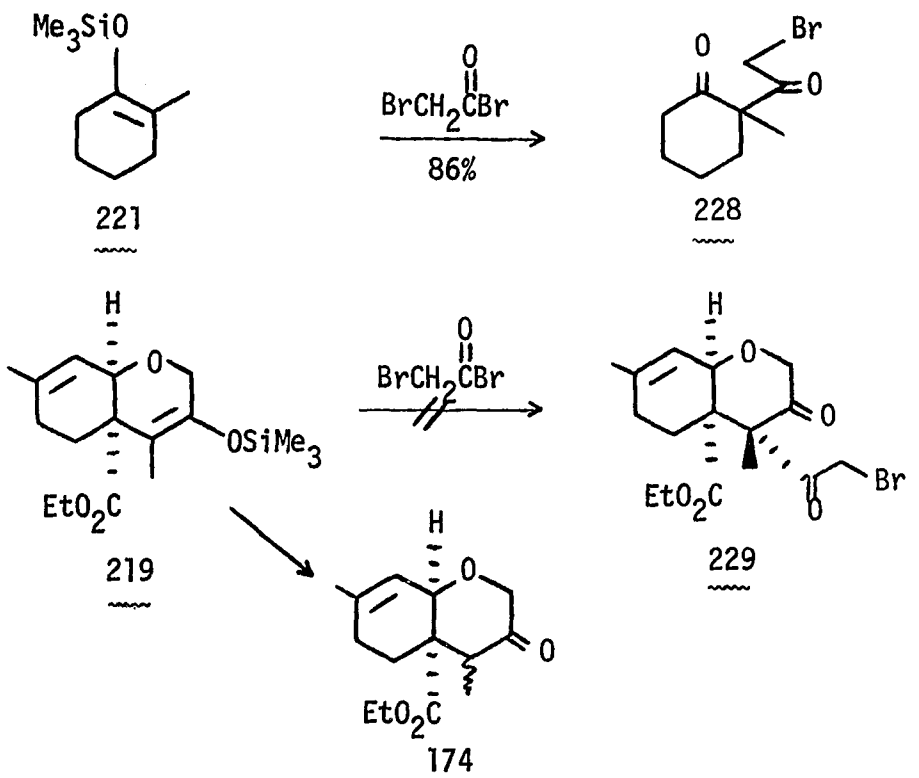
226

When silyl enol ether 219 and ethyl glyoxylate were mixed with titanium tetrachloride, keto ester 174 was again the only product isolated. Reaction with benzyloxyacetaldehyde afforded the same result.

Miyashita et al. developed a procedure whereby titanium tetrachloride was used to induce Michael additions between silyl enol ethers and nitroethylene (91). This procedure afforded 1,4-dicarbonyl compounds directly. We reacted the silyl enol ether 219 with nitroethylene and titanium tetrachloride. The reaction, however, yielded spurious results.

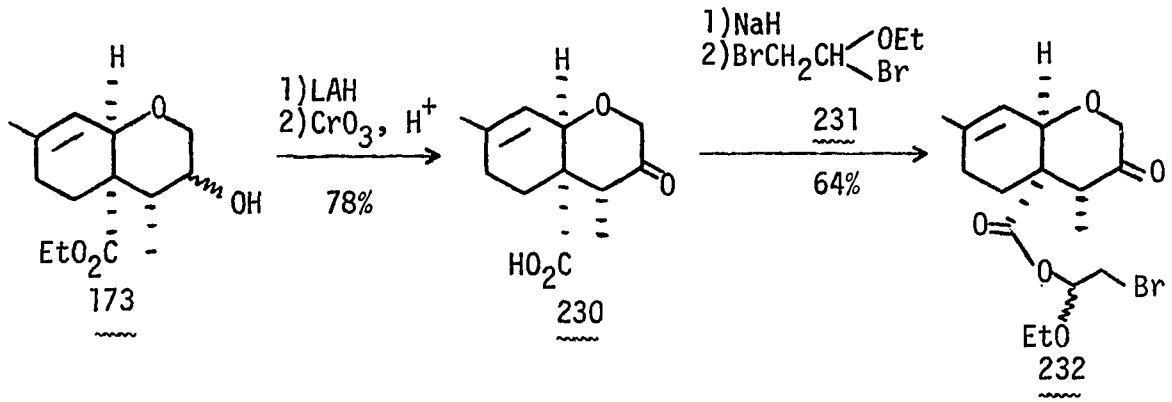


We had also discovered a report that polyhaloacetyl chlorides reacted with silyl enol ethers to produce 1,3-diketones (92). Extending this procedure, we tested the reaction of bromoacetyl bromide with 1-methyl-2-trimethylsiloxy-1-cyclohexene. After one day at room temperature, the dicarbonyl 228 was obtained in high yield. If diketone 229 could be prepared in a similar manner, we would have progressed a long way toward the preparation of verrucarol. Even rigorously purified bromoacetyl bromide hydrolyzed the silyl enol ether 219 cleanly and completely.



In retrospect, it appears that attempts to form two contiguous quaternary centers via intermolecular reactions failed because of steric interference. The success obtained by Bruce Roth in generating the quaternary center at C-5 via intramolecular reaction prompted us to adopt similar strategies (49b).

Keto ester 174 proved to be exceedingly difficult to hydrolyze, but keto acid 230 was easily obtained by slight modification of our previous synthetic scheme. Having prepared the acid 230, we sought a suitable two carbon unit that could be used to esterify the acid and then undergo intramolecular cyclization. The dibromide 231 (93) appeared to possess all of the characteristics we required. Reaction with the sodium carboxylate of acid 230 afforded the bromoketone 232 in good yield.

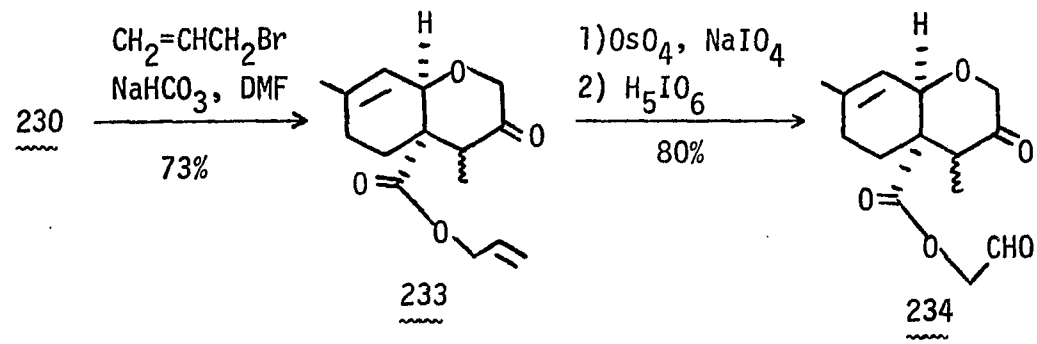


We were unable to generate any intramolecular cyclizations of 232 (t-BuOK/t-BuOH). Apparently, the ethoxy group of bromoketone 232 interfered in the intramolecular alkylation. Analysis of molecular models generated some insights and led us to believe that unfavorable steric interactions of both of the diastereomers of bromoketone 232 prevented

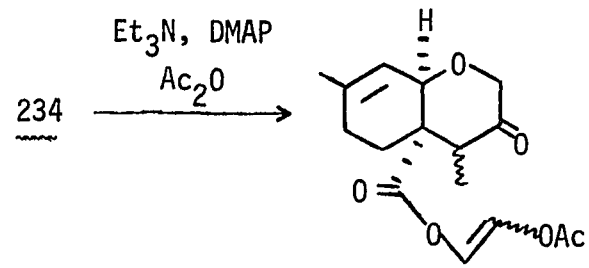
attainment of necessary transition states. Kieczykowski et al. had reported similar difficulties in applications of dibromide 231 (93).

In a further attempt to utilize bromoketone 232, it was reacted with iodotrimethylsilane and hexamethyldisilazane (88). However, the silyl enol ether 233 was not obtained. The iodotrimethylsilane reacted with the acetal to regenerate keto acid 230.

We sought an intermediate that would avoid the unfortunate steric interactions encountered with bromoketone 232. Such an intermediate was prepared by reaction of keto acid 230 with allyl bromide to afford the allyl ester 233 in high yield. Selective reaction of the allyl group with osmium tetraoxide afforded a diol which was reacted with periodic acid to afford keto aldehyde 234. Osmium tetraoxide could have been used to generate the aldehyde directly. However, we felt the aqueous conditions would generate hydrates of the desired product. The periodic acid reaction was conducted in anhydrous ether, thus avoiding any hydrate problem.



To induce intramolecular aldol cyclization, keto aldehyde 234 was treated with triethylamine. No apparent reaction was observed. It was possible that the condensation was indeed occurring but that the retro-aldol reaction prevented isolation of the cyclized product. In an effort to trap the aldol product, acetic anhydride was added. Dimethylamino-pyridine was also added to aid in the formation of the acetate, but this resulted in the apparent generation of enol acetate 235.



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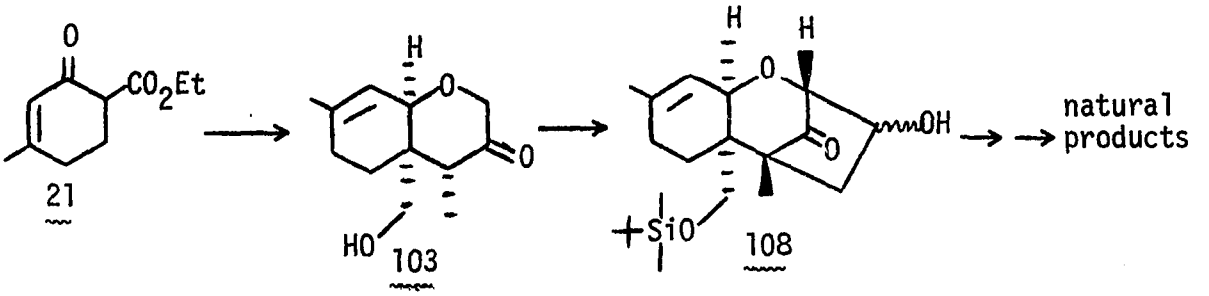
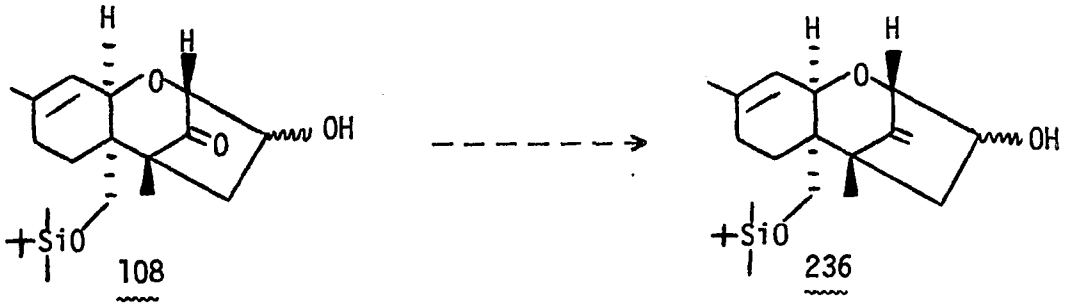
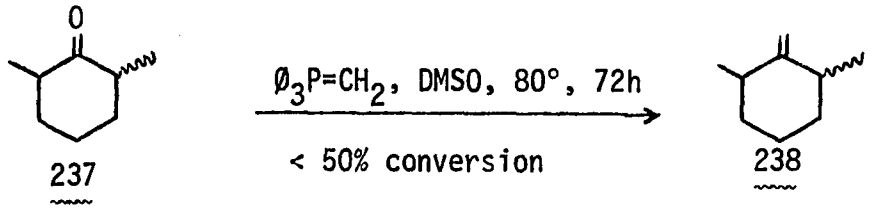
The difficulties encountered in generating the C ring utilizing keto ester 174 prompted us to reevaluate the direction of our research. My coworker, Bruce Roth, had already developed a practical synthesis of the trichothecene skeleton utilizing keto alcohol 103 (vide supra). Rather than develop another route, we have decided to attack the challenges of converting keto alcohol 108 into the naturally occurring epoxytri-chothecenes. The combination of our improved synthesis of keto alcohol 103 and the efficient generation of the trichothecene skeleton 108 should ultimately provide elegant total syntheses of many trichothecenes.



Future Research

Investigations are currently underway to convert keto alcohol 108 to diene 236. Welch et al. (94) and Smith and Jerris (95) recently reported the successful Wittig reactions of very hindered enolizable ketones. Applying the methodology of Welch et al., we reacted 2,6-dimethylcyclohexanone with methylenetriphenylphosphorane in scrupulously dried dimethylsulfoxide. Although the reaction proceeded smoothly for less hindered ketones, 2,6-dimethylcyclohexanone afforded olefin 238 exceedingly slowly (<50% conversion after 72 h). Since keto alcohol 108 is more hindered than 237, we felt there was little reason to react 108 under the same conditions.





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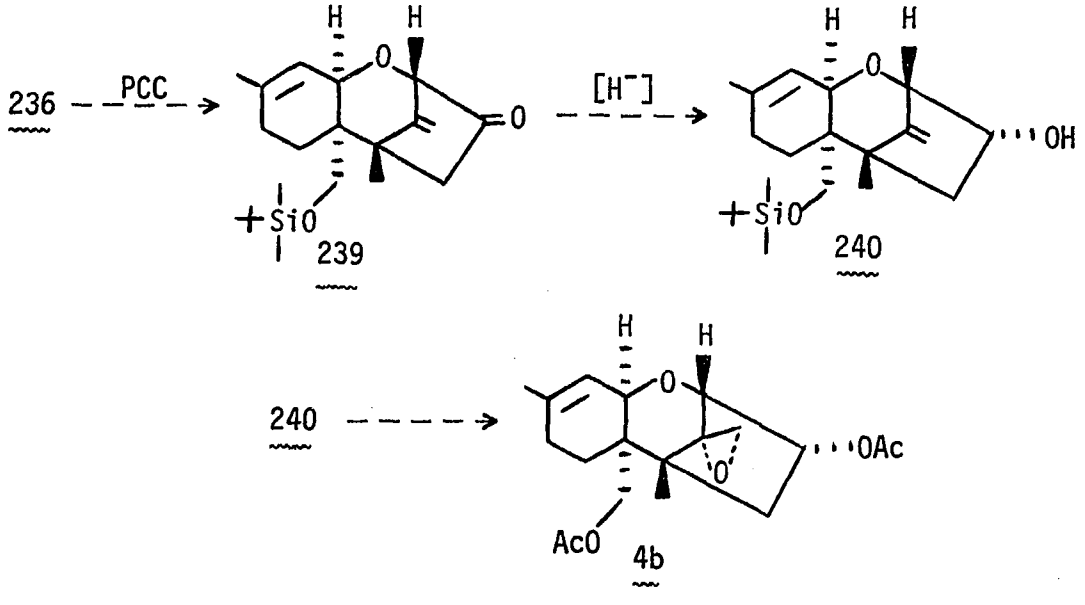
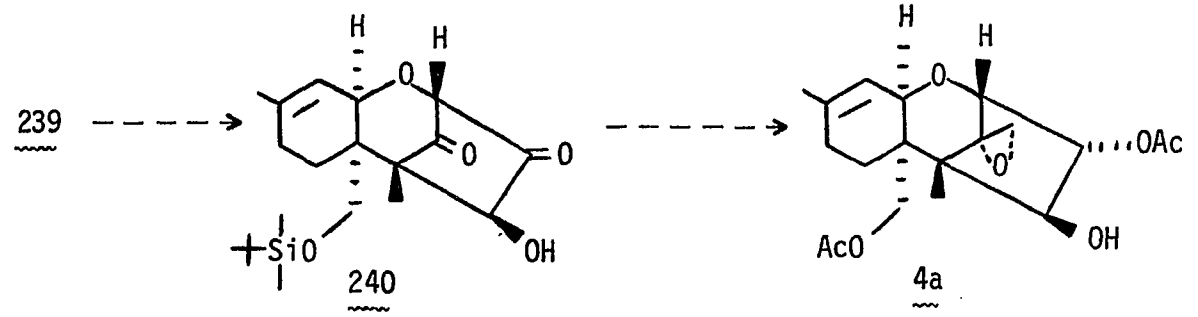
The method of Conia and Limasset ($Ø_3P^+CH_3I^-$, t-AmOK, toluene, 115°C) (96) appears to work well with very hindered ketones (e.g., camphor). The recent report of Smith and Jerris indicated that this procedure worked on a system which failed to react under the conditions developed by Welch et al. (95). Attempts are underway to apply this methodology to keto alcohol 108.

Once the Wittig product is obtained, very few steps will be required to convert the dienic alcohol 236 to a variety of natural products. Oxidation of dienic alcohol 236 will produce ketone 239. Reduction of the carbonyl with a bulky hydride reagent should occur selectively from the exo face of ketone 239. Desilylation, acetylation and epoxidation should then complete the first synthesis of calonectrin (4b).



Ketone 239 could also serve as a valuable intermediate in the synthesis of anguidin (4a). A variety of synthetic methods are known that would stereospecifically introduce the necessary C-4 hydroxyl. Procedures similar to those described above could then be used to convert hydroxy ketone 240 into the valuable natural product anguidin.



The efficient route to the trichothecene skeleton employing the improved synthesis of intermediate keto alcohol 103 has provided major advances toward the synthesis of the naturally occurring 12,13-epoxytrichothecenes. The course of this research also led to the development of novel synthetic methodologies: conversion of epoxides to allylic alcohols, and selective reduction via enolate protection. These procedures now provide practical transformations in areas where useful methods have been lacking.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether and THF were distilled from $LiAlH_4$ prior to use. All reactions were conducted under an inert atmosphere (nitrogen or argon), and all organic extracts were dried over Na_2SO_4, except where otherwise noted. All silica gel chromatographies used ether-hexane mixtures. Melting points were determined on a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or an Acculab 2 spectrometer. Nuclear magnetic resonance spectra were recorded using a Varian EM-360, A-60, or HA-100 spectrometer or a Hitachi-Perkin Elmer R-20B spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. The C-13 NMR spectra were recorded using a Joel FX-90Q. The chemical shifts for C-13 NMR are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). An AEI-MS902 mass spectrometer was used for mass spectral data.

2-(2-Nitroethoxy)tetrahydropyran

To 2-nitroethanol (9.1 g, 100 mmol) in 50 ml of CH_2Cl_2 was added dihydropyran (13.8 ml, 150 mmol) and pyridinium p-toluenesulfonate (2.51 g, 10 mmol). This solution was stirred at ambient temperature under nitrogen for 2 h. After dilution with chloroform, the solution was washed twice with H_2O, dried and concentrated. A fast silica gel

chromatography yielded 15.4 g (88%) of a pale yellow oil: IR (film) 1560, 1350 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.31-2.03 (m, 6H), 3.37-4.30 (m, 4H), 4.35-4.83 (m, 3H).

3-Hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane

To a solution of K_2CO_3 (2.28 g, 16 mmol) in 10 ml of a 1:1 ethanol-H_2O mixture at room temperature was added 2-(2-nitroethoxy)tetrahydropyran (5.26 g, 30 mmol) in 5 ml of ethanol. Freshly distilled acetaldehyde (1.85 ml, 35 mmol) in 5 ml of ethanol was then added dropwise. The solution was stirred for 30 min then neutralized with 1N HCl. The mixture was extracted twice with chloroform, dried and concentrated. The crude product (5.189 g, 78.6%) was used without further purification: IR (film) 3450, 1560, 1350 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.30 (m, 3H), 1.40-1.86 (m, 6H), 3.37-4.40 (m, 6H; with D_2O added, 5H), 4.55-4.81 (m, 2H).

2-Nitro-1-(2-tetrahydropyranyloxy)-2-butene (118)

The crude 3-hydroxy-2-nitro-1-(2-tetrahydropyranyloxy)butane (2.19 g, 10 mmol) was stirred in 10 ml of CH_2Cl_2 at 0°C under nitrogen. To this solution was added, all at once, mesityl chloride (0.77 ml, 10 mmol). After a few minutes, triethylamine (2.79 ml, 20 mmol) was added dropwise. Stirring was continued for 15 min. The solution was then diluted with CH_2Cl_2 and washed twice with H_2O and once with brine. The organic layer was dried and concentrated. Silica gel chromatography yielded 865 mg (43%) of 118 as a viscous orange-red oil: IR (film) 1630,

1530, 1320 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.33-1.82 (m, 6H), 2.01 (d, $\underline{J}$ = 8 Hz, 3H), 3.35-4.08 (m, 4H), 4.55-4.71 (m, 1H), 7.37 (q, $\underline{J}$ = 8 Hz, 1H).

1-Cyano-4-methyl-1-cyclohexene (120)

4-Methylcyclohexanone (6.1 ml, 50 mmol) was added over a period of 30 min to an ice-cold solution of sodium bisulfite (7.8 g, 75 mmol) in 15 ml of H_2O. Then, KCN (4.88 g, 75 mmol) in 10 ml of H_2O was added slowly to the cooled solution. The mixture was allowed to warm to room temperature and stirred overnight. The solution was extracted three times with ether, dried and concentrated *in vacuo*. The crude cyanohydrin (4.34 g, 62%) obtained was used without further purification. The cyanohydrin was then dissolved in pyridine (7 ml, 90 mmol) at 0°C under nitrogen. Thionyl chloride (6.27 ml, 86 mmol) was added dropwise. The solution was warmed to room temperature and stirred overnight. The mixture was then poured into 100 ml of H_2O, the pH adjusted to 4 with 1N NaOH and the mixture extracted three times with ether. The extracts were dried and concentrated. Distillation of the residue afforded 2.78 g (78% from cyanohydrin) of 120 as a pale yellow oil: bp 118°C/11 mm [lit bp 98-100°C/5 mm (97)]; IR (film) 3040, 2215, 1635 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.99 (d, $\underline{J}$ = 6 Hz, 3H), 1.21-2.50 (m, 7H), 5.50-6.72 (m, 1H).

1-Cyano-1-(4-hydroxy-3-nitro-2-butyl)-4-methyl-2-cyclohexane (121)

To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.93 ml, 5.5 mmol) in 5 ml of THF at 0°C under nitrogen was added 2.52 ml (5.5 mmol) of a 2.1 M solution of n-butyllithium in hexane. After 15 min, nitrile 120 in 5 ml of THF was added dropwise. The red solution was stirred for 30 min at 0°C then cooled to -78°C. Nitro olefin 118 in 5 ml THF was then added slowly. After 5 min, the solution was warmed to 0°C and quenched with acetic acid (0.63 ml, 11 mmol). The solution was diluted with ether, washed once with H_2O, dried and concentrated in vacuo. The crude product was then dissolved in 10 ml of 95% ethanol. A trace of p-toluenesulfonic acid was added and the solution refluxed for 4 h. After the mixture cooled, 15 ml of H_2O was added, and the solution was extracted three times with ether. The extracts were dried and concentrated. Silica gel chromatography yielded 512 mg (43%) of 121 as a mixture of diastereomers: IR (film) 3450, 2230, 1560, 1350 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.82-2.34 (m, 12H), 3.08 (br s, 1H, OH), 3.80-4.34 (m, 3H), 5.33-5.71 (m, 1H), 5.84-6.12 (m, 1H); high resolution mass spectrum, calcd for $C_{12}H_{18}N_2O_3$ m/e 238.13173, found m/e 238.13251.

Attempted Cyclizations of 121

A solution of phenylselenyl chloride (70 mg, 0.36 mmol) in 1 ml of CH_2Cl_2 was added dropwise to olefinic alcohol 121 (87 mg, 0.36 mmol) in 1 ml of CH_2Cl_2 at -78°C. The solution was stirred 1 h at -78°C then warmed to 0°C for 3 h. TLC monitoring of the reaction indicated starting

materials only. The solution was warmed to room temperature and stirred an additional 24 h. Removal of the solvent yielded starting materials.

To a stirred solution of 121 (119 mg, 0.5 mmol) in 2 ml of THF was added mercuric trifluoroacetate (427 mg, 1 mmol). The mixture was stirred 12 h at room temperature. Monitoring of the reaction by TLC indicated no new products. The solution was then heated to 65°C for 3 h with no apparent change. The THF was removed and 121 was recovered unchanged.

Attempted Hydrolyses of 121

A solution of nitrile 121 (100 mg, 0.51 mmol) in 5 ml of 3% HCl in methanol was refluxed for 12 h. The methanol was removed affording starting material 121 unchanged.

Nitrile 121 (100 mg, 0.51 mmol) was heated to reflux in 2 ml of water containing barium hydroxide octahydrate (630 mg, 2 mmol). No evolution of ammonia could be detected (wet litmus paper held over lip of flask). After 4 h, the solution was cooled and extracted with ether. The extracts were dried and concentrated yielding 121 unchanged.

Attempted Reduction of Nitrile 121

To a stirred solution of 121 (119 mg, 0.50 mmol) in 1 ml of toluene at -78°C was added 1.05 ml (1.05 mmol) of 1M DIBAH in THF. After 15 min at -78°C, the solution was poured into 5 ml of ice-cold 10% acetic acid solution with vigorous stirring. This solution was diluted with $CHCl_3$ and stirred at room temperature for 1 h. The organic layer was

separated and dried. Removal of the solvent afforded an intractable tar.

Bromination of 121 and Attempted Cyclizations of the Allylic Bromide

A 0.5M CCl_4 solution of 121 (184 mg, 0.77 mmol) and NBS (165 mg, 0.90 mmol) was heated to reflux with a sun lamp until bromination was complete. The solution was cooled, filtered and concentrated to yield 221 mg (93%) of an unstable allylic bromide. Evidence for this product is based on the appearance of a broad singlet, δ 1.83, in the proton NMR. This product was used without further purification.

To a 0.5M toluene solution of the allylic bromide (110 mg, 0.35 mmol) at -40°C was added DBN (0.05 ml, 0.38 mmol) in 1 ml of toluene. The solution was stirred for 1 h as the temperature increased slowly to 0°C. TLC at this point indicated only spotting at the origin. Workup afforded no identifiable products.

A 0.5M acetonitrile solution of allylic bromide (110 mg, 0.35 mmol), silver nitrate (53 mg, 0.35 mmol) and 1 drop of pyridine was stirred overnight at room temperature. No identifiable products were observed upon workup.

Epoxidation of 121

A 0.5M $CHCl_3$ solution of 121 (1.23 g, 5.9 mmol) and p-nitroperbenzoic acid (1.59 g, 8.7 mmol) was stirred at room temperature for 4 days. The solution was filtered then washed once with saturated sodium

bicarbonate solution. The organic layer was separated, dried and concentrated. Silica gel chromatography afforded 1.28 g (5.7 mmol, 97%) of epoxide 126 as a mixture of diastereomers: IR (film) 3440, 2230, 1560, 1350 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.83-2.40 (m, 12H), 2.78 (br s, 1H, OH), 2.94-3.50 (m, 2H), 3.94-4.81 (m, 3H); high resolution mass spectrum, calcd for $C_{12}H_{18}N_2O_4$ m/e 254.12664, found m/e 254.12681.

General Preparation of Allylic Alcohols from Epoxides

Method A

To a stirred solution of the epoxide (2.5 mmol) in 5 ml of acetonitrile at 0°C was added DBN (5 mmol), followed by dropwise addition of iodotrimethylsilane (2.75 mmol). After 15 min, the dark solution was heated to reflux for 12-48 h. The cooled solution was then concentrated *in vacuo*, diluted with brine and extracted three times with ether. The silyl ether was hydrolyzed by shaking the organic extracts with aqueous acid (0.1N HCl) in a separatory funnel. The organic layer was dried and concentrated. The residue was chromatographed on silica gel to afford pure allylic alcohol.

Method B

To a stirred solution of the epoxide (2.5 mmol) in 5 ml of benzene at 10°C was added dropwise iodotrimethylsilane (2.75 mmol). After 30 min, the solution was concentrated *in vacuo* and 5 ml of acetonitrile and DBN (5 mmol) were then added. The solution was heated to reflux for 12-48 h. The cooled reaction mixture was worked up as in method A.

2-Cyclohexen-1-ol (131) This allylic alcohol was prepared in 79% yield using method A: IR (film) 3400, 1070 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.40-2.18 (m, 6H), 3.95-4.30 (m, 2H), 5.50-5.75 (m, 2H).

2-Methylenecyclohexanol (133) This allylic alcohol was prepared in 69% yield using method A: IR (film) 3400, 1640, 905 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.20-2.40 (m, 8H), 3.97 (br s, 2H), 4.74 (br s, 1H), 4.85 (m, 1H).

2-Phenyl-2-cyclohexen-1-ol (135) This allylic alcohol was prepared in 68% yield using method B: IR (film) 3450, 1060 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.40-2.60 (m, 6H), 3.28-3.50 (m, 1H), 4.63 (br s, 1H), 5.90-6.15 (m, 1H), 6.90-7.60 (m, 5H).

Mixture of methyl 9-hydroxy-10-heptadecenoate and methyl 8-hydroxy-9-heptadecenoate (137a&b) This mixture was prepared in 75% yield using method A. No attempt was made to separate the isomers: IR (film) 3400, 1735, 1165 cm^{-1}; 60 MHz ($CDCl_3$) δ 0.70-2.50 (m, 27H), 3.65 (s, 3H), 3.90-4.10 (m, 2H), 5.40-5.63 (m, 2H).

Methyl 2-hydroxy-1-methyl-3-cyclohexenoate (139) This allylic alcohol was prepared in 70% yield using method A: IR (film) 3430, 1735, 1115 cm^{-1}; 60 MHz NMR ($CDCl_3$) (one diastereomer) δ 1.20 (s, 3H), 1.40-2.25 (m, 4H), 3.73 (s, 3H), 4.55 (m, 1H), 4.85 (br s, 1H), 5.65 (br s, 1H), 5.76 (br s, 1H); (other diastereomer) δ 1.26 (s, 3H), 1.40-2.25 (m, 4H), 3.73 (m, 3H), 4.05 (m, 1H), 4.85 (br s, 1H), 5.65 (br s, 1H), 5.76 (br s, 1H).

Ethylene ketal of 5-hydroxy-6-methyl-6-hexen-2-one (141) This allylic alcohol was prepared in 50% yield using method A: IR (film) 3460, 1655, 1070 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.50-1.90 (m, 7H), 2.85 (m, 1H), 3.92 (s, 4H), 4.10 (br s, 1H), 4.80 (m, 1H), 4.93 (m, 1H); C-13 NMR ($CDCl_3$) 17.468, 23.590, 29.115, 34.751, 64.383, 75.218, 109.781, 110.539, 147.324.

Attempted Allylic Alcohol Formation from Epoxy Nitrile 126

Epoxy nitrile 126 was reacted using the same conditions employed for the preparation of allylic alcohols 131 through 141. Regardless of whether method A or method B was used, addition of iodotrimethylsilane to the epoxy nitrile resulted in immediate formation of an insoluable tar on the side of the flask. No identifiable products were isolated.

1-(Carbomethoxy)-4-methyl-2,5-cyclohexadiene (142)

To 200 ml of liquid ammonia was added 7.5 ml of H_2O, p-toluic acid (3.4 g, 25 mmol), and lithium (870 mg, 125 mmol). The lithium was added quickly over a period of approximately 3 min. The ammonia was allowed to evaporate over a period of several hours. Water (50 ml) was then added and the pH adjusted to 4 with 3N HCl. The mixture was extracted with ether three times, and the extracts were combined and dried. Removal of the solvent yielded 3.09 g of crude material [mp 98-102°C; lit mp 105-106°C (98)] which was dissolved in 50 ml of dry methanol. Boron trifluoride etherate (3.2 ml) was added and the solution refluxed

for 24 h. The mixture was poured into 100 ml of H_2O, extracted three times with ether, and the extracts dried and concentrated. Dienic ester 142 (2.82 g, 74%) was obtained as white needles from silica gel chromatography: mp 69-71°C; IR (Nujol) 3040, 1735, 1640 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.01-1.23 (m, 3H), 2.29-3.30 (m, 2H), 3.78 (s, 3H), 5.67-6.09 (br s, 4H).

9,10-Epoxy-2,5,7-trioxadecane (147)

Glycidol (1.33 ml, 20 mmol) and diisopropylethylamine (5.22 ml, 30 mmol) were mixed in 20 ml of CH_2Cl_2 at room temperature. (β-Methoxyethoxy)methyl chloride (3.42 ml, 30 mmol) in 20 ml of CH_2Cl_2 was then added dropwise. The solution was stirred for 3 h then diluted with ether and washed once with H_2O, 1N HCl and brine. The organic layer was dried and concentrated. Silica gel chromatography afforded 2.99 g (92%) of 147 as a colorless oil: IR (film) 2835, 1095 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 2.40-2.89 (m, 2H), 2.98-3.28 (m, 1H), 3.37 (s, 3H), 3.45-3.97 (m, 6H), 4.84 (br s, 2H).

1-Oxo-3-(2,4,7-trioxaoct-1-yl)-8-methyl-2-oxaspiro[4.5]deca-6,10-diene (148)

To a stirred solution of 2,2,6,6-tetramethylpiperidine (0.56 ml, 3.3 mmol) in 3 ml of THF at 0°C was added 1.57 ml (3.3 mmol) of a 2.1 M solution of n-butyllithium in hexane. After 15 min, diene ester 142 (457 mg, 3 mmol) in 3 ml of THF was added dropwise. The enolate was stirred 15 min at 0°C and then cooled to -78°C. A solution of epoxide

147 (487 mg, 3 mmol) in 3 ml of THF was then added dropwise. The solution was warmed to room temperature, stirred for 2 h, and then quenched with acetic acid (0.38 ml, 6.6 mmol). The mixture was diluted with ether, washed once with H_2O and brine, and dried. Removal of the solvent yielded 794 mg (94%) of spiro lactone 148 after silica gel chromatography. Proton NMR clearly indicated 148 to be a mixture of diastereomers: IR (film) 1770, 1670, 1095 cm^{-1}; 60 MHz ($CDCl_3$) δ 1.01-1.25 (m, 6H), 2.02-2.95 (m, 3H), 3.44 (s, 3H), 3.53-3.82 (m, 7H), 4.85 (br s, 1H), 5.48-6.12 (m, 4H); high resolution mass spectrum, calcd for $C_{15}H_{22}O_5$ m/e 282.14571, found m/e 282.14689.

$LiAlH_4$ Reduction of 148

To a stirred solution of lithium aluminum hydride (144 mg, 3.8 mmol) in 3 ml of ether at 0°C was added 148 (549 mg, 1.95 mmol) in 2 ml of ether. The solution was stirred for 30 min at 0°C and then quenched by slow addition of 5 drops of H_2O, 5 drops of 1N NaOH, and 0.4 ml of H_2O. After being stirred for 30 min, the solution was diluted with ether, filtered through Celite and dried. Evaporation of solvent yielded 413 mg (74%) of a pale yellow oil: IR (film) 3410, 1070 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.97-1.19 (m, 3H), 1.37-1.56 (m, 2H), 1.90-2.12 (m, 1H), 3.38 (s, 3H), 3.52-4.10 (m, 9H), 4.27 (br s, 2H, OH), 4.85 (br s, 2H), 5.34-6.15 (m, 4H).

1-[(Benzoyloxy)methyl]-1-[2-(benzoyloxy)-4,6,9-trioxadec-1-yl]-4-methyl-2,5-cyclohexadiene

To a solution of the crude diol from 148 (413 mg, 1.44 mmol) and triethylamine (0.89 ml, 6.35 mmol) in 10 ml of CH_2Cl_2 was added benzoyl chloride (0.37 ml, 3.18 mmol). The mixture was refluxed 24 h, diluted with ether, washed twice with brine, and dried. Removal of the solvent yielded after silica gel chromatography 618 mg (87%) of the dibenzoylated product: IR (film) 1715, 1260, 1090 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.95-1.15 (m, 3H), 1.28-1.47 (m, 2H), 1.92-2.15 (m, 1H), 3.40 (s, 3H), 3.49-3.90 (m, 9H), 4.82 (br s, 2H), 5.34-6.12 (m, 4H), 7.29-8.41 (m, 10H).

1-[(Benzoyloxy)methyl]-1-[2-(benzoyloxy)-3-hydroxy-prop-1-yl]-4-methyl-2,5-cyclohexadiene (149)

To a solution of the dibenzoylated MEM ether (306 mg, 0.62 mmol) in 10 ml of a 2:1 CH_2Cl_2-hexane mixture at 0°C was added dropwise a five-fold excess of titanium tetrachloride (0.34 ml, 3.1 mmol). The solution was stirred at 0°C for 30 min followed by quenching with 1 ml of concentrated ammonium hydroxide. The suspension was stirred for 30 min, diluted with CH_2Cl_2, and filtered through Celite. The organic layer was separated, dried and concentrated. Silica gel chromatography afforded 227 mg (90%) of 149 as a colorless oil: IR (film) 3440, 1710, 1260 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.95-1.12 (m, 3H), 1.26-1.48 (m, 2H), 1.92-2.15 (m, 1H), 3.01 (br s, 1H, OH), 3.37-3.94 (m, 5H), 5.40-6.01 (m, 4H), 7.42-8.99 (m, 10H); high resolution mass spectrum, calcd for $C_{25}H_{26}O_5$ m/e 406.17801, found m/e 406.17781.

Attempted Cyclizations of 149

Dienic alcohol 149 (127 mg, 0.31 mmol) and phenylselenyl chloride (60 mg, 0.31 mmol) were mixed in the same manner as in the attempted cyclization of hydroxy nitrile 121. After stirring for 24 h at room temperature, starting material 149 was recovered unchanged.

Mercuric trifluoroacetate (213 mg, 0.5 mmol) and 149 (100 mg, 0.24 mmol) were mixed in 2 ml of THF. The mixture was stirred for 24 h at room temperature then refluxed for 6 h. No reaction was detected.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-7-methyl-2H-1-benzopyran-2-one (152)

Method A

Aluminum chloride (67 mg, 0.5 mmol) was stirred in 5 ml of benzene at 0°C. To this suspension was added dropwise, methyl coumalate (99) (750 mg, 5 mmol) in 5 ml of benzene. On addition of the coumalate, a sticky precipitate formed in large clumps; presumably this was an aluminum chloride-coumalate complex. This mixture was stirred 30 min at 0°C then isoprene (2.5 ml, 25 mmol) was added all at once. The solution was allowed to warm to room temperature and stirred for 48 h. The catalyst was destroyed by addition of 10 ml of 1N HCl followed by vigorous stirring for 30 min. The mixture was then diluted with ether and filtered through Celite. The organic layer was separated, dried and concentrated. Silica gel chromatography yielded 723 mg of a mixture of the methyl regioisomers 152a and b and an undesired product. The last

few fractions yielded 46 mg of 152 free of the unwanted material. This pure mixture of regioisomers existed as a viscous oil: IR (film) 1730, 1750 (sh), 1640, 1260 cm^{-1}; 300 MHz NMR ($CDCl_3$) (7-methyl isomer, 85% by integration) δ 1.69 (br s, 3H), 2.08-2.43 (m, 2H), 2.56-2.74 (m, 2H), 3.77 (s, 3H), 4.99 (m, 1H), 5.43 (br s, 1H), 6.04 (d, J = 8 Hz, 1H), 6.93 (d, J = 8 Hz, 1H); (6-methyl isomer, 15%) δ 1.71 (br s, 3H), 2.08-2.43 (m, 2H), 2.56-2.74 (m, 2H), 3.83 (s, 3H), 4.95 (m, 1H), 5.34 (br s, 1H), 6.05 (d, J = 8 Hz, 1H), 6.91 (d, J = 8 Hz, 1H).

Method B

Methyl coumalate (18.5 g, 120 mmol) and isoprene (36 ml, 360 mmol) in 80 ml of benzene were heated 48 h at 110°C in a sealed tube. The solvent was removed and silica gel chromatography yielded 14.17 g of a mixture of products. The product mixture was essentially identical to the product mixture produced by method A. The undesired material did not interfere in the subsequent conjugate addition. Since the tedious separation proved to be impractical for obtaining large amounts of 152, the undesired material was carried along into the next reaction.

(±)-(4α,4aα,8aα)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2H-1-benzopyran-2-one (153)

Cuprous iodide (19.05 g, 100 mmol) was suspended in 200 ml of ether at 0°C. Methyllithium-lithium bromide complex as a solution in ether was added slowly to the suspension until the initially formed yellow precipitate just disappeared. The solution was then stirred 5 min at 0°C. The Diels-Alder product mixture (14.17 g) in 50 ml of ether was added

slowly and the solution stirred 30 min at 0°C after the addition was completed. The bright yellow suspension was then poured slowly into an ice-cold saturated ammonium chloride solution (200 ml). The mixture was filtered through Celite and the organic layer separated. The aqueous layer was extracted two times with ether, and all the organic fractions were combined and dried. Removal of solvent and silica gel chromatography afforded 4.93 g (17.5% from methyl coumalate) of conjugate addition product as white needles: mp 82-83.5°C; IR (Nujol) 1735, 1640, 1200 cm^{-1}; 400 MHz NMR ($CDCl_3$) (7-methyl isomer, 85% by integration of olefinic proton) δ 1.01-1.03 (m, 3H), 1.63 (br s, 3H), 2.05-2.12 (m, 2H), 2.20 (br d, J = 18.6 Hz, 1H), 2.32 (dd; J = 16.5 Hz, 18.6 Hz; 1H), 2.53-2.63 (m, 2H), 2.71 (dd; J = 16.5, 18.6 Hz; 1H), 3.71 (s, 3H), 4.87-4.90 (m, 1H), 5.31-5.36 (m, 1H); (6-methyl isomer, 15%) δ 1.01-1.03 (m, 3H), 1.63 (br s, 3H), 2.05-2.12 (m, 2H), 2.20 (br d, J = 18.6 Hz, 1H), 2.32 (dd; J = 16.5, 18.6 Hz; 1H), 2.53-2.63 (m, 2H), 2.71 (dd; J = 16.5, 18.6 Hz; 1H), 3.71 (s, 3H), 4.83-4.86 (m, 1H), 5.23-5.28 (m, 1H).

(±)-(3α,4α,4aα,8aα)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-3-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one and the C-3 Epimer (155)

To diisopropylamine (1.55 ml, 11 mmol) in 10 ml of THF at -78°C was added 4.58 ml (11 mmol) of 2.4 M n-butyllithium solution in hexane. After 15 min, the lactone 153 (2.38 g, 10 mmol) in 5 ml of THF was added dropwise and the mixture was stirred for 10 min. Then the molybdenum peroxide reagent, MoO_5·pyridine·HMPA (MoOPH; 6.51 g, 15 mmol), was added

all at once. The solution quickly turned orange while much of the MoOPH remained as a suspension. The solution was stirred for 2 h at -78°C and then warmed to 0°C. On warming, the orange solution turned dark brown, and the remaining MoOPH dissolved. Water (15 ml) and ether (15 ml) were then added. The organic layer was separated and washed one time with 1N HCl, saturated bicarbonate solution, and brine and then dried. Removal of solvent and silica gel chromatography yielded 2.86 g (75%) of α-hydroxy lactone 155 as an oily white solid. Several attempts at recrystallization failed: IR (Nujol) 3460, 1735, 1200 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.13-1.21 (m, 3H), 1.64 (m, 3H), 1.90-2.60 (m, 4H), 3.71 (m, 3H), 3.91-4.13 (m, 1H), 4.82-5.04 (m, 1H), 5.20-5.45 (m, 1H); no hydroxyl proton was observed.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one (156)

N-Chlorosuccinimide (2.04 g, 15 mmol) was stirred in 40 ml of CH_2Cl_2 at 0°C. Dimethyl sulfide (1.51 ml, 20.5 mmol) was added dropwise, and the solution was then cooled to -25°C. The α-hydroxy lactone 155 (2.54 g, 10 mmol) dissolved in 10 ml of CH_2Cl_2 was added dropwise and stirred for 2 h at -25°C. Triethylamine (2.09 ml, 15 mmol) in 2 ml of CH_2Cl_2 was slowly added and the cooling bath removed. The solution was stirred 5 min and then poured into 80 ml of ether, washed twice with 20% HCl, dried and concentrated. Silica gel chromatography afforded 2.51 g (∿100%) of 156 as white crystals: mp 92-93°C; IR (Nujol) 3480, 1740, 1200 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.67 (br s, 3H), 1.82 (br s, 3H),

2.10-2.43 (m, 4H), 3.73 (s, 3H), 4.89-5.11 (m, 1H), 5.20-5.56 (m, 1H), 5.72 (s, 1H, OH).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4,7-dimethy-3-methoxy-4a,5,8,8a-tetrahydro-2H-1-benzopyran-2-one (157)

Sodium hydride (396 mg, 16.5 mmol) was stirred in 15 ml of THF and hexamethylphosphoramide (2.61 ml, 15 mmol) at 0°C. Compound 156 (3.78 g, 15 mmol) in 5 ml of THF was added and the solution stirred for 30 min. Methyl iodide (1.87 ml, 30 mmol) was then added all at once. The solution was stirred 2 h at 0°C and poured into hexane, washed once with H_2O and then brine. The organic layer was dried and concentrated to afford 2.88 g (72%) of the O-methylated product: IR (film) 1740, 1690, 1200 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.67 (br s, 3H), 1.84 (s, 3H), 2.10-3.03 (m, 4H), 3.77 (s, 6H), 4.92-5.06 (m, 1H), 5.23-5.56 (m, 1H).

(±)-(2α,4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-4,7-dimethyl-3-methoxy-2H-1-benzopyran and the C-2 Epimer (158)

The enol ether lactone 157 (2.66 g, 10 mmol) was stirred in 10 ml of CH_2Cl_2 at -25°C. DIBAH (10.68 ml, 11 mmol) as a 1.03 M solution in hexane was added dropwise. After 1 h at -25°C, the solution was poured into 10 ml of 10% acetic acid. Chloroform (50 ml) was added and the mixture was stirred vigorously for 2 h. The organic layer was separated, dried and concentrated. Silica gel chromatography afforded 2.52 g (94%) of lactol 158 as an oily solid. Recrystallization (hexane) yielded only

crystals which rapidly became oily again: mp 52-66°C; IR (Nujol) 3430, 3020, 1730, 1690, 1210 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.68 (br s, 3H), 2.06-2.99 (m, 4H), 3.58-3.78 (m, 7H), 4.58-4.76 (m, 1H), 5.20-5.54 (m, 2H; D_2O added, 1H).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro 4-dimethyl-3-methoxy-2H-1-benzopyran (159)

The enol ether lactol 158 (2.52 g, 9.4 mmol) was dissolved in 20 ml of CH_2Cl_2 at -78°C along with triethylsilane (2.24 ml, 14.1 mmol). Boron trifluoride etherate (1.16 ml, 9.4 mmol) was added dropwise. Monitoring by TLC indicated an almost instantaneous reaction. Anhydrous K_2CO_3 (500 mg) was added followed by 2 ml of saturated sodium bicarbonate solution. The mixture was then warmed to 0°C. If the solution was warmed prior to addition of base, no desired product was obtained. The solution was diluted with CH_2Cl_2, washed several times with bicarbonate solution, dried and concentrated. Immediate silica gel chromatography afforded 2.27 g (96%) of enol ether 159: IR (film) 1740, 1690, 1210 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.02-1.75 (m, 6H), 2.00-2.80 (m, 4H), 3.52 (s, 3H), 3.68 (s, 3H), 3.95-4.29 (m, 2H), 4.50-4.72 (m, 1H), 5.16-5.53 (m, 1H).

(±)-(4α,4aα,8aα)-4a,5,6,8a-Tetrahydro-4a-(hydroxymethyl)-4,7-dimethyl-2H-1-benzopyran-3-(4H)-one and the C-4 Epimer (160)

Lithium aluminum hydride (380 mg, 10 mmol) was suspended in 10 ml of ether at 0°C. To this suspension was added 159 (1.25 g, 5 mmol) in 5 ml of ether, by dropwise addition. The solution was stirred for 30 min at

0°C. Workup was the same as for the $LiAlH_4$ reduction of 148. Silica gel chromatography yielded 1.10 g (98%) of the enol ether alcohol.

The enol ether alcohol (1.10 g, 4.9 mmol) was stirred for 18 h at room temperature in 20 ml of aqueous THF with 5 drops of 3N $HClO_4$. The solution was diluted with an equal amount of ether, washed once with bicarbonate and brine, then dried. Concentration and silica gel chromatography afforded 979 mg (95%) of keto alcohol 160 as a very viscous oil. This acid hydrolysis could also be carried out with crude alcohol without affecting overall yield (93%): IR (film) 3460, 1715, 1100, 1060 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.05 (d, J = 6.5 Hz, 3H), 1.69 (br s, 3H), 1.82 (br s, 1H, OH), 1.89-2.84 (m, 4H), 2.99 (q, J = 6.5 Hz, 1H), 3.38-3.76 (m, 2H), 4.08 (s, 2H), 4.14-4.26 (m, 1H), 5.24-5.36 (m, 1H); high resolution mass spectrum, calcd for $C_{12}H_{18}O_3$ m/e 210.12558, found m/e 210.12577.

Selenoetherification of Keto Alcohol 160

Phenylselenyl chloride (77 mg, 0.5 mmol) in 1 ml of CH_2Cl_2 was added dropwise to a solution of keto alcohol 160 (103 mg, 0.5 mmol) in 2 ml of CH_2Cl_2 cooled to -78°C. After completion of addition, the solution was warmed to room temperature. Removal of the solvent and silica gel chromatography yielded a mixture of selenides which were dissolved in 5 ml of toluene. This solution was heated to reflux with tri-n-butyltin hydride (0.20 ml, 0.75 mmol) and a catalytic amount of azo-bis-isobutyryl nitrile. After 1 h, the solvent was removed and silica gel chromatography afforded a mixture of 161a and 161b: IR (film)

2960, 1725, 1150 cm^{-1}; high resolution mass spectrum, calcd for $C_{12}H_{18}O_3$ m/e 210.12560, found m/e 210.12631. Relative amounts of the isomeric ethers were determined by capillary column gas chromatography (175°C; isothermal, 6 ft x 1/4 in, 5% SE 30 capillary column): 161a R_t = 9.38 min (82%), 161b R_t = 9.00 min (18%). Compound 161a was determined to be the major isomer by coinjection with an authentic sample of 161a prepared unambiguously (49a): 100 MHz NMR of 161a ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3H), 1.14 (s, 3H), 1.30-1.80 (m, 6H), 2.30 (q, J = 7 Hz, 1H), 3.60 (m, 1H), 4.10 (m, 4H).

6-(Carboethoxy)-3-methylcyclohex-2-en-1-one (21)

Ethyl acetoacetate (370 ml, 2.9 mol) and methyl vinyl ketone (200 g, 2.85 mol) were mixed in a dry flask. A catalytic amount (3 ml) of 1N sodium ethoxide in ethanol was then added. The reaction gradually became quite hot and the temperature of the reaction was moderated with a cold water bath. The mixture was left standing for 12 h, then 300 ml of toluene was added and the solution was cooled to 0°C. Gaseous HCl was bubbled into the solution for 10-15 min. The mixture was then allowed to warm to room temperature and stirred for 12 h. The solution was diluted with ether (1 L), washed twice with H_2O (2 x 100 ml), and once with 100 ml of 3N NaOH. After an additional brine wash, the solution was dried and concentrated. The residue was distilled to yield 300.2 g (58%) of 21 as a yellow oil: bp 100-110/~1 mm [lit bp 119-120°C/3.5 mm (100)]; IR (film) 1735, 1670, 1635 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.22 (t,

J = 6 Hz, 3H), 1.92 (br s, 3H), 2.04-2.46 (m, 4H), 3.14-3.34 (m, 1H), 4.15 (q, J = 6 Hz, 2H), 5.84 (br s, 1H).

6-(Carboethoxy)-6-(1-oxo-3-butyl)-3-methylcyclohex-2-en-1-one (167)

The enone ester 21 (120.05 g, 0.659 mol) and dry freshly distilled crotonaldehyde (59.2 ml, 0.725 mol) were stirred with 50 ml of absolute ethanol. A catalytic amount of sodium ethoxide (15 ml of a 1N NaOEt solution in ethanol) was added. The solution gradually warmed but no external cooling was required. The mixture was stirred 12 h then acetic acid (0.85 ml, 15 mmol) was added to neutralize the ethoxide. The ethanol was removed to yield keto aldehyde 167. No further purification was necessary: IR (film) 2730, 1730, 1670, 1640 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.99 (m, 3H), 1.20 (t, J = 7 Hz, 3H), 1.89 (br s, 3H), 1.97-3.08 (m, 7H), 4.12 (q, J = 7 Hz, 2H), 5.84 (br s, 1H), 9.64 (br s, 1H).

6-(Carboethoxy)-6-(1-hydroxy-3-butyl)-3-methylcyclohex-2-en-1-one (168)

To a suspension of sodium borohydride (378 mg, 10 mmol) in 25 ml of benzene at reflux was added acetic acid (1.86 ml, 32.5 mmol). Refluxing was continued for 15 minutes. Aldehyde 167 (1.25 g, 4.95 mmol) was then added in 5 ml of benzene to the refluxing solution. Refluxing was continued for 30 min then the solution was cooled and poured into 10% acetic acid solution (10 ml). Chloroform (50 ml) was added and the

2-phase system was stirred vigorously for 1 h. The organic layer was separated, dried and submitted to silica gel chromatography. The enone alcohol 168 was obtained as a viscous oil (1.27 g, 86%): IR (film) 3410, 1725, 1670, 1630 (sh), 1180 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.99-1.13 (m, 3H), 1.20 (t, J = 6 Hz, 3H), 1.34-2.79 (m, 9H), 3.51-3.70 (m, 2H), 4.14 (q, J = 6 Hz, 2H), 5.87 (br s, 1H).

Attempted Cyclization of 168

Enone alcohol 168 (256 mg, 1 mmol) was mixed with triethylsilane (0.32 ml, 2 mmol) in 5 ml of CH_2Cl_2 at -78°C. Boron trifluoride etherate (0.13 ml, 1 mmol) was added dropwise. The solution was stirred at -78°C for 1 h then warmed to 0°C for 12 h. Normal basic workup yielded only starting material alcohol.

Attempted Ketalization of 168

Enone alcohol 168 (256 mg, 1 mmol), trimethylorthoformate (0.14 ml, 1.25 mmol) and a catalytic amount of ammonium nitrate were refluxed in 5 ml of dry methanol for 3 h. Compound 168 was recovered unchanged.

Compound 168 (256 mg, 1 mmol) in 5 ml of methanol was heated to reflux with a catalytic amount of p-TSA. The flask was equipped with a Dean-Stark trap for azeotropic removal of H_2O. After 48 h at reflux, enone alcohol 168 was unreacted.

Alcohol 168 (256 mg, 1 mmol) in 1 ml of CH_2Cl_2 was added to trimethylsilyl methyl ether (208 mg, 2 mmol) and trimethylsilyl triflate (2.2 mg, 0.01 mmol) in 1 ml of CH_2Cl_2 at -78°C. The solution was

stirred 2 h at -78°C, then warmed to 0°C for 6 h. Starting material 168 was recovered unchanged.

6-(Carboethoxy)-6-(1-oxo-3-butyl)-3-methylcyclohex-2-en-1-one, Ethylene Acetal (171)

Crude keto aldehyde 167 (from reaction of 0.659 mol of enone ester 21) was dissolved in 300 ml of benzene. Ethylene glycol (55 ml, 1 mol) and p-TSA (2.50 g, 13.2 mmol) were added and the mixture was heated to reflux. A Dean-Stark trap was used to azeotropically remove H_2O. When no more water was produced, the solution was cooled and washed two times with saturated sodium bicarbonate solution (2 x 150 ml). The solution was dried and concentrated. The viscous keto acetal 171 was >95% pure and was used without further purification: IR (film) 1720, 1670, 1630 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.03 (d, J = 6 Hz, 3H), 1.21 (t, J = 7 Hz, 3H), 1.50-1.63 (m, 2H), 1.89 (br s, 3H), 1.96-3.83 (m, 5H), 3.74-3.97 (m, 4H), 4.13 (q, J = 7 Hz, 2H), 4.87 (m, 1H), 5.83 (br s, 1H).

(±)-(4α,4aα,8aα)-4a(Carboethoxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-4H-1-benzopyran (22)

Crude keto acetal 171 (from 0.659 mol of enone ester 21) was dissolved in 300 ml of toluene and aluminum isopropoxide (403 g, 1.98 mol) was added. The amount was 3 equivalents of $Al(OiPr)_3$ based on 0.659 ml of 21; in reality, it was probably closer to 4 equivalents relative to keto acetal. The toluene solution was then refluxed for 48 h. The mixture was cooled and poured with vigorous stirring into 2 L of

ice-cold 3N NaOH. The organic layer was removed and the aqueous layer extracted twice with ether (2 x 100 ml). The organic layers were combined, dried, and concentrated. The remaining product mixture was then distilled to yield 62.3 g (40% from enone ester 21) of enol ether 22: bp 110-111°C/∿0.5 mm [lit bp 84-85°C/0.1 mm (34)]. The product collected from 90°C to 125°C was sufficiently pure (≳90%) for further transformation: IR (film) 1725, 1655 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.90-0.97 (m, 3H), 1.21 (t, J = 6 Hz, 3H), 1.66 (br s, 3H), 1.71-2.43 (m, 5H), 4.11 (q, J = 6 Hz, 2H), 4.42 (br d, J = 5 Hz, 1H), 4.70 (dd, J = 5 Hz, 1H), 5.78 (br d, J = 5 Hz, 1H), 6.24 (dd; J = 1 Hz, 6 Hz; 1H); high resolution mass spectrum, calcd for $C_{14}H_{20}O_3$ m/e 246.14125, found m/e 246.14131.

(±)-(4α,4aα,8aα)-4a-(Carboethoxy)-3-hydroxy-2-methoxy-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran; Diastereomeric Mixture About Carbons 2 and 3 (172)

Enol ether 22 (20.9 g, 88.45 mmol) was dissolved in 50 ml of anhydrous methanol. Five equivalents of $NaHCO_3$ (37 g, 440 mmol) were also added and the mixture was cooled to 0°C. Then, m-CPBA (22.45 g, 110.56 mmol) in 100 ml of methanol was added dropwise and stirred vigorously. The solution was slowly warmed to room temperature. After 3 h, 300 ml of ether were added and the solution was filtered and concentrated. The crude product was then dissolved in 100 ml of ether washed once with bicarbonate solution and once with brine. The solution was dried and concentrated to afford, after silica gel chromatography,

16.32 g (65%) of 172 as a mixture of diastereomers: IR (film) 3435, 1725 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.97-1.07 (m, 3H), 1.16-1.30 (m, 3H), 1.65 (br s, 3H), 1.71-2.44 (m, 5H), 2.85 (br s, 1H, OH), 3.43-3.49 (m, 3H), 3.61-3.92 (m, 2H), 4.01-4.21 (m, 2H), 4.32-4.64 (m, 1H), 5.33-5.63 (m, 1H). NMR clearly indicates this to be a mixture of diastereomers.

(±)-(3α,4α,4aα,8aα)-4a-(Carboethoxy)-3-hydroxy-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran and the C-3 Epimer (173)

Acetal alcohol 172 (9.887 g, 34.8 mmol) and three equivalents of triethylsilane (16.6 ml, 104 mmol) were stirred in 90 ml of CH_2Cl_2 at 0°C. Five equivalents of boron trifluoride etherate (21.4 ml, 174 mmol) were then added slowly. The mixture was refrigerated (-5°C) for 18 h. Anhydrous potassium carbonate (5 g) was then added and the solution diluted with 100 ml of ether. The organic layer was washed with saturated sodium bicarbonate solution until the aqueous washes remained basic. The ether layer was dried and concentrated to afford 7.70 g (87%) of alcohol 173 as the sole product: IR (film) 3440, 1730 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.96-1.08 (m, 3H), 1.17 (t, J = 6 Hz, 3H), 1.69 (br s, 3H), 1.75-2.31 (m, 5H), 3.41-3.89 (m, 4H; D_2O added, 3H), 4.17 (q, J = 6 Hz, 2H), 4.29 (br s, 1H), 5.38 (br s, 1H).

(±)-(4aα,8aα)-4a-(Carboethoxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (174)

Alcohol 173 (7.26 g, 28.5 mmol) was stirred in 100 ml of acetone at 0°C. Jones reagent (7.12 ml, 28.5 mmol) as a 4M solution in H_2O was

added dropwise. The solution was stirred 30 min at 0°C then diluted with 200 ml of ether. The mixture was washed two times with brine (2 x 100 ml), dried and concentrated. Silica gel chromatography yielded 6.91 g (96%) of the keto ester 174 as an oil: IR (film) 1735, 1710 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3H), 1.20 (t, J = 6 Hz, 3H), 1.75 (br s, 3H), 1.89-2.43 (m, 4H), 2.58 (q, J = 7 Hz, 1H), 4.00-4.20 (m, 4H), 4.29 (br s, 1H), 5.48 (br s, 1H); high resolution mass spectrum calcd for $C_{14}H_{20}O_4$ m/e 252.13615, found m/e 252.13587.

General Procedure for Enolate Protection and Reduction

To diisopropylamine (0.47 ml, 3.3 mmol) in 3 ml of THF at -78°C was added 1.32 ml (3.3 mmol) of a 2.5 M solution of n-butyllithium in hexane; the solution was stirred 10 min. Ketone (3 mmol) in 3 ml of THF was added dropwise at -78°C and stirred for 10 min. Then, lithium aluminum hydride (228 mg, 6 mmol) was added all at once. The solution was warmed to -25°C or 0°C for 30 min, then cooled to -78°C again. The reaction mixture was quenched by slowly pouring the enolate solution into 10 ml of vigorously stirred 3N HCl or 25 ml of vigorously stirred ammonium chloride solution. Use of the ammonium chloride solution gave slightly higher yields, in general. If the ammonium chloride solution was used, 15 ml of 1N HCl was added after all of the enolate solution had been introduced. In both procedures, the mixture was diluted with 50 ml of $CHCl_3$ and stirred for 1 h. The organic layer was separated,

dried and concentrated. Silica gel chromatography afforded pure selectively reduced products.

2-(Hydroxymethyl)-2-methylcyclopentanone (176)

Keto alcohol 176 was prepared in 76% yield using the generalized procedure: IR (film) 3450, 1730 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.60-2.50 (m, 6H), 3.12 (br s, 1H, OH), 3.54 (AB quartet, 2H); C-13 NMR ($CDCl_3$) 18.596, 19.052, 32.840, 38.107, 50.137, 66.655, 223.770.

5-(Hydroxymethyl)-5-(2-propenyl)-cyclohex-2-en-1-one (178)

Keto alcohol 178 was prepared in 62% yield using the generalized procedure: IR (film) 3420, 3080, 1670 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.90-2.45 (m, 6H), 3.32 (br s, 1H, OH), 3.44 (s, 2H), 4.92 (m, 1H), 5.15 (br s, 1H), 5.43-6.10 (m, 2H), 6.86 (m, 1H); C-13 NMR ($CDCl_3$) 32.190, 39.928, 41.424, 44.546, 66.785, 118.679, 129.019, 133.246, 148.399, 199.578.

(±)-(4α,4aα,8aα)-4a-(Hydroxymethyl)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2H-1-benzopyran-2-one (179)

Lactone alcohol 179 was prepared in 65% yield using the generalized procedure: IR (film) 3460, 1740 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.96-1.12 (m, 3H), 1.60 (br s, 3H), 1.95-2.90 (m, 7H), 3.57 (AB quartet, 2H), 4.07 (br s, 1H, OH), 4.63 (m, 1H), 5.30 (m, 1H).

3-(Hydroxymethyl)-3-methylhex-5-en-2-one (181)

Keto alcohol 181 was prepared in 81% yield using the generalized procedure: IR (film) 3430, 3090, 1715, 1640 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.15 (s, 3H), 2.17 (s, 3H), 2.32 (m, 2H), 2.67 (br s, 1H, OH), 3.62 (AB quartet, 2H), 4.85-6.10 (m, 3H); C-13 NMR 18.987, 26.142, 39.343, 52.674, 67.435, 118.354, 133.051, 213.820.

4,5-Dihydro-2,4,4-trimethypyrrole (183)

The amine 183 was prepared in 67% yield using the generalized procedure: IR (film) 1640 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.06 (s, 6H), 1.9 (t, J = 1 Hz, 3H), 2.22 (br s, 2H), 3.43 (q, J = 1 Hz, 1H); C-13 NMR ($CDCl_3$) 20.014, 27.924, 38.597, 53.565, 74.405.

3-Acetyl-2,2-dimethylpropanol (184)

The enolate of keto nitrile 183 was generated in the usual manner. After 10 min at -78°C, 3 ml (3 mmol) of a 1 M solution of DIBAH in THF was added dropwise and the solution was warmed to -25°C and stirred for 2 h. The solution was then poured into 20 ml of 10% acetic acid solution. Fifty ml of $CHCl_3$ were added and the mixture stirred for 2 h. The organic layer was separated and dried. Concentration and silica gel chromatography afforded a 46% yield of keto aldehyde 184: IR (film) 1730, 1715 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.10 (s, 6H), 2.06 (s, 3H), 2.65 (s, 2H), 9.47 (s, 1H).

(±)-(4aα,8aα)-4,7-Dimethyl-4a-(hydroxymethyl)-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (103)

To diisopropylamine (2.72 ml, 19.28 mmol) in 20 ml of THF at -78°C was added 7.71 ml (19.28 mmol) of a 2.5 M solution of n-butyllithium in hexane. The solution was stirred 15 min. Keto ester 174 (4.054 g, 16.07 mmol) as a 1 M solution in THF was then added dropwise. The orange-red solution was stirred for 15 min at -78°C, then lithium aluminum hydride (610 mg, 16.07 mmol) was added all at once. The solution was warmed to 0°C for 10 min, then cooled back to -78°C. The mixture was slowly poured into 100 ml of vigorously stirred saturated ammonium chloride solution. Chloroform (50 ml) was added followed by the addition of 25 ml of 3N HCl. The mixture was stirred 30 min, then the organic layer was removed. The aqueous portion was extracted twice with $CHCl_3$ (2 x 50 ml) and the organic fractions were combined, dried and concentrated. Silica gel chromatography afforded 2.37 g (70%) of keto alcohol 103 (an 18% yield of diol was also obtained): IR (film) 3450, 1720, 1090 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.16 (d, J = 7 Hz, 3H), 1.50-2.20 (m, 7H), 2.60 (q, J = 7 Hz, 1H), 3.55 (m, 2H), 4.00 (m, 2H), 4.26 (br s, 1H), 5.52 (br s, 1H); high resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.12560, found m/e 210.12605.

6-(Carboethoxy)-6-[3-(1-propanone)]-3-methylcyclohex-2-en-1-one (192)

To 15 ml of dry ethanol was added hydroquinone (50 mg) and 0.25 ml of 1M sodium ethoxide in ethanol. The solution was then cooled to -78°C. A mixture of freshly distilled acrolein (1 ml, 15 mmol) and enone ester 21 (1.882 g, 10 mmol) was added dropwise. The mixture was stirred for 1.5 h at -78°C then 30 min at room temperature. Acetic acid (0.25 mmol) was added to neutralize the base and the solution was concentrated. The crude product was dissolved in ether and washed with saturated bicarbonate solution. The organic layer was then dried and concentrated to yield 2.4 g (∿100%) of the Michael product 192 as a viscous oil: IR (film) 2730, 1730, 1670, 1640 (sh) cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.21 (t, J = 7 Hz, 3H), 1.95 (br s, 3H), 2.01-2.80 (m, 8H), 4.16 (q, J = 7H, 2H), 5.87 (br s, 1H), 9.80 (br s, 1H). The crude product was pure enough for further reactions.

6-(Carboethoxy)-6-[3-(1-hydroxypropyl)]-3-methylcyclohex-2-en-1-ol (193)

Enone aldehyde 192 (1.19 g, 5 mmol) was stirred in 10 ml of THF at -25°C. Diisobutylaluminum hydride (10 ml, 10 mmol) as a 1M solution in THF was added dropwise and the stirring continued at -25°C. After 30 min, the mixture was poured slowly into 15 ml of cold 10% acetic acid solution and 50 ml of $CHCl_3$ were added. The solution was stirred vigorously for 1 h. The organic layer was separated, washed once with

saturated sodium bicarbonate solution, dried, and concentrated. Silica gel chromatography afforded 1.05 g (87%) of diol 193 as a viscous oil: IR (film) 3410, 1735, 1635 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.17-2.54 (m, 14H), 2.95 (br s, 1H, OH), 3.50-3.72 (m, 2H), 4.02-4.40 (m, 2H), 4.45-4.60 (m, 1H), 5.47-5.67 (m, 1H).

(±)-(4aα,8aα)-4a-(Carboethoxy)-7-methyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran (194)

Diol 193 (296 mg, 1.22 mmol) was added to 10 ml of CH_2Cl_2 containing 1 drop of concentrated sulfuric acid. The mixture was stirred 15 min at room temperature. The CH_2Cl_2 solution was decanted from a brown oil that coated the side of the flask and the solution was then concentrated. Silica gel chromatography yielded 282 mg (∿100%) of cyclic ether 194 as a clear oil: IR (film) 1730, 1670 (sh) cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.04-2.43 (m, 14H), 3.19-4.28 (m, 5H), 5.28-5.50 (m, 1H). The methine proton was unfortunately masked by the methylene protons of the ester in the proton NMR. In an effort to determine if the product was a mixture of cis- and trans-fused ethers, compound 194 was reduced with excess lithium aluminum hydride in anhydrous ether. The alcohol (67%) was obtained as a clear oil: IR (film) 3400, 1670 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.07-2.13 (m, 11H), 3.21-3.51 (m, 4H), 3.61-3.79 (m, 2H; D_2O added, 1H-methine proton), 5.21-5.45 (m, 1H); C-13 NMR ($CDCl_3$) 21.91, 23.156, 25.215, 27.274, 28.249, 35.239, 65.250, 67.742, 73.430, 121.428. Capillary column gas chromatography (180°C, isothermal, 6 ft x 1/4 in, 5% SE 30 capillary column) indicated only 1 isomer. The chemical shift

of the methine proton (3.61-3.79) indicated this isomer was the cis-fused bicyclic ether.

6-(Carboethoxy)-6-[3-(1-acetoxyprop-1-enyl)]-3-methylcyclohex-2-en-1-one (195)

Enone aldehyde 192 (476 mg, 2 mmol), acetic anhydride (0.94 ml, 10 mmol), triethylamine (0.56 ml, 4 mmol), and dimethylaminopyridine (24 mg, 0.2 mmol) were mixed and heated to 50°C for 12 h. The mixture was cooled, 15 g of ice was added, and the solution was stirred vigorously for 3 h. After dilution with ether, the organic layer was washed with cold saturated sodium bicarbonate solution, dried and concentrated. Silica gel chromatography yielded 487 mg (87%) of an orange oil: IR (film) 1740, 1720, 1665, 1195 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3H), 1.92 (s, 3H), 2.05 and 2.13 (s, 3H), 2.19-2.90 (m, 6H), 4.13 (q, J = 7 Hz, 2H), 4.78-4.99 and 5.24-5.54 (m, 1H), 5.85 (br s, 1H), 7.00-7.19 (m, 1H).

6-(Carboethoxy)-6-[3-(2-ethoxyprop-1-enyl)]-3-methycyclohex-2-en-1-one (198)

Tetrakis(triphenylphosphine)palladium (1 g, 0.86 mmol) and 2-ethoxy-3-acetoxy-1-propene (80a) were dissolved in 15 ml of THF. Enone ester 121 (3.2 g, 17.6 mmol) and DBU (2.63 ml, 17.6 mmol) dissolved in 15 ml of THF were then added to the palladium-allylic acetate solution. The yellow solution was refluxed for 48 h, then the THF removed in vacuo. An ether-hexane mixture was added to the residue and

stirred for 30 min. The solution was then decanted from the amine salts (brown sludge) and concentrated. Silica gel chromatography afforded 2.11 g (45%) of 198 as a yellow oil: IR (film) 1730, 1680, 1645 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.19-1.32 (m, 6H), 1.70-2.86 (m, 8H), 3.01-3.16 (m, 1H), 3.56-3.77 (m, 2H), 3.94 (s, 2H), 4.03-4.24 (m, 2H), 5.87 (br s, 1H).

6-(Carboethoxy)-6-(3-butanoic acid)-3-methylcyclohex-2-en-1-one (201)

Enone aldehyde 167 (2.52 g, 10 mmol) was stirred in 50 ml of acetone at 0°C. Jones reagent (2.5 ml, 10 mmol) as a 4M solution in H_2O was then added dropwise. The mixture was stirred 30 min at 0°C then 200 ml of ether was added. The solution was washed with brine (2 x 100 ml) then dried and concentrated. The crude acid was run through a short silica gel column to afford 2.63 g (98%) of the pure keto acid 201: IR (film) 3300-2500, broad band from 1740-1640 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.87-1.28 (m, 6H), 1.73-2.79 (m, 10 H), 3.89-4.30 (m, 2H), 5.75 (br s, 1H), 10.51 (br s, 1H).

(±)-(4α,4aα,8aα)-4a-(Carboethoxy)-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran-2-one; and the C-4, C-8a Epimers (202 and 203)

Enone acid 201 (2.439 g, 9.08 mmol) was stirred in 20 ml of THF at -25°C. Diisobutylaluminum hydride (18.18 ml, 18.18 mmol) as a 1M solution in THF was added dropwise. The mixture was stirred 1 h at -25°C

then poured slowly into a solution of 10% sulfuric acid. The mixture was stirred at room temperature overnight then extracted with $CHCl_3$ (2 x 100 ml). The extracts were washed with saturated sodium bicarbonate solution (50 ml), and brine (50 ml), then dried. Concentration and silica gel chromatography afforded 1.90 g of bicyclic lactones 202 and 203. Lactone 202 (cis-fused) was the major product, 1.18 g (62%): IR (film) 1735 (sh), 1725 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.92-1.38 (m, 6H), 1.48-2.52 (m, 11H), 3.90-4.32 (m, 2H), 4.91-5.09 (m, 1H), 5.30-5.54 (m, 1H). The methine signal in the proton NMR clearly indicated lactone 203 (72 mg, 38%) was the trans-fused product: IR (film) 1735 (sh), 1725 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.92-1.38 (m, 6H), 1.48-2.52 (m, 11H), 3.90-4.32 (m, 2H), 4.60-4.80 (m, 1H), 5.40-5.52 (m, 1H).

Isomerization of the trans-Fused Lactone 203

Lithium hydroxide-monohydrate (65 mg, 1.5 mmol) was added to a solution of lactone 203 (120 mg, 0.5 mmol) in 5 ml of 4:1 THF-H_2O at room temperature. The two-phase system was stirred vigorously at ambient temperature for 30 min then cooled to 0°C. The solution was acidified (pH 5) with ice-cold saturated aqueous NaH_2PO_4 (pH 3.5) buffer then partitioned between 50 ml of CH_2Cl_2 and 10 ml of water. The organic layer was separated, dried, and reduced to a volume of 5 ml. A drop of concentrated sulfuric acid was added. After 15 min of vigorous stirring, the solution was decanted from the brown residue on the side of the flask and concentrated. The mixture of lactones (202 and 203) obtained was identical to that obtained from DiBAH reduction and lactonization of

enone acid 201. Integration of the methine protons (4.91-5.09 and 4.60-4.80) indicated a 2:1 ratio of cis:trans lactones.

(±)-(2α,4α,4aα,8aα)-2-(Phenylthio)-4a-(carboethoxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2 Epimer

To a 1M solution of diisopropylamine (0.14 ml, 1 mmol) in THF at -78°C was added 0.42 ml of n-butyllithium (1 mmol) as a 2.4 M solution in hexane. The solution was stirred at -78°C for 10 min. Keto ester 174 (126 mg, 0.5 mmol) was then added as a 1M solution in THF. Stirring continued at -78°C for 30 min then the mixture was warmed to -25°C. Diphenyl disulfide (218 mg, 1 mmol) dissolved in 0.5 ml of THF was added dropwise and the solution was warmed to room temperature. After 1 h, 100 ml of ether was added and the solution quenched with 10 ml of 10% HCl solution. The aqueous phase was removed and the organic layer was then washed once with 10 ml of saturated aqueous sodium bicarbonate solution. The solution was dried and concentrated. Silica gel chromatography of the residue afforded 94 mg (52%) of the β-keto sulfide as a mixture of diastereomers: IR (film) 1735, 1710 (sh) cm^{-1}; 60 MHz NMR ($CDCl_3$) (one diastereomer) δ 0.97-1.45 (m, 6H), 1.63-2.84 (m, 8H), 4.01-4.44 (m, 3H), 5.36 (s, 1H), 5.48-5.88 (m, 1H), 7.25-7.80 (m, 5H); (other isomer) δ 0.97-1.45 (m, 6H), 1.63-2.84 (m, 8H), 4.01-4.44 (m, 3H), 5.48-5.88 (m, 1H), 5.86 (s, 1H), 7.25-7.80 (m, 5H).

(±)-(2α,4α,4aα,8aα)-2-(Phenylsulfinyl)-4a-(carboethoxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2 Epimer (207)

The β-keto sulfide (94 mg, 0.26 mmol) was dissolved in 3 ml of methanol. Sodium periodate (67 mg, 0.31 mmol) was added as a 1M solution in water and the mixture was refluxed for 4 h. The mixture was poured into 5 ml of brine and extracted with CH_2Cl_2. The extracts were dried and concentrated to afford, after silica gel chromatography, 84 mg (86%) of β-keto sulfoxide 207: IR (film) 1735 (br), 1040 cm^{-1}.

(±)-(2α,4aα,8aα)-2-(Phenylsulfinyl)-4a-(carboethoxy)-4a,5,8,8a-tetrahydro-3-[1-(prop-2-enyloxy)]-4,7-dimethyl-2H-1-benzopyran and the C-2 Epimer (208)

To a 1M solution of diisopropylamine (0.08 ml, 0.55 mmol) in THF at -78°C was added 0.22 ml of n-butyllithium (0.55 mmol) as a 2.5 M solution in hexane. The solution was stirred at -78°C for 10 min and β-keto sulfoxide 207 (188 mg, 0.5 mmol) was then added as a 1M solution in THF. Stirring was continued at -78°C for 15 min then allyl bromide (0.06 ml, 0.70 mmol) was added dropwise. After stirring at -78°C for 2 h, the mixture was left overnight in the refrigerator (-5°C). The solution was then poured into 10 ml of 1N HCl and diluted with 50 ml of ether. The organic fraction was then washed with 10 ml of a saturated sodium bicarbonate solution, dried, and concentrated. Silica gel chromatography afforded 130 mg (61%) of allyl enol ether 208 as the only

product: IR (film) 1735, 1680, 1060 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.67 (s, 3H), 1.75 (br s, 3H), 4.16 (q, J = 7 Hz, 2H), 4.30-4.42 (m, 2H), 4.95-6.18 (m, 5H), 7.18-7.63 (m, 6H).

Benzyloxyacetaldehyde

A 1M solution of 1,4-dibenzyloxy-2-butene (8.04 g, 30 mmol) (prepared from 2-buten-1,4-diol, NaH, and benzyl bromide) in CH_2Cl_2 was cooled to -78°C. Ozone was bubbled through the solution until a pale blue color appeared. Nitrogen was passed through the solution to purge the system of excess ozone. Triphenylphosphine (7.86 g, 30 mmol) was added all at once and the mixture was allowed to stand 12 h. The CH_2Cl_2 was removed and 100 ml of hexane was added. The triphenylphosphine oxide was then filtered and the solution was concentrated again. Distilling the residue under reduced pressure yielded 5.22 g (58%) of pure aldehyde: bp 85-87°C/1 mm [lit bp 121°C/15 mm, 112°/10 mm (101)]; 100 MHz NMR ($CDCl_3$) δ 4.00 (d, J = 1.5 Hz, 2H), 4.58 (s, 2H), 7.12-7.43 (m, 5H), 9.52 (t, J = 1.5 Hz, 1H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2a-[1-(2-benzyloxy-1-hydroxyethyl)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2, C-9 Epimers (209)

To a 1M solution of diisopropylamine (0.72 ml, 5.1 mmol) in THF at -78°C was added 2.21 ml of n-butyllithium (5.1 mmol) as a 2.3 M solution in hexane. The solution was stirred at -78°C for 10 min. Keto ester

174 (1.26 g, 5 mmol) was added as a 1M solution in THF. Stirring was continued at -78°C for 30 min to ensure complete enolate formation. Benzyloxyacetaldehyde (1.13 g, 7.5 mmol), dissolved in 5 ml of THF, was then added dropwise. The mixture was stirred at -78°C for 5 min then quenched with acetic acid (0.58 ml, 10.2 mmol). After warming to 0°C, the solution was partitioned between 50 ml of ether and 10 ml of H_2O. The organic layer was washed with 10 ml of saturated sodium bicarbonate solution then dried and concentrated. Silica gel chromatography afforded 1.83 g (91%) of keto alcohol 209 as a mixture of diastereomers: IR (film) 3430, 1770 (sh), 1730, 1100 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.89-1.30 (m, 6H), 1.70 (br s, 3H), 1.86-2.21 (m, 4H), 2.42-2.78 (m, 1H), 3.18-3.73 (m, 4H; D_2O added, 3H), 3.90-4.26 (m, 3H), 3.40-3.62 (m, 3H), 5.28-5.45 (m, 1H), 7.28 (br s, 5H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2a-[2-(1-benzyloxy-3,5-oxahexyl)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2, C-9 Epimers (210)

Keto alcohol 209 (1.83 g, 4.55 mmol) and diisopropyl ethylamine (1.19 ml, 6.83 mmol) were stirred in 10 ml of CH_2Cl_2 at 0°C. Chloromethyl methyl ether (0.52 ml, 6.83 mmol) was added dropwise. The solution was warmed to room temperature and stirred overnight. The mixture was then diluted with 50 ml of ether and washed with water, saturated bicarbonate solution, and brine. The organic layer was dried and concentrated. Silica gel chromatography afforded the protected

keto alcohol 210 (1.99 g, 98%) as a mixture of diastereomers: IR (film) 1780 (sh), 1735, 1105, 1085 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.96-1.29 (m, 6H), 1.72 (br s, 3H), 1.79-2.43 (m, 4H), 2.49-2.64 (m, 1H), 3.34 (br s, 3H), 3.61-3.68 (m, 2H), 3.94-4.80 (m, 9H), 5.42-5.53 (m, 1H), 7.08-7.24 (m, 5H); high resolution mass spectrum, calcd for $C_{25}H_{34}O_7$ m/e 446.23044, found m/e 446.23096.

Hydrogenolysis of Benzyl Ether 210

Benzyl ether 210 (446 mg, 1 mmol) and 106 mg of 10% palladium on charcoal (0.1 mmol) were stirred in 3 ml of absolute ethanol under an atmosphere of hydrogen. After stirring overnight at ambient temperature, the solution was filtered through Celite and concentrated. Silica gel chromatography of the residue afforded 175 mg (63%) of furan 211 as an orange oil: IR (film) 3040, 1735, 1665, 1280 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.11-1.31 (m, 6H), 1.68 (br s, 3H), 1.79-2.35 (m, 4H), 2.72-2.94 (m, 1H), 4.02-4.29 (m, 2H), 4.58 (br d, J = 5 Hz, 1H), 5.80 (br d, J = 5 Hz, 1H), 6.04 (br s, 1H); C-13 NMR 14.112, 18.011, 23.085, 26.012, 29.003, 35.181, 48.511, 60.282, 69.841, 102.812, 120.695, 125.833, 128.239, 128.369, 140.075, 172.525; high resolution mass spectrum, calcd for $C_{16}H_{20}O_4$ m/e 276.13610, found m/e 276.13561.

Reaction of Keto Ester 174 with Ethyl Glyoxylate

Keto ester 174 (126 mg, 0.5 mmol) and freshly prepared ethyl glyoxylate (102) (102 mg, 1 mmol) were reacted in the same manner as

the successful aldol condensation of keto ester 174 and benzyloxyacetaldehyde. The only products isolated were polymeric tars.

2,2-Diethoxyacetaldehyde

Crotonaldehyde diethyl acetal (103) (8.52 ml, 50 mmol) was dissolved in 50 ml of CH_2Cl_2 then cooled to -78°C. Ozone was bubbled through the solution until a faint blue color appeared. The system was then purged with nitrogen to remove excess ozone. Triphenylphosphine (13.11 g, 50 mmol) was added all at once and the solution was allowed to warm to room temperature overnight. The solution was concentrated and 100 ml of hexane was added. The mixture was filtered, concentrated again, and the residue distilled under reduced pressure. Diethoxyacetaldehyde (4.07 g, 62%) was obtained as a clear oil: bp 57°C/15 mm; IR (film) 2765, 1715 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.07-1.44 (m, 6H), 3.41-3.93 (m, 4H), 4.60 (d, J = 1.5 Hz, 1H), 9.46 (d, J = 1.5 Hz, 1H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2-[1-(2,2-diethoxy-1-hydroxyethyl)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2, C-9 Epimers (212)

The aldol condensation of keto ester 174 (504 mg, 2 mmol) and 2,2-diethoxyacetaldehyde (397 mg, 3 mmol) was carried out in the same manner as the preparation of keto benzyl ether 209. Crude product 212, 677 mg, was reacted without further purification: IR (film) 3430, 1730, 1090 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.04-1.37 (m, 12 H), 1.61-2.81 (m, 8H),

3.46-3.83 (m, 5H), 3.98-4.41 (m, 4H), 4.50-4.81 (m, 1H), 5.26-5.53 (m, 1H), 5.68-5.75 (m, 1H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2-[1-(2,2-diethoxy-1-acetoxyethyl)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2, C-9 Epimers (213)

Crude keto alcohol 212 (677 mg, 1.64 mmol), triethylamine (0.69 ml, 4.92 mmol), and acetic anhydride (0.63 ml, 6.72 mmol) were stirred in 5 ml of ether at room temperature overnight. Ice was then added and the mixture stirred vigorously for 2 h. More ether (25 ml) was added and the aqueous layer was removed. The organic portion was then washed with saturated sodium bicarbonate solution, dried and concentrated. Silica gel chromatography afforded 587 mg (84%) of 213 as a mixture of diastereomers: IR (film) 1740, 1110, 1060 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.04-1.37 (m, 12 H), 1.61-2.81 (m, 11 H), 3.46-3.88 (m, 4H), 3.98-4.41 (m, 3H), 4.50-4.97 (m, 2H), 5.26-5.53 (m, 1H), 5.68-5.75 (1H).

The acetate could also be prepared by addition of acetic anhydride directly to the reaction mixture of keto ester 174 and 2,2-diethoxyacetaldehyde. In this manner 213 was prepared in 96% yield from keto ester 174.

(±)-(4α,4aα,8aα)-4a-(Carboethoxy)-2-(2-benzyloxyethylidene)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one; E and Z Isomers (214)

Keto alcohol 209 (198 mg, 0.5 mmol) and the triethylamine (0.14 ml, 1 mmol) were stirred in 3 ml of CH_2Cl_2 at 0°C. Mesyl chloride (0.04 ml, 0.5 mmol) was added in one portion and the solution was warmed slowly to room temperature. After 1 h, 25 ml of ether was added and the solution was washed with H_2O, saturated sodium bicarbonate solution, and brine. The organic fraction was dried and concentrated to afford 235 mg of the crude mesylate: IR (film) 1775, 1735, 1365, 1180 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.01-1.50 (m, 6H), 1.80 (br s, 3H), 1.94-2.31 (m, 4H), 2.48-2.80 (m, 1H), 2.99-3.24 (m, 4H), 3.30-3.52 (m, 1H), 3.67-3.90 (m, 1H), 3.99-4.69 (m, 6H), 5.49-5.62 (m, 1H), 7.42 (s, 5H).

The mesylate (235 mg) was stirred at 0°C in 3 ml of CH_2Cl_2 and DBN (0.06 ml, 0.5 mmol) was added dropwise. The solution was stirred at 0°C for 15 min then at room temperature for 1 h. Ether was added and the solution was washed with 5 ml of 1N HCl. The solution was dried and concentrated. Silica gel chromatography yielded 145 mg (75%) of enone ester 214 as a mixture of E and Z double bond isomers: IR (film) 1735, 1680, 1180 cm^{-1}; 100 MHz NMR ($CDCl_3$) (E isomer, 50%) δ 1.12-1.31 (m, 6H), 1.72-2.36 (m, 7H), 2.48-2.71 (m, 1H), 4.06-4.29 (m, 4H), 4.42-4.80 (m, 3H), 5.44-5.52 (m, 1H), 5.94-6.12 (m, 1H), 7.31 (s, 5H); (Z isomer, 50%) δ 1.12-1.31 (m, 6H), 1.72-2.36 (m, 7H), 2.48-2.71 (m, 1H), 4.06-4.29 (m, 4H), 4.42-4.80 (m, 3H), 5.44-5.52 (m, 1H), 5.60-5.72 (m, 1H), 7.31 (s, 5H).

Attempted Deconjugations of α,β-Unsaturated Ketone 214

A 0.5 M solution of lithium diisopropylamide (0.27 mmol) was made in the usual manner at -78°C. Enone 214 (69 mg, 0.18 mmol) was added as a 0.2 M solution in THF. After 15 min at -78°C, the solution contained no starting material, as determined by TLC. The solution was poured into 3 ml of 10% acetic acid solution and extracted with ether. Concentration of the organic fractions yielded no identifiable products.

Enone 214 (57 mg, 0.15 mmol) and potassium tert-butoxide tert-butanol complex (270 mg, 1.5 mmol) were stirred in 3 ml of THF at room temperature for 2 h. A solution of 10% acetic acid (3 ml) was added and the mixture was extracted with ether. Concentration of the organic portions afforded no identifiable products.

Reductions of α,β-Unsaturated Ketone 214

A 1M solution of enone 214 (96 mg, 0.25 mmol) in THF was cooled to -78°C. L-Selectride (0.25 ml, 0.25 mmol) as a 1M solution in THF was added dropwise. After 30 min at -78°C, the solution was slowly poured into 2 ml of 10% acetic acid solution. The mixture was stirred for 1 h then extracted with chloroform. The organic fractions were dried and concentrated. Proton NMR and IR spectra clearly indicated a mixture of 1,2 and 1,4 reduction products.

Sodium borohydride (10 mg, 0.25 mmol) and enone 214 (96 mg, 0.25 mmol) were stirred in 2 ml of pyridine for 1 h. The mixture was slowly added to 10 ml of 10% acetic acid solution and diluted with 10 ml of

chloroform. The two-phase mixture was stirred for 1 h then the organic layer was removed, washed with 1N HCl, and dried. The solvent was removed to afford a mixture of products. Proton NMR and IR spectra indicated a preponderance of 1,2 reduction product.

Phenyl 1-Phenylthiovinyl Sulfoxide 216

Thiophenol (25.7 ml, 250 mmol), formaldehyde (9.5 g of a 40% aqueous solution, 125 mmol) and acetic acid (30 ml) were mixed at 0°C. Concentrated hydrochloric acid (21 ml) was added dropwise and the solution was stirred 4.5 h at 0°C. Ether (200 ml) was added and the solution was extracted once with brine and three times with saturated sodium bicarbonate solution. The organic layer was dried over $CaCl_2$ then concentrated. Excess thiophenol was then removed by heating the residue *in vacuo*. The thioacetal was used without further purification: 60 MHz NMR ($CDCl_3$) δ 4.33 (s, 2H), 7.20-7.71 (m, 10H).

The crude thioacetal (2.32 g, 10 mmol) was stirred in 100 ml of methanol. Sodium periodate (257 mg, 12 mmol) was added as a 1M solution in water. The mixture was then refluxed overnight. The solution was concentrated, dissolved in ether, and washed with water. The organic phase was dried and concentrated to afford 2.40 g of phenyl thiophenylmethyl sulfoxide: IR (film) 1045 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 4.19 (s, 2H), 7.27-7.92 (m, 10H).

To a 1M solution of phenyl thiophenylmethyl sulfoxide (758 mg, 3.05 mmol) at 0°C was added 1.24 ml of *n*-butyllithium (3.1 mmol) as a 2.5 M solution in hexane. The solution was stirred for 30 min, then

paraformaldehyde (93 mg, 3.1 mmol) was added in one portion. The reaction was warmed to room temperature and stirred for 4 h. Acetic anhydride (0.29 ml, 3.1 mmol) was added and the solution was stirred at ambient temperature for an additional 2 h. The mixture was diluted with ether, washed with water and brine, then dried and concentrated. Silica gel chromatography yielded 170 mg (22%) of 216 and the acetoxy precursor (63%). The acetate product could also be eliminated according to the procedure of Herrmann et al. (KOH, benzene, 0°C) (87) to afford 216 in high yield: IR (film) 1635 (w), 1040 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 5.90 (d, J = 1.5 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 7.15-7.80 (m, 10 H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2-[2-(1-phenylthio-1-phenysulfinylethyl)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2 Epimer (217)

To a 0.5 M solution of diisopropylamine (0.09 ml, 0.65 mmol) in THF at -78°C was added 0.26 ml of n-butyllithium (0.65 mmol) as a 2.5 M solution in hexane. The lithium amide was stirred 10 min at -78°C and keto ester 174 (164 mg, 0.65 mmol), dissolved in 0.5 ml of THF, was added dropwise. After 30 min, a 1M solution of thioketene acetal monoxide 216 (170 mg, 0.65 mmol) in THF was added to the enolate. The solution was stirred 2 h at -78°C, quenched with acetic acid (0.07 ml, 1.3 mmol), and poured into 10 ml of water. The mixture was extracted with ether and the extracts were dried and concentrated. Silica gel chromatography afforded 140 mg (42%) of keto thioacetal monoxide:

IR (film) 1735, 1710 (sh), 1040 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.01-1.43 (m, 6H), 1.54-2.60 (m, 9H), 3.98-4.61 (m, 4H), 5.18-5.50 (m, 2H), 7.10-7.80 (m, 10 H).

(±)-(2α,4α,4aα,8aα)-4a-(Carboethoxy)-2-[2-(1-ethanone)]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-2 Epimer (205)

The keto thioacetal (78 mg, 0.15 mmol) generated from the Michael addition of keto ester 174 with ketene thioacetal monoxide 216, was dissolved in 1 ml of acetonitrile. Two drops of 3N $HClO_4$ solution were added and the mixture was left standing overnight. The mixture was concentrated and silica gel chromatography of the residue afforded 40 mg (∿100%) of keto aldehyde 205: IR (film) 2730, 1735, 1700 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.10-1.32 (m, 6H), 1.78 (br s, 3H), 1.84-2.21 (m, 4H), 2.50-2.95 (m, 3H), 4.08-4.30 (m, 3H), 4.38-4.62 (m, 1H), 5.42-5.60 (m, 1H), 9.66-9.80 (m, 1H); high resolution mass spectrum, calcd for $C_{16}H_{22}O_5$ m/e 294.14671, found m/e 294.14740.

Attempted Intramolecular Aldol Cyclization of Keto Aldehyde 205

Keto aldehyde 205 (13 mg, 0.04 mmol) was stirred in 0.2 ml of 40% Triton B in methanol at room temperature. After 2 days, keto aldehyde 205 remained unchanged. The solution was heated to 50°C for 6 h, which resulted in the destruction of compound 205.

Keto aldehyde 205 (15 mg, 0.05 mmol) was stirred in 0.2 ml of 1M sodium ethoxide in ethanol at room temperature. No reaction had occurred after 2 days. Again, heating destroyed keto aldehyde 205.

(±)-(4aα,8aα)-4a-(Carboethoxy)-4a,5,8,8a-tetrahydro-4,7-dimethyl-3-trimethylsiloxy-2H-1-benzopyran (219)

Hexamethyldisilazane (0.16 ml, 1.11 mmol) and keto ester 174 (295 mg, 1.17 mmol) in 5 ml of CH_2Cl_2 were cooled to -25°C. Iodotrimethylsilane was added dropwise to the stirred solution. Stirring was continued at -25°C for 15 min then the solution was left to stand at -5°C for 2 h. The solution was decanted from the white solid and poured into 50 ml of pentane. The pentane solution was washed with water, saturated sodium bicarbonate solution, and brine. The organic phase was dried and concentrated to afford, after silica gel chromatography, 352 mg (92%) of silyl enol ether 219. None of the isomeric silyl enol ether 220 was detected in the proton NMR spectrum: IR (film) 1735, 1660 (sh) cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.10 (s, 9H), 1.08-1.32 (m, 3H), 1.38-1.49 (m, 3H), 1.58 (br s, 3H), 1.70-2.20 (m, 4H), 3.65-4.22 (m, 5H), 5.28-5.40 (m, 1H).

Attempted Aldol Condensation of the Tetra-n-butylammonium Enolate of Keto Ester 174

Freshly distilled benzyloxyacetaldehyde (300 mg, 2 mmol) and silyl enol ether 219 (488 mg, 1.5 mmol) were stirred in 5 ml of THF at -78°C.

Tetra-n-butylammonium fluoride (2 mmol) was added dropwise as a 1M solution in THF. The reaction was warmed to -20°C and left standing overnight. The solution was poured into 100 ml of ether and washed with saturated sodium bicarbonate solution and brine. The organic layer was then dried and concentrated. Silica gel chromatography afforded the keto ester 174. When the reaction was stirred at room temperature for 2 days, small amounts of aldol products were obtained. These products, however, were the result of aldol reactions at C-2.

1-[(Carboethoxy)hydroxymethyl]-1-methylcyclohexanone 222

Freshly prepared ethyl glyoxylate (102) (224 mg, 2.2 mmol) and titanium tetrachloride (0.22 ml, 2 mmol) were stirred in 5 ml of CH_2Cl_2 at -78°C. A solution of 1-trimethylsiloxy-2-methylcyclohex-1-ene 221 (88) (368 mg, 2 mmol) in 1 ml of CH_2Cl_2 was added dropwise. Stirring was continued at -78°C for 20 min, then the solution was warmed to -20°C for 3 h. The solution was poured into 10 ml of H_2O and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate solution and brine, dried, and concentrated. Silica gel chromatography yielded 490 mg (86%) of keto alcohol 222: IR (film) 3460, 1790, 1735 cm^{-1}; 100 MHz NMR ($CDCl_3$) (one diastereomer) δ 1.00 (s, 3H), 1.22 (t, J = 7 Hz, 3H), 1.68-2.68 (m, 8H), 3.30 (br s, 1H), 4.17 (q, J = 7 Hz, 2H), 4.61 (s, 1H); (other diastereomer) δ 1.00 (s, 3H), 1.22 (t, J = 7 Hz, 3H), 1.68-2.68 (m, 8H), 3.30 (br s, 1H), 4.17 (q, J = 7Hz, 2H), 4.49 (s, 1H).

Attempted Reaction of Silyl Enol Ether 219 with Ethyl Glyoxylate and Titanium Tetrachloride

Freshly prepared ethyl glyoxylate (102) (195 mg, 1.9 mmol) and titanium tetrachloride (0.19 ml, 1.7 mmol) were stirred in 5 ml of CH_2Cl_2 at -78°C. A solution of silyl enol ether 219 (556 mg, 1.17 mmol) in 1 ml of CH_2Cl_2 was added dropwise. The mixture was stirred 20 min at -78°C, then warmed to -20°C for 12 h. The solution was poured into 10 ml of H_2O and extracted with ether. The extracts were washed with saturated sodium bicarbonate solution and brine, and concentrated. The crude residue contained regenerated keto ester 174 and polymerized glyoxylate. No aldol product was detected.

Attempted Michael Addition of Silyl Enol Ether 219 with Nitroethylene

Titanium tetrachloride (0.54 ml, 0.49 mmol) was added to a solution of freshly distilled nitroethylene (104) (33 mg, 0.45 mmol) in 3 ml of CH_2Cl_2 at -78°C. Silyl enol ether 219 (148 mg, 0.45 mmol) dissolved in 0.5 ml of CH_2Cl_2 was added dropwise. The solution was stirred 2 h at -78°C, then left to stand at -5°C for 8 h. The mixture was poured into 5 ml of H_2O and extracted with ether. The extracts were washed with saturated sodium bicarbonate solution, dried, and concentrated. The products obtained could not be identified. No aldehyde or nitro functionalities were present in the infrared spectrum. Also, a hydrated form of keto aldehyde 227 was not supported by spectral data.

2-(Bromoacetyl)-2-methylcyclohexanone 228

To a 0.5 M solution of 1-trimethylsiloxy-2-methylcyclohex-1-ene (184 mg, 1 mmol) in CH_2Cl_2 at 0°C was added freshly distilled bromoacetyl bromide (0.9 ml, 1 mmol). The solution was warmed to room temperature and stirred for 24 h. Methanol (1 ml) was added and the solution was concentrated. Silica gel chromatography afforded 262 mg (86%) of diketone 228: IR (film) 1730 (sh), 1710 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.46-2.80 (m, 8H), 4.18 (s, 2H).

Attempted Reaction of Silyl Enol Ether 219 with Bromoacetyl Bromide

To a 0.5 M solution of silyl enol ether 219 (108 mg, 0.33 mmol) in CH_2Cl_2 at 0°C was added freshly distilled bromoacetyl bromide (0.03 ml, 0.33 mmol). The solution was warmed to room temperature and stirred for 24 h. Methanol (0.5 ml) was added and the solution was concentrated. Silica gel chromatography afforded 81 mg (98%) of keto ester 174.

(±)-(3α,4α,4aα,8aα)-4a-(Hydroxymethyl)-3-hydroxy-4,7-dimethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran and the C-3 Epimer

Hydroxy ester 173 (3.00 g, 11.8 mmol) dissolved in 15 ml of ether was added dropwise to a suspension of lithium aluminum hydride (896 mg, 23.6 mmol) in 25 ml of ether at 0°C and the mixture was stirred 30 min.

Careful addition of 0.9 ml of H_2O was followed by the addition of 0.9 ml of 1N NaOH and 2.7 ml of H_2O. Ether (100 ml) was added and the mixture was stirred overnight. The solution was filtered through Celite, dried, and concentrated to yield 2.09 g (84%) of diol: IR (film) 3370, 1680, 1060 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.02-2.24 (m, 11H), 3.26-3.94 (m, 7H), 4.26-4.44 (m, 1H), 5.21-5.33 (m, 1H).

(±)-(4α,4aα,8aα)-4a-(Carboxy)-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (230)

The crude diol (2.09 g, 9.84 mmol), obtained from the $LiAlH_4$ reduction of hydroxy ester 173, was dissolved in 50 ml of acetone and cooled to 0°C. Jones reagent (7.38 ml, 29.5 mmol) as a 4M solution in H_2O was added dropwise and the solution was stirred for 30 min at 0°C. The solution was diluted with ether and washed three times with brine. The organic layer was then dried and concentrated. Silica gel chromatography yielded 2.05 g (93%) of keto acid 230: IR (film) 3700-2300, 1780 (sh), 1730, 1710, 1080 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.13 (d, J = 7 Hz, 3H), 1.79 (s, 3H), 1.84-2.48 (m, 4H), 2.55 (q, J = 7 Hz, 1H), 4.00-4.15 (m, 2H), 4.38 (br s, 1H), 5.53 (br s, 1H), no CO_2H observed.

(±)-(4α,4aα,8aα)-4a-[1-(2-Bromo-1-ethoxyethyl)]carboxylate-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (232)

Keto acid 230 (108 mg, 0.48 mmol), dissolved in 1 ml of THF, was added to a suspension of oil free sodium hydride (13 mg, 0.48 mmol) in 2 ml of THF at 0°C. When bubbling had ceased, the carboxylate solution was added to a freshly prepared 0.5 M solution of 1,2-dibromoethyl ethyl ether 231 (0.48 mmol) in THF at 0°C. (Dibromide 231 was prepared by the addition of bromine to a solution of ethyl vinyl ether in THF at 0°C.) The reaction mixture was stirred at 0°C for 1 h, then diluted with 50 ml of ether and washed with saturated sodium bicarbonate solution. The organic layer was dried and concentrated to afford, after silica gel chromatography, 115 mg (64%) of bromoketone 232: IR (film) 1735, 1710 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.11-1.29 (m, 6H), 1.74-2.50 (m, 7H), 2.56-2.77 (m, 1H), 3.33-3.40 (m, 2H), 3.55-3.87 (m, 2H), 4.08 (br s, 2H), 4.36-4.48 (m, 1H), 5.49-5.58 (m, 1H), 5.84-6.00 (m, 1H).

Attempted Intramolecular Alkylations of Bromoketone 232

Bromoketone 232 (69 mg, 0.18 mmol) and potassium tert-butoxide tert-butanol complex (21 mg, 0.18 mmol) were mixed in 2 ml of THF at 0°C. The reaction was warmed to room temperature and stirred for 12 h. The solution was acidified (pH 7) with 3% HCl in methanol. Removal of the solvent afforded compound 232 unchanged. The reaction was repeated

with 42 mg (0.11 mmol) of bromoketone 232 and 13 mg (0.11 mmol) of potassium tert-butoxide tert-butanol complex. The solution was heated to 50°C for 6 h. Acidification and concentration afforded the hydrolyzed keto acid 230.

Attempted Formation of the Silyl Enol Ether of Bromoketone 232

Bromoketone 232 (188 mg, 0.5 mmol), hexamethyldisilazane (0.10 ml, 0.45 mmol), and iodotrimethylsilane (0.06 ml, 0.45 mmol) were reacted in 10 ml of CH_2Cl_2 at -25°C according to the procedure of Miller and McKean (88). The solution turned dark brown immediately upon addition of the silyl iodide. The reaction was worked up to afford 105 mg (94%) of keto acid 230.

(±)-(4α,4aα,8aα)-4a-[1-(Prop-2-enyl)carboxylate]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-4 Epimer (233)

Keto acid 230 (882 mg, 3.93 mmol), sodium bicarbonate (1.65 g, 20 mmol), and allyl bromide (0.68 ml, 7.87 mmol) were stirred in 4 ml of dry DMF at room temperature for 20 h. The mixture was concentrated and 50 ml of ether was added. The ether solution was decanted from the excess sodium bicarbonate and washed with 20 ml of 1N HCl solution. The organic layer was dried and concentrated to afford, after silica gel chromatography, 758 mg (73%) of allyl ester 233: IR (film) 1735, 1710 (sh), 1640 cm^{-1}; 100 MHz NMR ($CDCl_3$) (major diastereomer, 90%)

δ 1.04-1.17 (m, 2H), 1.68-2.75 (m, 8H), 4.11 (br s, 2H), 4.30-4.41 (m, 1H), 4.52-4.65 (m, 2H), 5.18-6.09 (m, 4H); (minor diastereomer, 10%) δ 1.12 (d, J = 7 Hz, 3H), 1.68-2.51 (m, 7H), 3.12 (q, J = 7 Hz, 1H), 4.11 (br s, 2H), 4.30-4.41 (m, 1H), 4.78-4.88 (m, 2H), 5.18-6.09 (m, 4H).

(±)-(4α,4aα,8aα)-4a-[1-(2,3-Dihydroxypropyl)carboxylate]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-4 Epimer

Allyl ester 233 (384 mg, 1.45 mmol) and sodium periodate (295 mg, 1.38 mmol) were dissolved in 5 ml of a 4:1 THF-H_2O mixture. Osmium tetraoxide (10 mg) was added as a 5 mg/ml solution in H_2O. The solution became cloudy and a precipitate formed within 1 min. After the mixture was stirred at room temperature 12 h, 50 ml of ether was added and the solution was washed with sodium bicarbonate solution and brine. The organic layer was then dried and concentrated. Silica gel chromatography afforded 363 mg (84%) of keto diol: IR (film) 3430, 1735 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.01-3.24 (m, 11H), 3.45-4.91 (m, 10 H), 5.44-5.58 (m, 1H).

(±)-(4α,4aα,8aα)-4a-[2-(1-oxoethyl)carboxylate]-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one and the C-4 Epimer (234)

The diol (271 mg, 0.91 mmol) obtained from the osmolysis of allyl ester 233, was stirred in 5 ml of ether with periodic acid (228 mg,

1 mmol). After 12 h, the solution was decanted and concentrated. Silica gel chromatography yielded 229 mg (95%) of keto aldehyde 234: IR (film) 1735 (sh), 1710, 1080 cm^{-1}; 100 MHz NMR ($CDCl_3$) (major isomer, 90%) δ 1.12-1.19 (m, 3H), 1.80 (br s, 3H), 1.88-2.86 (m, 5H), 3.57 (d, J = 1.5 Hz, 2H), 4.06-4.57 (m, 3H), 5.49-5.61 (m, 1H), 9.50 (t, J = 1.5 Hz, 1H); (other diastereomer, 10%) δ 1.12-1.19 (m, 3H), 1.72 (s, 3H), 1.88-2.69 (m, 4H), 3.12-3.38 (m, 1H), 3.86 (d, J = 1.5 Hz, 2H), 4.06-4.57 (m, 3H), 5.49-5.61 (m, 1H), 9.67 (t, J = 1.5 Hz, 1H); high resolution mass spectrum, calcd for $C_{14}H_{18}O_5$ m/e 266.11541, found m/e 266.11609.

Attempted Cyclization of Keto Aldehyde 234

Keto aldehyde 234 (49 mg, 0.18 mmol) and triethylamine (0.04 ml, 0.30 mmol) were stirred in 2 ml of CH_2Cl_2 at room temperature. After 12 h, the solution was concentrated to afford starting material unchanged.

Keto aldehyde 234 was again mixed with triethylamine (0.04 ml, 0.30 mmol) in 2 ml of CH_2Cl_2 and acetic anhydride (0.02 ml, 0.20 mmol) was added. After 24 h at room temperature, TLC indicated no reaction. Dimethylaminopyridine (1 crystal) was added, to aid in acetylation, and the mixture was stirred 12 h. The solution was diluted with 50 ml of ether, washed with saturated sodium bicarbonate solution, dried, and concentrated. Silica gel chromatography afforded a new product which was identified as enol acetate 235: IR (film) 3110, 1750 (br),

1710 (sh) cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.04-1.21 (m, 3H), 1.56-2.49 (m, 10 H), 2.55-2.78 and 3.07-3.24 (m, 1H, C<u>H</u>-Me), 4.01-4.46 (m, 3H), 5.45-5.60 (m, 1H), 6.63-6.90 (m, 2H).

1,3-Dimethyl-2-methylenecyclohexane (<u>238</u>)

Dimethylsulfoxide (3 ml), which had been distilled from sodium hydride onto flame dried molecular sieves, was added to oil-free sodium hydride (12 mg, 5 mmol). The mixture was heated to 80°C for 30 min, then cooled. Triphenylphosphoniummethyl iodide (2.02 g, 5 mmol), dissolved in 3 ml of warm dimethylsulfoxide, was added. After 10 min, 2,6-dimethylcyclohexanone (0.14 ml, 0.5 mmol) was added and the solution was heated to 80°C for 72 h. The solution was cooled and 10 ml of H_2O was added. The mixture was then extracted with ether. The organic fractions were combined and washed 3 times with H_2O, dried, and concentrated. Silica gel chromatography afforded 15 mg (24%) of olefin <u>238</u>: IR (film) 1645 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 0.89-1.85 (m, 12H), 1.95-2.40 (m, 2H), 4.59 (br s, 2H). Starting material <u>237</u> (33 mg, 52%) was also recovered.

CONCLUSION

Two routes to the AB ring system of the epoxytrichothecenes have been developed. The first synthetic scheme involved the Diels-Alder reaction between methyl coumalate and isoprene. The cis-fused bicyclic lactone obtained from this reaction was successfully converted to the β-keto ether of the trichothecene AB ring system.

A second, more practical, and efficient route to the AB ring system was developed. This sequence involved as a key step, the reductive deoxygenation of an acetal to a cyclic ether. The bicyclic keto alcohol produced via this synthetic scheme was converted into the trichothecene skeleton utilizing procedures previously developed in our research group. This route to the tricyclic system was adopted only after extensive research directed toward introducing the C ring via a myriad of other synthetic schemes proved unsuccessful. This efficient route to the trichothecene skeleton employing the improved synthesis of the intermediate bicyclic keto alcohol has provided major advances toward the synthesis of the 12,13-epoxytrichothecenes.

Another significant aspect of this research was the development of two novel synthetic methods: preparation of allylic alcohols from epoxides using iodotrimethylsilane, and selective reductions via enolate protection. The conversion of epoxides to allylic alcohols was found to proceed regiospecifically with trisubstituted epoxides and compliments previously developed methods. The use of enolate anions as protecting groups served as a convenient procedure for selective reductions of

various functionalities employing a variety of reducing agents. These two procedures should find general applicability in systems other than the trichothecenes, and they should prove to be useful additions to the stockpile of synthetic procedures available for use in the construction of complex organic molecules.

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