

Synthetic studies in the Trichothecane  
Field

THESIS

presented to the University of Glasgow  
for the degree of Doctor of Philosophy

by

Swiatoslaw Malchenko

1972

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I should like to thank my advisors, Mr. J. S. Roberts, Professor R. L. Smith, and Mr. E. W. Colver for their advice, criticism and help during the course of this research. Their enthusiasm and friendship has been a source of constant encouragement to me.

It is a distinct pleasure to acknowledge the assistance of my friends in the preparation of this thesis.

To my Parents

З ВЛИКОЮ ПОШАНОЮ

My parents, Mr. J. S. Roberts and Mrs. E. W. Colver, have been a source of constant encouragement and help during the course of this research.

My friends, Mr. J. S. Roberts, Professor R. L. Smith, and Mr. E. W. Colver, have been a source of constant encouragement and help during the course of this research.

The assistance of my friends in the preparation of this thesis is gratefully acknowledged.

## Acknowledgements

I should like to thank most sincerely Dr. J.S. Roberts, Professor R.A. Raphael F.R.S. and Dr. E.W. Colvin for their advice, guidance and many efforts on my behalf during the course of this research. Their enthusiasm and friendship has been a source of constant encouragement to me.

It is also a distinct pleasure to acknowledge the help of my parents in the preparation of this thesis.

Over the period of this work it has been my pleasure to have been associated with a number of outstanding research students; specifically I am indebted to Dr. C. Thomson and Mr. W.M. Motherwell for arousing scientific interest and to Mr. T.C. Hogg for moments of comic relief during periods of depression.

Technical services were freely and competently rendered by the staff of Glasgow University Chemistry Department and to them I express my gratitude.

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## Summary

Two synthetic routes towards 3,6-dimethyl-8-oxo-9-oxabicyclo[4,3,0]non-2-ene, a crucial intermediate in the synthesis of the sesquiterpenoid mould metabolite trichodermin, are discussed.

The strategy and ultimate approach towards the most widely distributed sesquiterpenoid component of the trichothecanes, verrucarol, via 3-methyl-6-hydroxymethyl-8-oxo-9-oxabicyclo[4,3,0]non-2-ene, are fully described.

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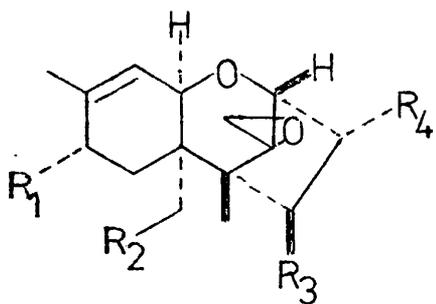
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## INTRODUCTION

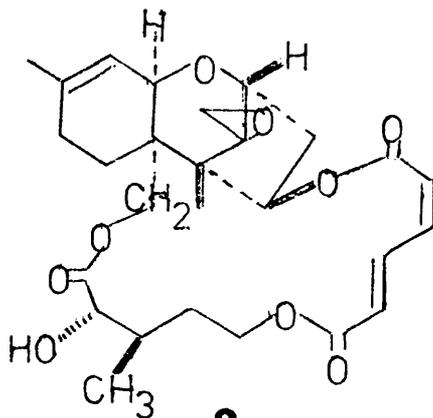
The trichothecanes are a relatively new group of sesquiterpenoid mould metabolites which have come into chemical prominence over the last decade primarily due to the efforts of Tamm and Grove and their coworkers. Work has mainly been concentrated upon the isolation and structural determination of members of this class of natural products. Studies on their chemical reactivity and biogenesis have been investigated in a more limited fashion and the subject of their synthesis in vitro has been comparatively neglected.

The object of this introduction is to collate the available literature on this group of sesquiterpenoids and thus place the ensuing discussion in a more comprehensible environment.

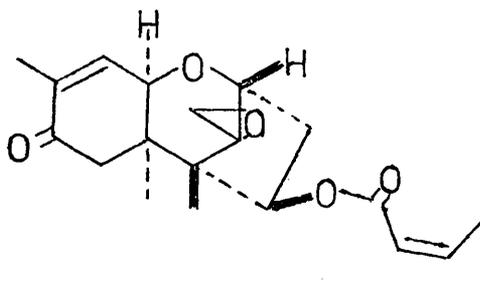
Antagonistic activity to other fungi by Trichothecium roseum Link (syn. Cephalothecium roseum Cerda) had been reported as early as 1909 by Whetzel<sup>1</sup>. It was not until 1948, however, that Freeman<sup>2</sup> was able to isolate the substance directly responsible for this activity and suggest the name trichothecin for the biologically active, crystalline compound. Since then it has been found that the naturally occurring esters of this novel class of sesquiterpenoid alcohols containing the tetracyclic 12,13 epoxy-trichothec-9-ene nucleus [1, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H] are produced by a fairly wide



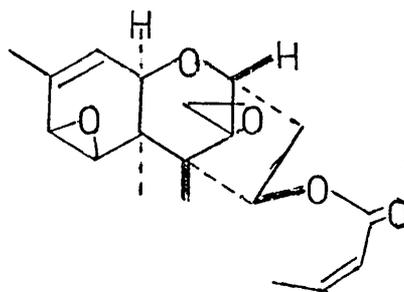
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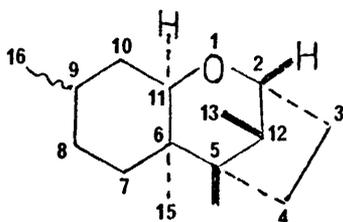
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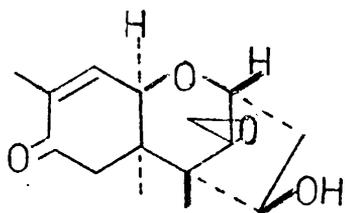
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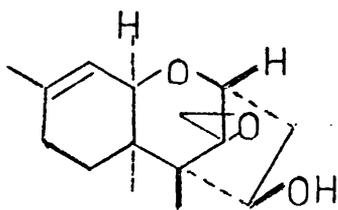
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range of soil fungi. Trichodermin [1, R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = H, R<sup>3</sup> = OAc] has been isolated from Trichoderma viride<sup>3</sup>. Diacetoxyverrucarol<sup>4</sup> [1, R<sup>1</sup> = R<sup>4</sup> = H, R<sup>2</sup> = R<sup>3</sup> = OAc] and the verrucarins and roridins, of which the macrolide verrucarin A (2)<sup>5,6</sup> is the principal member, are produced by a number of strains of Myrothecium verrucaria and Myrothecium roridum. Diacetoxy-scirpentriol<sup>7,8</sup> [1, R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> = OAc, R<sup>4</sup> = H] has been obtained from a number of related Fusarium species, notably F. equiseti, F. sambucium, F. scirpi and F. trincinctum<sup>9,10,11</sup>. Trichothecin (3), as already mentioned, is obtained from Trichothecium roseum<sup>12</sup> and crotocin (4) from Cephalosporium crotocingenum<sup>13</sup>.

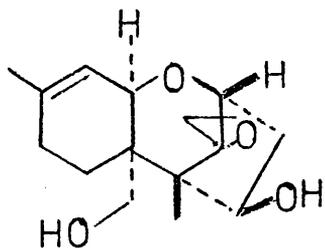
Chemical and physical investigations have shown that all the above mentioned products possess one and the same, novel, tricyclic ring skeleton (5). The only difference in their structure manifests itself in the different functional groupings attached to the carbon atom periphery. Practical reasons deem it desirable to introduce a nomenclature and numbering system for the basic carbon skeleton in order to allow the naturally occurring trichothecanes and their derivatives to be named in a systematic manner. The basic ring system (5), for historical reasons, has been called TRICHOTHECANE and numbered in the indicated manner<sup>14</sup>. The angular C<sub>15</sub> methyl group is taken as a point of reference as regards the configuration of the various asymmetric centres contained in the



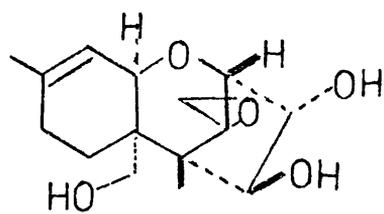
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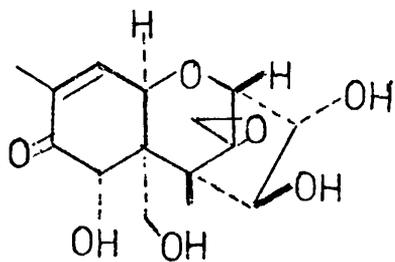
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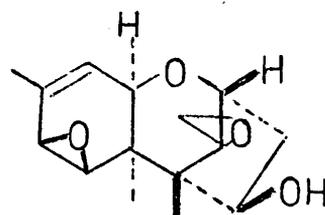
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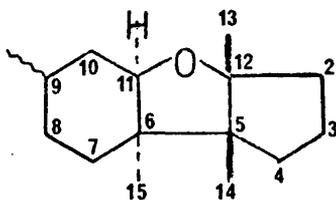
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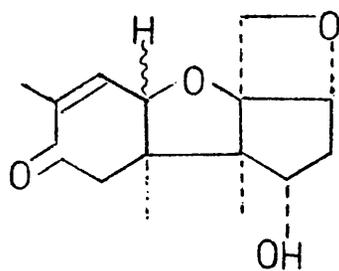


**12**

molecule and is considered to be below the plane of the paper. This representation also corresponds to the absolute configuration of the trichothecanes as established by X-ray analysis<sup>15</sup> and chemical correlation of verrucarin A (2)<sup>5</sup>. The suffixes  $\alpha$  and  $\beta$  have their normal steroidal meaning. The sesquiterpenoid alcohols which constitute the basic building blocks of the naturally occurring trichothecane ester antibiotics, by this nomenclature, assume the following names.

- Trichothecolone (6)  $4\beta$ -hydroxy-12,13-epoxy- $\Delta^{9,10}$ -trichothecen-8-one.
- Trichodermol (7)  $4\beta$ -hydroxy-12,13-epoxy- $\Delta^{9,10}$ -trichothecene.
- Verrucarol (8)  $4\beta,15$ -dihydroxy-12,13-epoxy- $\Delta^{9,10}$ -trichothecene.
- Scirpentriol (9)  $3\alpha,4\beta,15$ -trihydroxy-12,13-epoxy- $\Delta^{9,10}$ -trichothecene.
- $3\alpha,4\beta,7\alpha,15$ -tetrahydroxy-scirp-9-en-8-one (10)  $3\alpha,4\beta,7\alpha,15$ -tetrahydroxy-12,13-epoxy- $\Delta^{9,10}$ -trichothecen-8-one.
- Crotocol (11)  $4\beta$ -hydroxy- $7\beta,8\beta,12,13$ -diepoxy- $\Delta^{9,10}$ -trichothecene.

The ring system (12), corresponding to the structures encountered in the majority of trichothecane derivatives is called APOTRICHOTHECANE<sup>14</sup>. The numbering system, though strange at first sight, has the advantage of maintaining the numbers

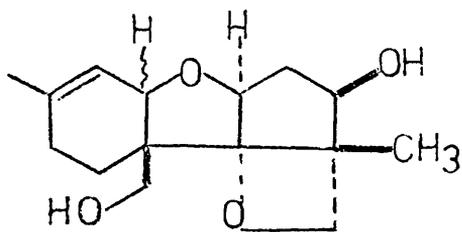


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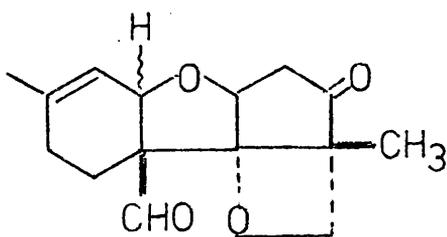
originally assigned to the trichothecane skeleton, thus simplifying chemical and spectral comparisons.

As already mentioned, the isolation of the first member of the trichothecane group, the mould metabolite trichothecin, was achieved by Freeman from culture filtrates of Trichothecium roseum<sup>12</sup>. The antifungal compound, after fractional precipitation and chromatographic purification on alumina, was obtained as long fibrous needles. Fairly extensive work, over a period in excess of ten years, showed the compound to be an isocrotonic ester, furnishing on methanolic base hydrolysis an  $\alpha,\beta$ -unsaturated keto alcohol, trichothecolone<sup>16</sup>, to which structure (13) was assigned<sup>17,18</sup>. A remarkable feature of this proposed structure and one not commented upon by the authors, was the presence of an oxetane moiety, a functional grouping not encountered previously in natural product chemistry.

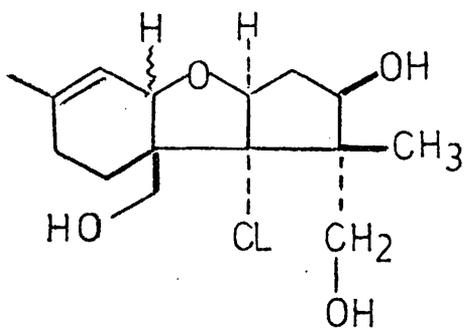
In 1962 Tamm and coworkers found that culture fluids of Myrothecium verrucaria and Myrothecium roridium showed high cytostatic activity; this, coupled with the antibiotic properties of the fluids prompted them to investigate the substances responsible for these prominent biological characteristics. Their labours were rewarded with the isolation of a group of chemically related, crystalline compounds which were shown to be the carriers of the antibiotic and anti-mitotic properties of the organisms<sup>6</sup>. In all fourteen new



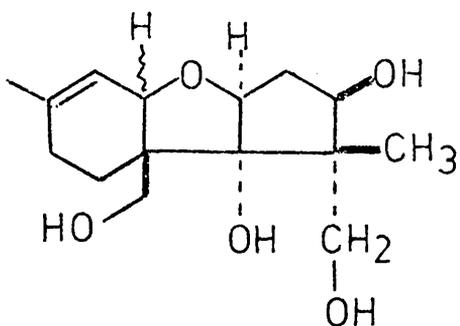
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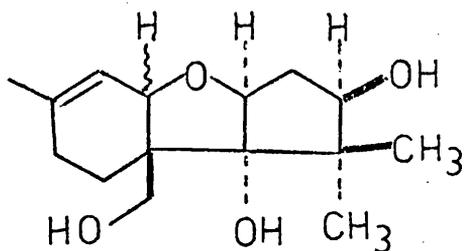
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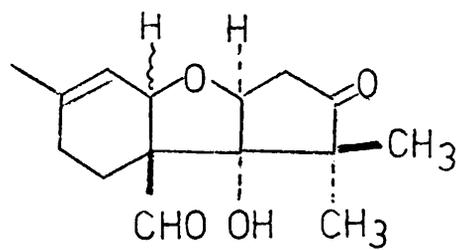
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**18**

compounds were obtained which, depending on their original source, are called verrucarins A, B, C, D, E, F, G, H and J<sup>6</sup> and roridin A, B, C, D<sup>6</sup> and E<sup>19</sup>. All, with the exception of verrucarin E<sup>20,21,22</sup>, are di- and triester antibiotics which on base hydrolysis give rise to verrucarol<sup>23</sup>, the sesquiterpenoid component of their structures. The challenge presented by this new compound was taken up actively and the tetracyclic structure (14)<sup>24,25</sup> suggested as being best suited to explain the wealth of chemical and spectroscopic data accumulated for the sesquiterpenoid. Thus, verrucarol, on treatment with Jones reagent, gave a keto-aldehyde (15) demonstrating the presence of both primary and secondary hydroxyl groupings. The former, in view of nuclear magnetic resonance (n.m.r.) data, was believed to exist as a hydroxymethyl grouping. The latter, from infra-red (i.r.) evidence of the oxidation product (15), showed its presence in a five membered ring<sup>24</sup>. An epoxide group, initially thought to be a structural feature of verrucarol, remained unconfirmed; instead the presence of an oxetane was proposed.

The various rearrangements which verrucarol was capable of undergoing were explained on the basis of oxetane ring fission. Thus hydrochloric acid treatment was believed to give rise to the chlorhydrin (16), aqueous sulphuric acid to the tetrol (17) and lithium aluminium hydride to the dihydro derivative (18). Since (17) remained unaffected on



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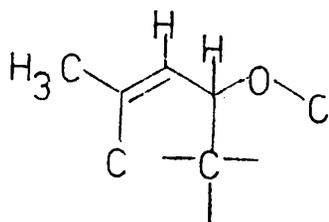
treatment with lead tetraacetate, the newly formed hydroxyls were postulated to exist in a 1,3 relationship to one another. The tertiary nature of one of the hydroxyls in (18) was demonstrated convincingly by oxidation of this compound to a keto-aldehyde (19), which still showed a hydroxyl band in the i.r. This evidence was certainly compatible with an oxetane grouping, as were the strong C-O-C stretching frequencies in the i.r. at 970 and 960  $\text{cm.}^{-1}$ , present in all simple verrucarol derivatives and which were absent on fission of the oxetane moiety<sup>24</sup>. These spectroscopic data, however, could hardly be cited as concrete evidence for the proposed ring system for, as Tamm noted, oxetanes had only been investigated very superficially and the C-O-C stretching frequencies could equally well have been assigned to an epoxide. However, on the basis of the evidence presented above and the n.m.r. data of a large number of verrucarol derivatives, the authors were prompted to assign structure (14) to verrucarol<sup>24</sup>. This structural assignment perhaps reflects a slight degree of bias which may be excused in the light of the extensive circumstantial evidence presented. Thus the authors, although not convinced of the correctness of their own structural assignment, no doubt were reassured by the chemical and spectroscopic similarity with trichothecolone<sup>17</sup> and, accepting the validity of its structural assignment, proposed the same ring skeleton for verrucarol. In fairness it should be poin-

ted out that their structural proposal did, indeed, appear to account for the chemical and physical data recorded. Although their evidence did not allow an unambiguous preclusion of an oxirane, they incorporated an oxetane moiety into the ring system; indeed, an epoxide was initially proposed to account for the lithium aluminium hydride reduction which verrucarol underwent<sup>25</sup>, only to be discarded for no apparent reason at a later stage<sup>24</sup>.

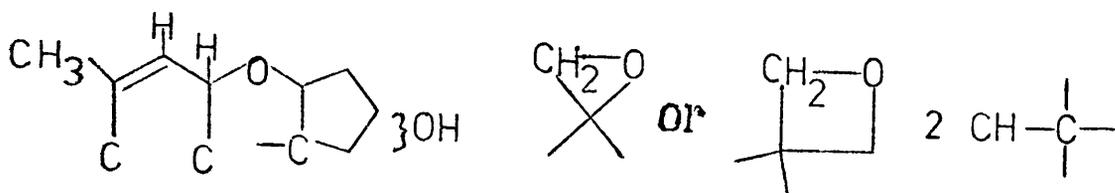
Matters, of course, were immensely complicated by the molecular acrobatics which verrucarol and the trichothecanes generally were capable of undergoing and which confused the early structural elucidations. However, incorrect structural assignments are not a novel feature of the chemical literature and corrections to earlier proposals abound. So too with verrucarol and trichothecin, where a revision of their structures was the direct consequence of the discovery of a new member of this group of sesquiterpenoids.

From the culture filtrates of Trichoderma viride, obtained from a New Guinea soil sample, a further antibiotic in the trichothecane series was isolated. This mould metabolite, trichodermin, showed activity against a variety of pathogenic fungi and inhibited in low concentrations the growth of various cell types<sup>26,27</sup>. It was shown to be the acetate of a sesquiterpenoid alcohol, trichodermol<sup>27</sup>.

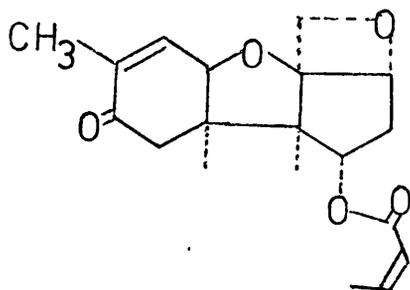
A study of the n.m.r. spectra of trichodermin, tricho-



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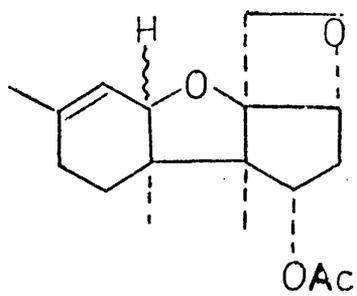


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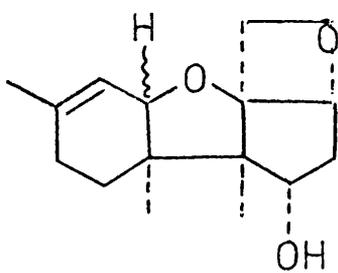


**22**

dermol and its oxidation product trichodermonol, proved invaluable in shedding light on these structures. Two singlets at  $\tau$  9.23 and  $\tau$  9.18 in trichodermol indicated the presence of two quaternary methyl groups and a signal at  $\tau$  8.30 was attributed to an olefinic methyl. An AB quartet at  $\tau$  7.21 and  $\tau$  6.93 ( $J_{AB}$ , 4Hz.) was characteristic of an oxirane methylene but could, conceivably, arise from the methylene protons of an oxetane grouping. The magnitude of the coupling constant favoured the former, however. Three ethereal methine protons were observed at  $\tau$  6.5,  $\tau$  6.19 and  $\tau$  5.66. Of these, the quartet at  $\tau$  5.66 was attributed to a proton on a carbon bearing a hydroxyl group. In trichodermin, for instance, it is shifted to lower field ( $\tau$  4.22) and is completely lacking in trichodermonol. The presence of only one vinylic proton suggested a trisubstituted double bond. Spin-spin decoupling experiments showed the complex olefinic pattern to arise as a result of long range methyl to vinyl coupling, since irradiation at the methyl caused it to collapse into a doublet. The proton neighbouring it was assumed to be the one at  $\tau$  6.5. This suggested (20) as a possible structural fragment for trichodermin. A combination of spectroscopic and chemical data consequently implied that trichodermin comprised the structural fragments (21). From this it became obvious to the authors<sup>22</sup> that a relationship might, indeed exist between trichodermin and trichothecin (22). It should be noted that



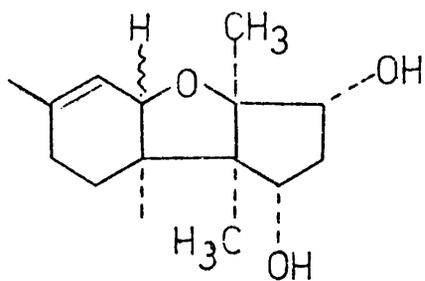
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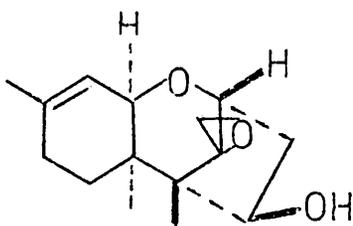
**24**

(22) contained all the characteristics deduced for trichodermol, the difference only manifesting itself in the  $\alpha, \beta$ -unsaturated ketone and the crotonic ester grouping. Since the empirical formula showed that trichothecolone possessed one oxygen more and two hydrogens less than trichodermol and since the chemical reactions of these two alcohols proceeded in a reasonably analogous manner, the authors were tempted to seek a chemical correlation between suitable derivatives of these two compounds.

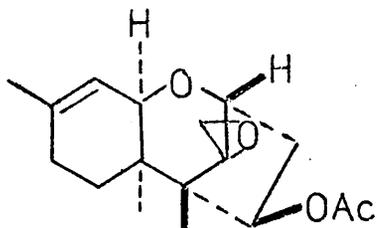
This was readily achieved. Trichodermin, on vigorous oxidation with chromium trioxide, furnished a small quantity of trichothecolone acetate correlating these two compounds. As a direct consequence of this, assuming temporarily the validity of the initially proposed structure for trichothecolone (13) and the absence of any rearrangements within trichodermin, structures (23) and (24) could be proposed for trichodermin and trichodermol respectively. That these structures accounted for most of the chemical and spectroscopic evidence available was unchallenged; at the same time the fact that they did not explain all the observed data satisfactorily was equally obvious. The major difficulty in accepting the proposed structures was the outcome of lithium aluminium hydride reduction of trichodermol. A diol ( $C_{15}H_{24}O_3$ ) was obtained, the n.m.r. spectrum of which showed one more quaternary methyl than starting material. The AB spectrum attri-



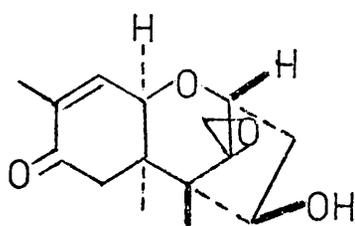
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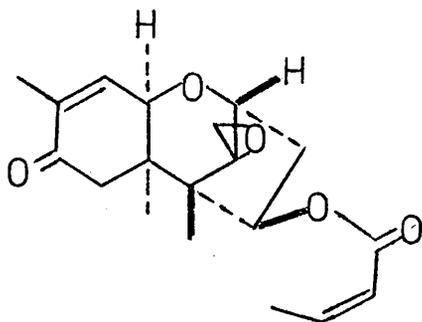
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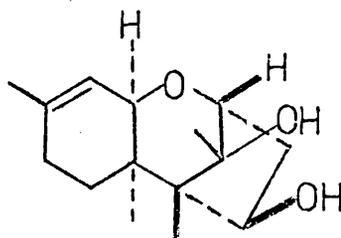
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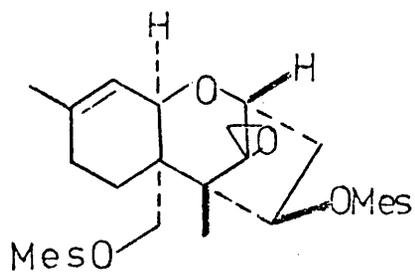
buted to the oxetane methylene protons had disappeared and structure (25) should obviously have been assigned to the reduced material. Acylation of (25) only gave a monoacetate, however, and oxidation a hydroxy ketone, indicating the newly formed hydroxyl to tertiary in nature. This data was inconsistent with the postulated structure (23) for trichodermin; if anything it pointed to the presence of an oxirane moiety. Because of this discrepancy the p-bromobenzoate of trichodermol was subjected to X-ray analysis by Abrahamsson and Nilsson<sup>28</sup>. The crystallographic study confirmed the presence of an epoxide and established the correct structure and relative configuration of trichodermol as (26).

In view of the chemical correlation between trichodermin (26a) and trichothecolone acetate, the structures of trichothecolone and trichothecin were revised to (27) and (28)<sup>27</sup>. The diol, obtained by lithium aluminium hydride reduction of trichodermol, must be represented by (29).

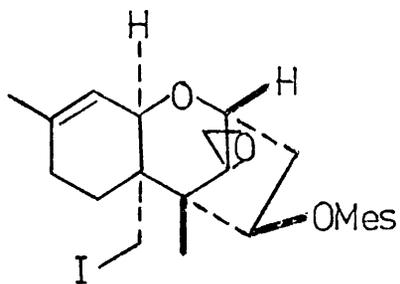
The relationship between Trichodermol and Verrucarol

The identity of trichodermol and roridin C, a minor metabolite produced by Myrothecium roridium, prompted Godtfredsen and Vangedal to suggest that verrucarol, the sesquiterpenoid moiety of the verrucarins and roridins, possessed the same basic ring skeleton encountered in trichodermol (26)<sup>26</sup>.

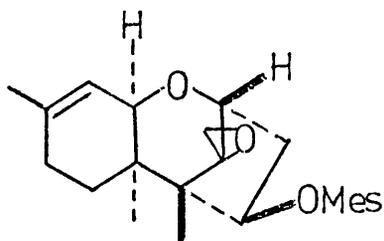
Chemical evidence inconsistent with the initially proposed structure for verrucarol (14) and gentle prompting by the



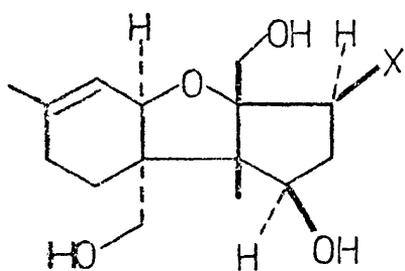
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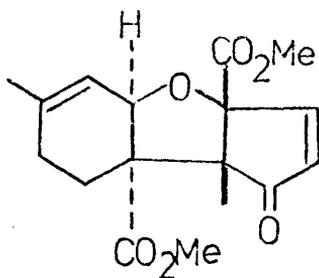
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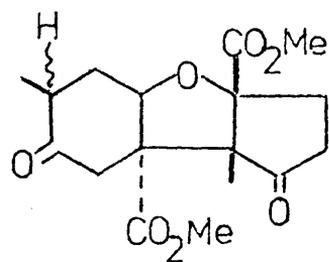
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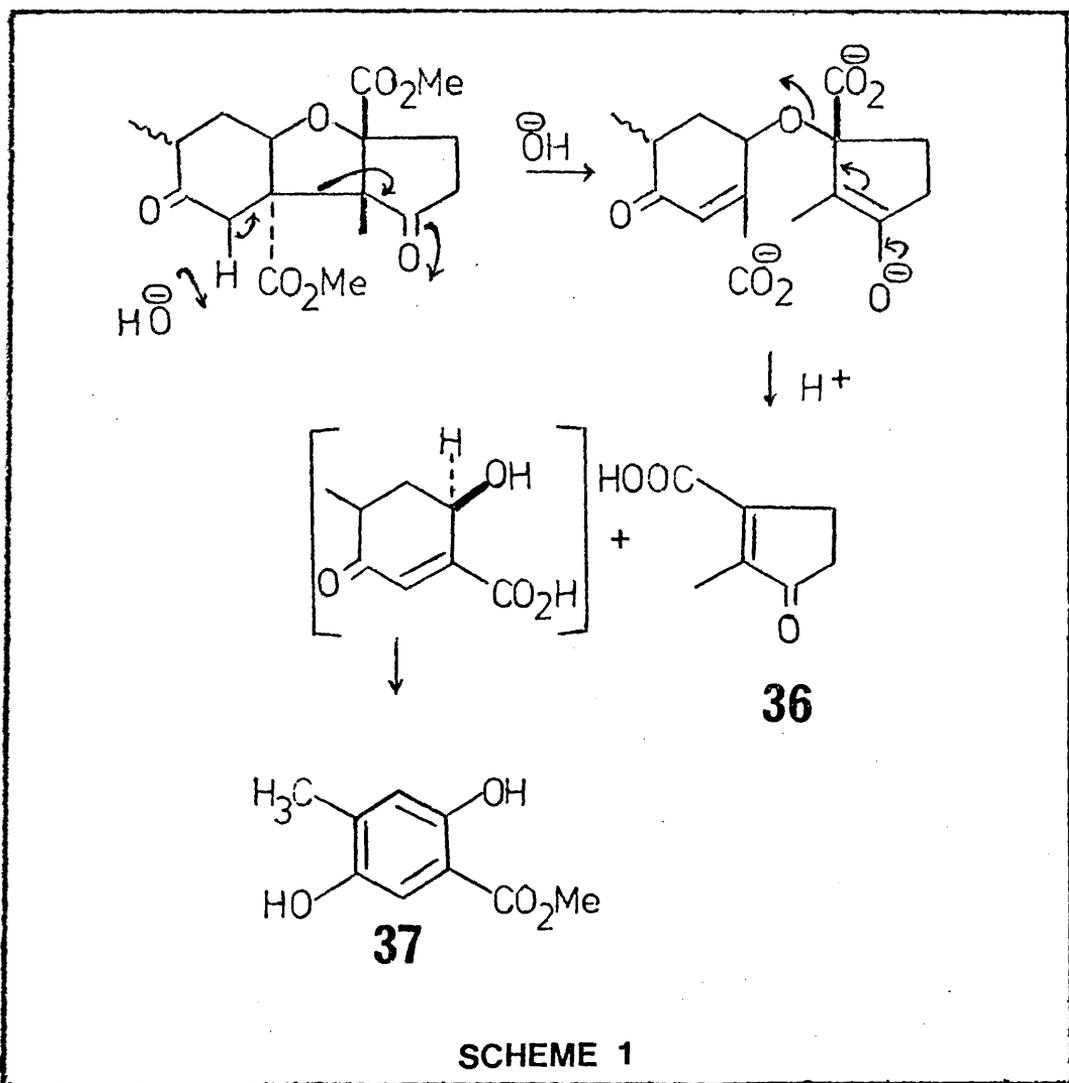
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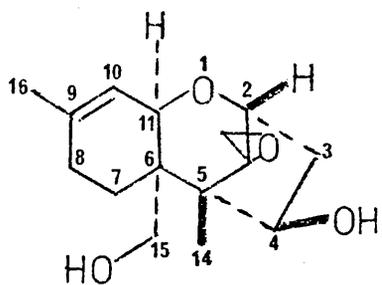


**35**

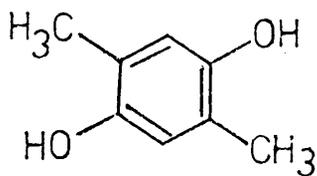


above mentioned authors stimulated Tamm and coworkers to re-investigate verrucarol<sup>23</sup>. The aforementioned chemical and physical similarity between trichodermol and verrucarol led them to attempt a correlation between these sesquiterpenoids. Treatment of the di-mesylate derivative of verrucarol (30) with sodium iodide in acetone allowed a selective nucleophilic substitution at the primary function to furnish the iodo-mesylate (31). Reductive dehalogenation gave mono-mesyl-deoxy-verrucarol (32). Since hydrolysis of this compound, even under severe conditions proved unsuccessful, trichodermol and roridin C (26) were mesylated and shown to be identical in all respects with (32). The above reaction sequence, which did not involve any asymmetric centres, thus correlated verrucarol and trichodermol, but did not allow an unambiguous positional assignment to the primary hydroxyl in the former. With this objective in mind, verrucarol was rearranged under mild acid conditions to the apotrichothecane derivative (33, X=Cl). Chromic oxide oxidation and subsequent esterification gave the keto-ester (34) which, on selenium dioxide in acetic acid oxidation and catalytic hydrogenation furnished (35). Base-induced cleavage of 1,5-diketones is well established and thus the diketone (35) underwent the anticipated retro-Michael reaction in the expected manner, as indicated in Scheme 1.

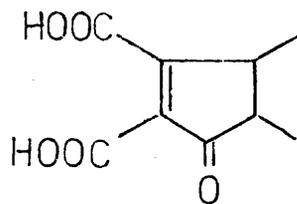
An excellent yield of (36) was obtained, the other major



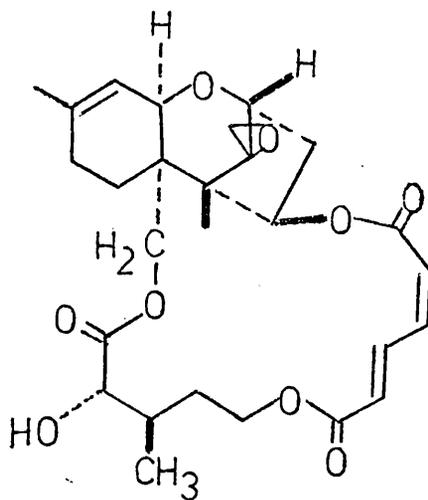
**38**



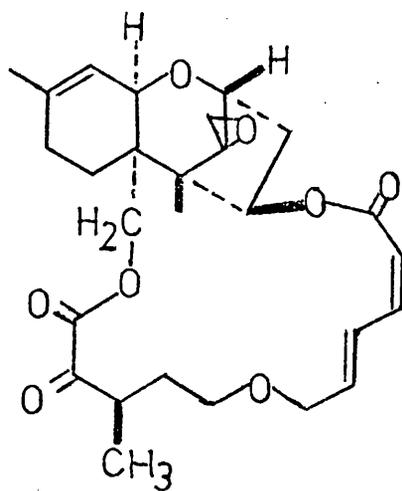
**39**



**40**



**41**

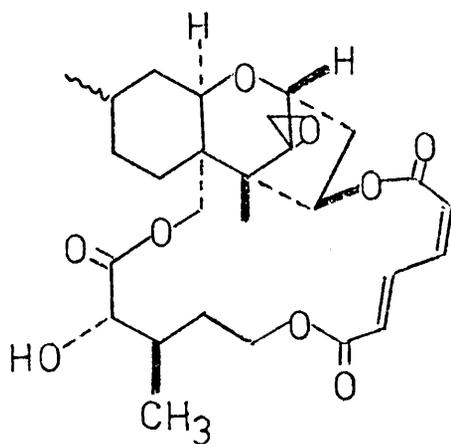


**42**

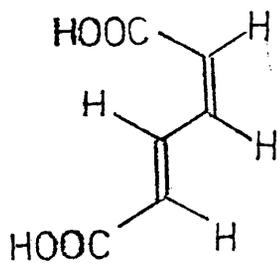
product, on esterification, being the aromatic compound (37). This structural degradation sequence allowed an unambiguous positional assignment of the hitherto elusive hydroxyl to C<sub>15</sub>, thus revising the structure of verrucarol to (38). Attachment of the hydroxyl to the other possible site at C<sub>14</sub> would have led to (39) and (40) as reaction products in the degradative sequence.

With the structure of verrucarol (38), the sesquiterpenoid component of the verrucarins and roridins, fully elucidated, the problem of full structural clarification of this group of compounds became one of unravelling the intricacies of the macrocyclic side chain linking the two oxygenated sites of verrucarol at C<sub>15</sub> and C<sub>4</sub>.

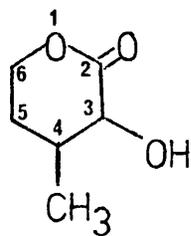
Simple, yet very elegant work by Tamm and coworkers solved the problem associated with some of the structures in a relatively short period of time. The elucidative approach, relying mainly upon spectroscopic data and the isolation and characterisation of the hydrolysis products of this group of antibiotics, will be described for verrucarin A<sup>6</sup>, the principal metabolite of the verrucarins. Structure (41)<sup>5</sup> has been ascribed to the molecule. U.v. and i.r. data indicated the presence of an  $\alpha, \beta, \gamma, \delta$ -unsaturated ester as well as the presence of a hydroxylic moiety. The secondary nature of the hydroxyl was established by chromium trioxide oxidation of (41), which gave rise to a neutral dehydroverrucarin A (42),



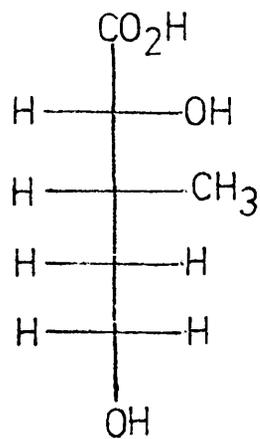
**43**



**44**



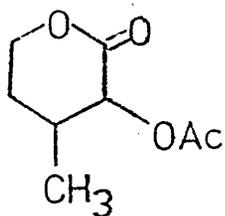
**45**



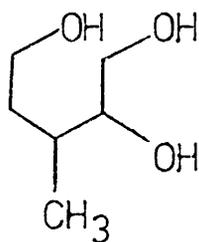
**46**

whose n.m.r. spectrum precluded the presence of an aldehyde group and whose i.r. spectrum showed no further hydroxyl bands. The n.m.r. spectrum of verrucarín A indicated three different methyls; a tertiary one at  $\tau$ 9.13, a secondary methyl at  $\tau$ 9.11 (J,7Hz.) as well as an olefinic methyl at  $\tau$ 8.24. A complex vinylic region was in evidence and will be discussed at a later stage. Catalytic hydrogenation of the metabolite produced hexahydroverrucarol (43) no longer showing any selective u.v. absorption. Spectroscopic data revealed a carbonyl stretch at  $1725\text{ cm}^{-1}$  and the absence of vinylic protons. Treatment of verrucarín A with aqueous, methanolic potassium carbonate, at room temperature, quantitatively produced three fragments: cis, trans muconic acid (44), verrucarínolactone (45), the lactone of the novel dihydroxy- $\beta$ -methyl valeric acid (46) and verrucarol (38).

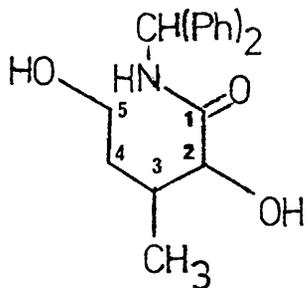
Of the three possible geometric isomers of muconic acid, the all trans form is known to be the thermodynamically most stable. It may be obtained from the cis, cis or cis, trans isomers by heating in aqueous solution, or by u.v. irradiation. Indeed, when verrucarín A was hydrolysed by refluxing with aqueous potassium hydroxide, all trans muconic acid was isolated. Whereas the three isomers of the acid show little or no difference in their u.v. or i.r. spectra, they may be differentiated by n.m.r. and their melting points. Thus the n.m.r. spectrum of the isolated muconic acid showed eleven



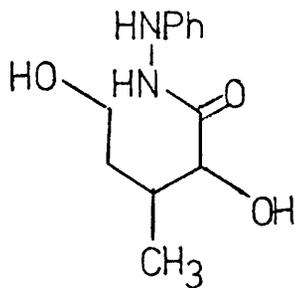
**47**



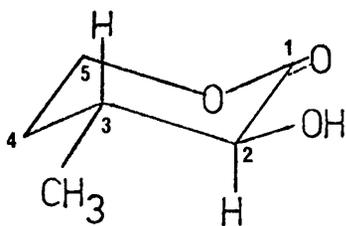
**48**



**49**

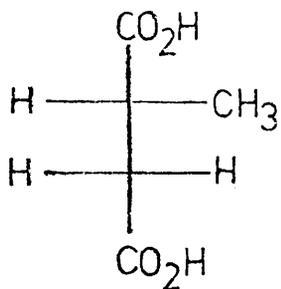


**50**

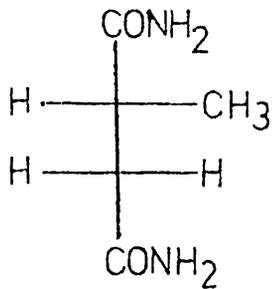


**51**

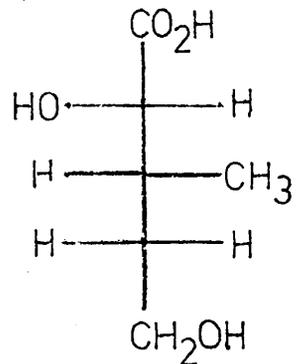
asymmetric signals in the olefinic region, distinguishing it quite clearly from the symmetric  $A_2X_2$  systems of the cis, cis and trans, trans forms. Since verrucaric acid shows an n.m.r. spectral pattern quite similar to that encountered in the cis, trans forms of muconic acid, one can postulate its presence in the antibiotic with a high degree of certainty. The i.r. spectrum of verrucarinolactone suggested a  $\delta$ -lactone and a hydroxylic moiety. The molecule was readily converted into the acetate (47) and on lithium aluminium hydride treatment furnished a triol (48), which consumed one mole of periodic acid, suggesting the presence of a 1,2 glycolic linkage. The lactone was convertible into a crystalline benzhydrylamide (49) and phenylhydrazide (50) both of which were inert to periodic acid, precluding the positioning of the hydroxyl in the  $C_4$  position and establishing it at  $C_2$ . The n.m.r. spectrum of (45) showed a secondary methyl at  $\tau$  8.74 (J, 6Hz.) fixing the methyl to  $C_3$ . An alternate positioning of the substituent, at  $C_4$  was excluded on the basis of the  $C_2$  methine proton which appeared as a doublet at  $\tau$  6.13 (J, 10Hz.) and the  $C_3$  methine proton which exhibited a triplet at  $\tau$  5.56 (J, 5.5Hz.). The high vicinal coupling of the  $C_2$ - $C_3$  protons (J, 10Hz.) pointed to a dihedral angle of  $180^\circ$ , suggesting a diaxial configuration of these hydrogens and the existence of the molecule in the thermodynamically more stable chair conformation (51). The relative configuration of the ring



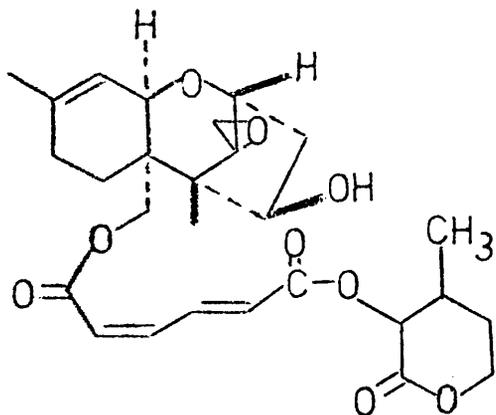
**52**



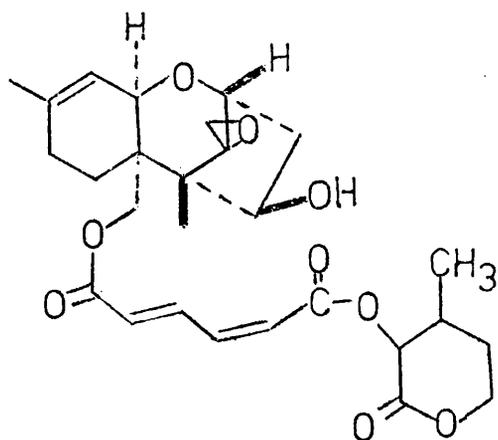
**53**



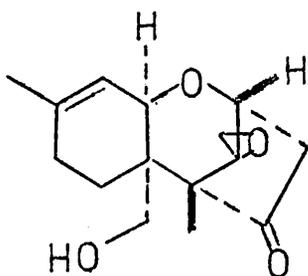
**54**



**55**



**56**



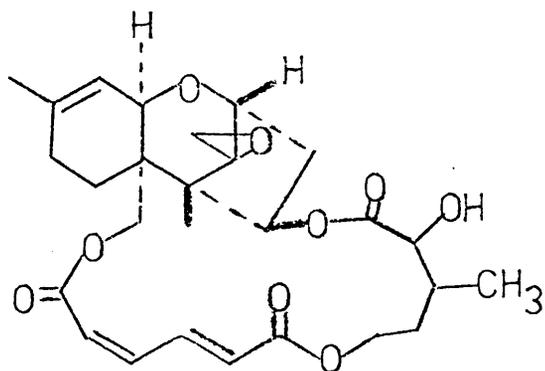
**57**

substituents was thus established.

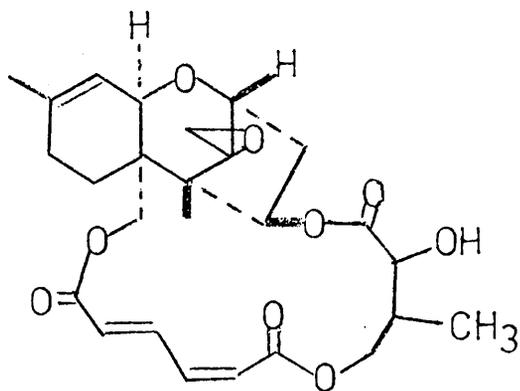
Oxidative degradation of verrucarinolactone with aqueous potassium permanganate gave (+) methyl succinic acid (52) characterised as the (+) diamide (53). Since dextrarotary methyl succinic acid has the (R) configuration, verrucaric acid must have the absolute configuration of 2(S), 3(R) 2,5-dihydroxy-3-methyl valeric acid (54).

The outstanding problem for a complete structural assignment of verrucarin A was the relationship of the three components of base hydrolysis with one another.

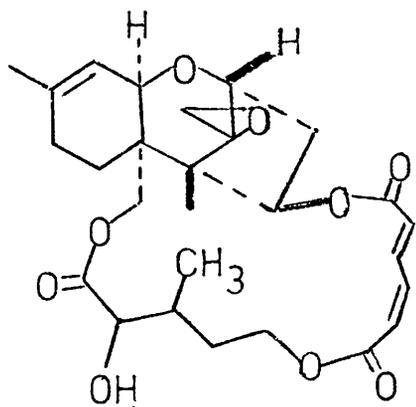
Three carboxyls and four hydroxyls had to be utilised in such a manner as to give rise to a neutral triester possessing a secondary hydroxyl. More fundamentally, however, it was necessary to establish the exact form in which the isolated verrucarinolactone was present in the antibiotic, for it might merely have been a secondary product obtained during work-up of the hydrolysis products of verrucarin A. On the assumption that verrucarinolactone (51) was, indeed, a discreet structural entity of verrucarin A, there were two possible structures (55) and (56) for the antibiotic in question. Both of these could be discounted, however, since Jones oxidation of verrucarin A, followed by hydrolysis, gave verrucarol and cis, trans muconic acid but no verrucarinolactone. The anticipated dehydroverrucarol (57) was not in evidence, thus precluding the possibility of either of the above men-



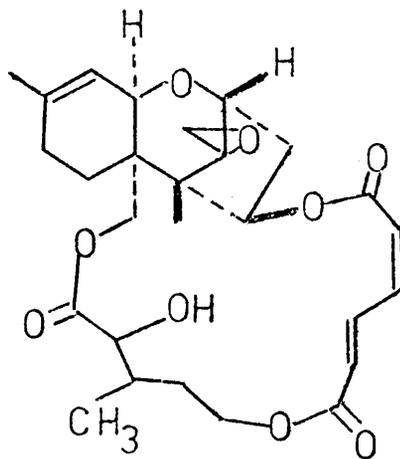
**58**



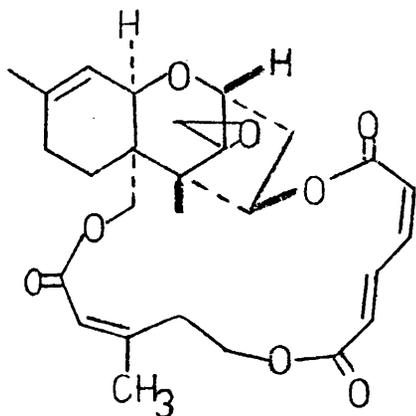
**59**



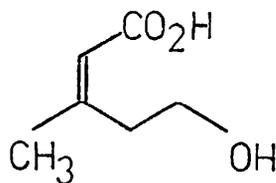
**60**



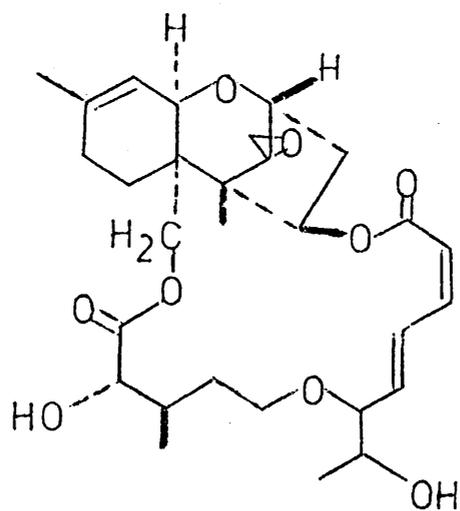
**61**



**62**



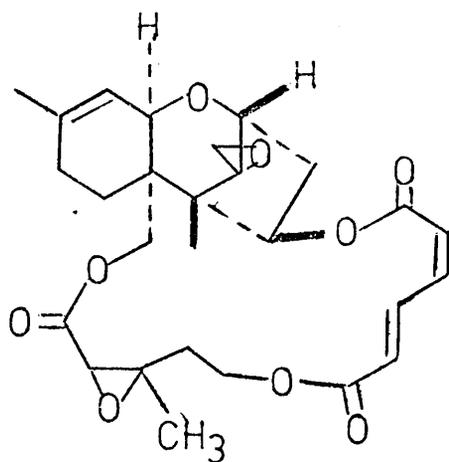
**63**



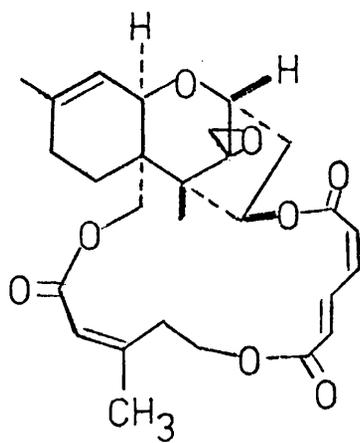
64

tioned structures (55) and (56), suggesting the presence of the secondary hydroxylic moiety in a macrocyclic side chain of the metabolite and thus pointing to verrucaric acid (46) as being a true building block of the molecule.

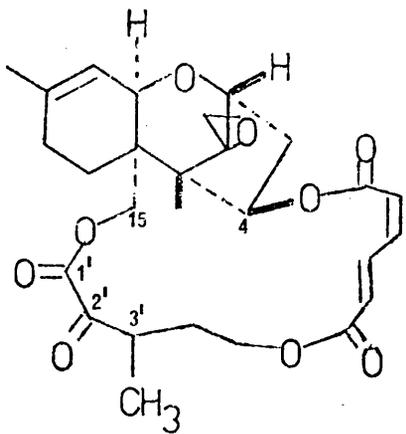
Statistically there remained four possible structures for verrucaric acid, (58), (59), (60) and (61), depending upon the orientation and site of esterification of the muconic acid with respect to verrucarol. Attempts to shed light on this problem, by means of a partial hydrolysis of verrucaric acid, were uniformly unsuccessful. It was, however, possible to achieve a partial cleavage of verrucaric acid (62), a companion metabolite of verrucaric acid, possessing, instead of verrucaric acid, anhydroverrucaric acid (63) as a structural component. The acid (63) was shown to be bonded to the primary hydroxyl of verrucarol. In view of the close structural and possibly biogenetic relationship between verrucaric acid and verrucaric acid, Tamm<sup>19,29</sup> thought it conceivable that an analogous structural assembly was present in the former, suggesting either (60) or (61) as the structure for verrucaric acid. Of these (61) was preferred by analogy with roridin A (64)<sup>30</sup>, for which the cis, trans grouping of the conjugated double bonds though not rigorously established, nonetheless appeared very likely. Confirmation of this proposed structure and the establishment of the absolute configuration of the molecule (41) was the outcome of X-ray analysis of the p-iodo-



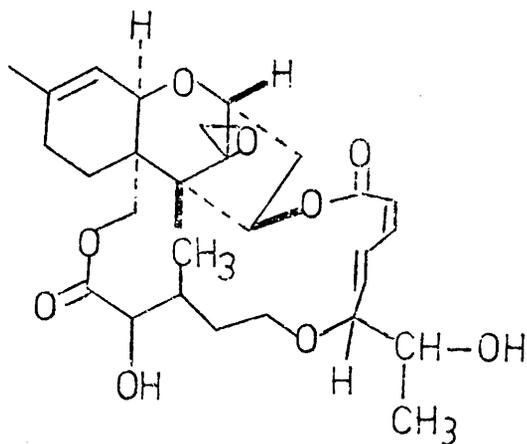
**65**



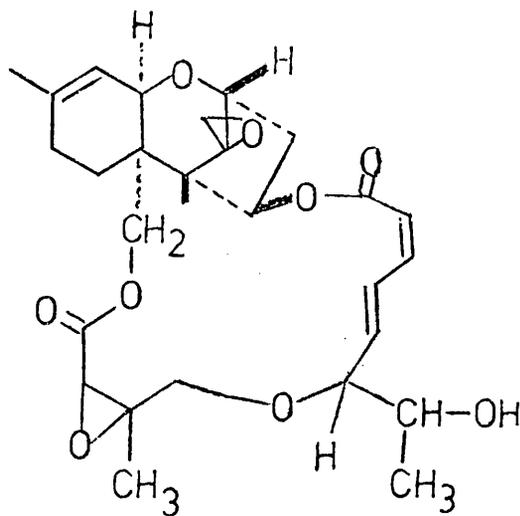
**66**



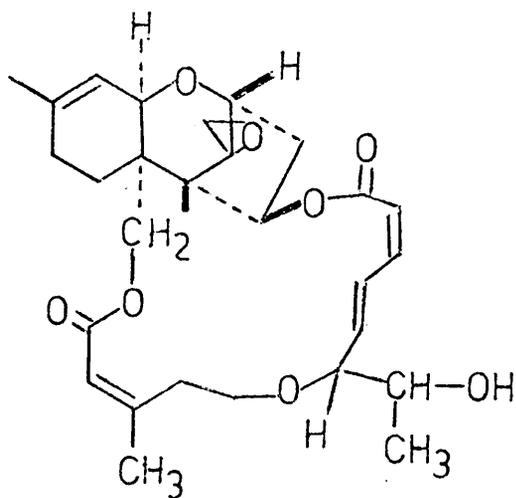
**67**



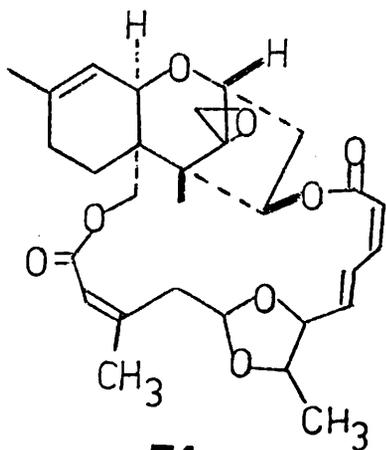
**68**



**69**



**70**



**71**

benzene sulphonate of verrucarins A<sup>15,31</sup>. Chemical substantiation of this structure has recently been published<sup>32</sup>.

To date the structures of several members of this series of closely related compounds have been elucidated. They may be divided into two broad categories - the verrucarins and the roridins - macrocyclic tri - and diester derivatives of verrucarol.

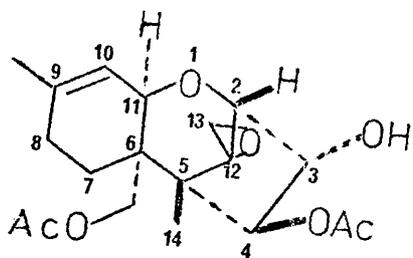
Structure (65) has been suggested for verrucarins B<sup>33</sup>. The relative configuration of the oxirane moiety embedded in the macrocyclic side chain has not been established as yet.

Verrucarins C and D<sup>66</sup> have only been isolated in trace quantities with no structural work having been reported.

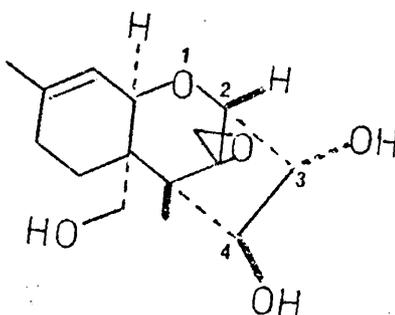
Verrucarins E has been shown to be 3 acetyl-4-hydroxymethyl pyrrole<sup>21</sup> and need be of no concern to us here.

Whereas no structural assignment has been made to verrucarins H<sup>19</sup>, verrucarins J has been fully elucidated and shown to have structure (66)<sup>29</sup>.

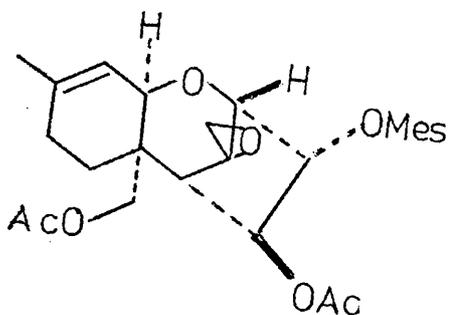
2'-Dehydroverrucarin has been assigned structure (67)<sup>34</sup>. Furthermore the structures of roridins A, C, D, E and H have been fully clarified, structures (68)<sup>30</sup>, (69)<sup>26</sup>, (69)<sup>35</sup>, (70)<sup>36</sup> and (71)<sup>37</sup> being assigned for them. There is some ambiguity about the relative configuration of the five-membered acetal in roridin H<sup>37</sup> and to date the stereochemical problem has not been solved.



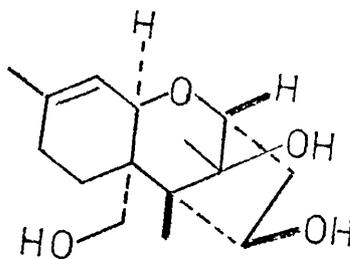
**72**



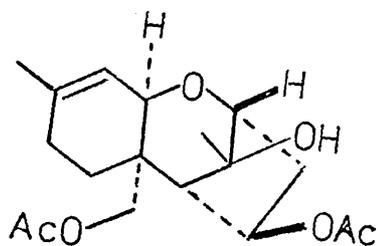
**73**



**74**

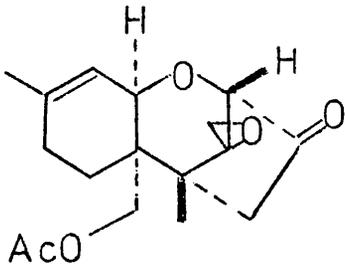


**75**

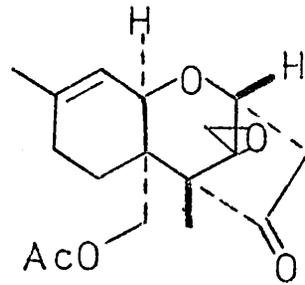


**76**

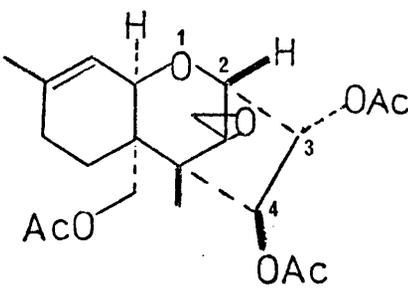
Diacetoxyscirpenol (72) is the major metabolic product isolated from several strains of Fusaria. It was initially detected by Brian, Grove and coworkers in Fusarium scirpivar, Fusarium equiseti and Gibberella intricans<sup>9</sup> and was later found to occur also in the culture filtrates of Fusarium sambucinum and Fusarium diversisporum by Sigg and coworkers<sup>8</sup>. The structural assignment of this compound was carried out independently by the above-mentioned groups of workers, who arrived at a common structure (72) for the natural product<sup>7,8,10,39</sup>. Chemical and spectroscopic evidence for scirpentriol (73), the hydrolysis product of diacetoxyscirpenol (72), pointed very strongly to the existence of a new trichothecane and suggested a close structural similarity with verrucarol (38). This suspected relationship was confirmed in the sense that when diacetoxy-mesyloxy-scirpene (74) was reduced with lithium aluminium hydride, a triol (75) was obtained which, on acetylation, gave rise to the diacetoxy alcohol (76). An identical product (76) was also the outcome of lithium aluminium hydride reduction and acetylation of verrucarol (38). Scirpentriol is thus a hydroxy-verrucarol whose complete structural analysis necessitated the establishment of the site and relative stereochemistry of the additional hydroxyl group. N.m.r. data suggested the presence of a 1,2 glycolic linkage and the correlation of verrucarol (38) with scirpentriol (73) allowed the positioning of one of these hydroxyls at C<sub>4</sub>,



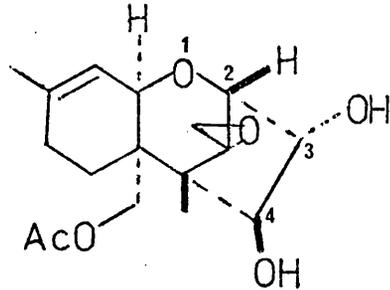
**77**



**78**



**79**

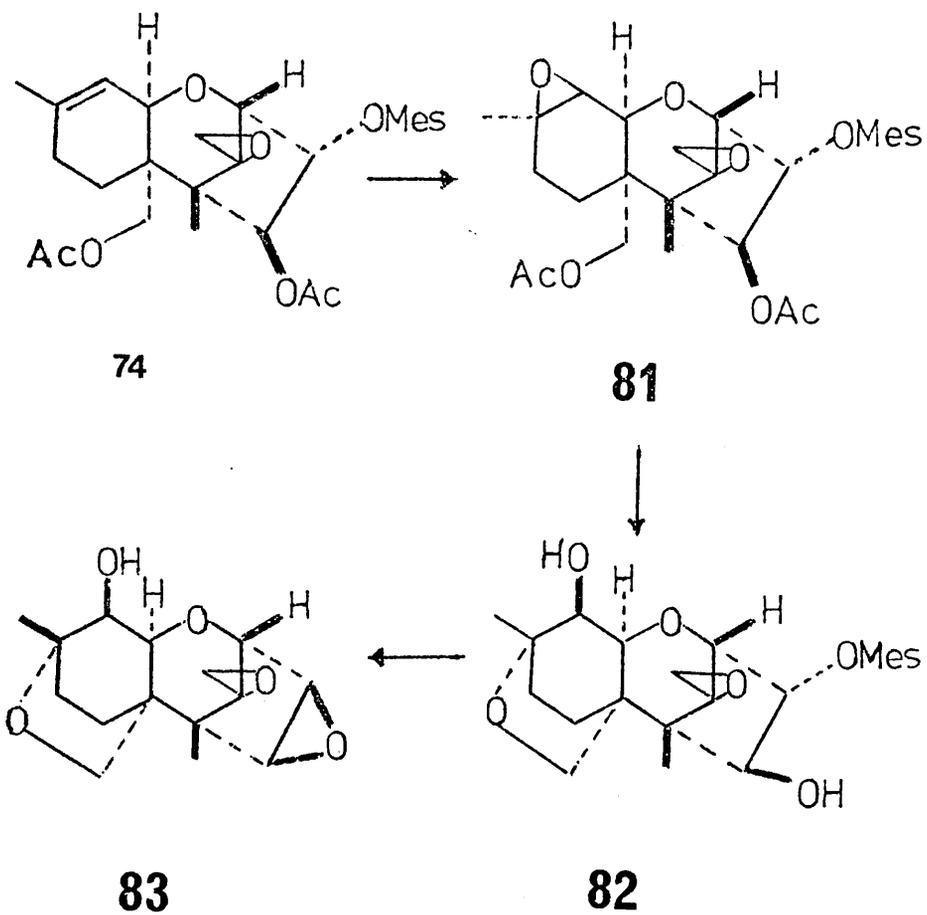


**80**

which, in turn, quite unambiguously, placed the other hydroxylic moiety at C<sub>3</sub>.

In accord with this assignment, chromic oxide in acetic acid oxidation of (72), followed by zinc and hydrogen reduction, gave a small quantity of an acetoxy-ketone (77), isomeric with the material (78) furnished by C<sub>15</sub> monoacetylation and oxidation of verrucarol. With the relative configuration of six of the seven asymmetric centres in scirpentriol (73) established, there only remained the problem of the relative configuration of the C<sub>3</sub> hydroxyl. The C<sub>3</sub> and C<sub>4</sub> vicinal protons of triacetoxyscirpene (79) showed a coupling constant of 3.5 Hz., the corresponding coupling constant between the C<sub>2</sub> and C<sub>3</sub> methine protons being 5 Hz. From the Karplus equation this suggested dihedral angles of 115° and 40° respectively. An inspection of models indicated that a cis grouping of the protons at C<sub>2</sub> and C<sub>3</sub> and a corresponding trans arrangement of the hydrogens at C<sub>3</sub> and C<sub>4</sub> would, indeed, be in accord with the magnitude of the dihedral angles cited. This inference of a trans 1,2-diol was also compatible with the fact that scirpentriol (73) and 15-acetoxy-scirpen-3 $\alpha$ ,4 $\beta$ -diol (80) were inert to periodic acid and lead tetraacetate in acetic acid. Since it was known that the secondary alcohol at C<sub>4</sub> was  $\beta$ , it followed that the substituent at C<sub>3</sub> had to be in the  $\alpha$  configuration.

The evidence for the above stereochemical assignments

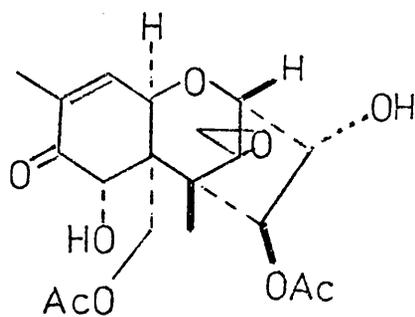


Scheme 2

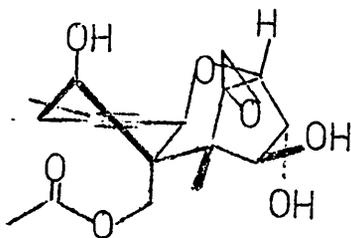
rested heavily on spectral data and, consequently, Sigg and coworkers were motivated to confirm the stereochemistry established for scirpentriol, and in particular the spatial arrangement of the glycolic moiety, in a more rigorous manner<sup>10</sup>. This was achieved in the manner indicated in Scheme 2. Potassium tert. butoxide treatment of the hydroxy-mesylate (82) brought about a smooth elimination of methane sulphonic acid to give the dioxirane (83). This relative ease of formation of the new epoxide argued well for the existence of the glycol in question in the trans configuration. Since (38) represented the absolute configuration of verrucarol, structures (73) and (72) correspond to the absolute configurations of scirpentriol and diacetoxyscirpenol respectively.

It is noteworthy to observe the mushrooming effect which the structural clarification of trichodermin (26a) has had upon the entire field of trichothecane chemistry. Trichodermin (26a) has served as a stepping-stone to all subsequent attempts to unravel the intricacies of newly isolated trichothecanes all of which, directly or indirectly, have been chemically correlated with this simplest member of the trichothecane family.

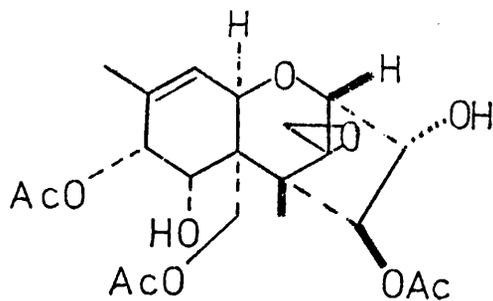
This was strikingly in evidence in the structural assignments to two further metabolites isolated from Fusarium scirpi<sup>9</sup>. Formula (84) was initially attributed to a C<sub>19</sub>H<sub>29</sub>O<sub>9</sub> diacetate mainly on the strength of n.m.r. data<sup>7,39</sup>; it was



**84**



**85**

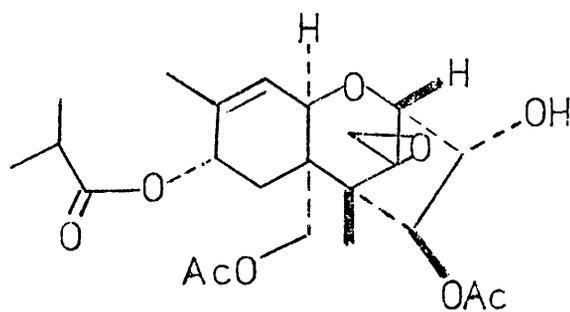


**86**

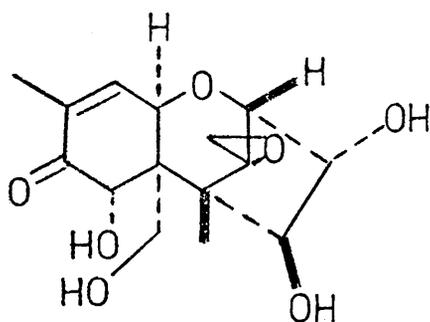
substantiated, however, by its chemical correlation with diacetoxyscirpenol (72) of known absolute configuration<sup>40,41</sup>. The stereochemical assignment of the C<sub>7</sub> hydroxyl has been cited to be in accord with chemical evidence. Thus when the diacetate (84) was treated with dilute, aqueous ammonium hydroxide, selective hydrolysis of the C<sub>15</sub> acetate residue occurred, the enhanced rate of hydrolysis of the primary acetate being attributed to the participation of the neighbouring 7 $\alpha$ -hydroxy substituent. The favourable proximity of the C<sub>7</sub> and C<sub>15</sub> functional groups is clearly seen from molecular models which also show that an intramolecularly assisted hydrolysis of the C<sub>15</sub> acetate would be sterically impossible with the C<sub>7</sub> hydroxyl in the  $\beta$  configuration (85).

A third phytotoxin, a triacetate C<sub>21</sub>H<sub>28</sub>O<sub>10</sub> (86)<sup>42</sup>, constitutes an additional member of this group of compounds with high mammalian toxicity. Its structure was based upon chemical correlation with the enone (84) and was in full accord with spectral data.

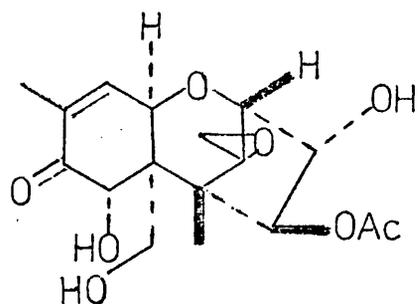
The occurrence of corn toxicosis and fescue foot disease in cattle, in Japan<sup>43</sup> and the United States<sup>44</sup>, led to an investigation into the organisms responsible for the intoxication of the animals. The most toxic fungi isolated from polluted corn were Fusarium trincinctum and Fusarium nivale. The toxic principles obtained from the former strain are diacetoxyscirpenol (72) and its 8 $\alpha$ -(3, methyl butyryloxy)-deri-



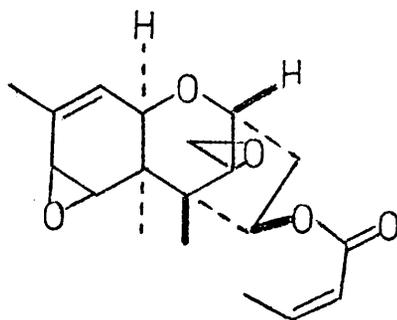
**87**



**88**



**89**



**90**

vative (87)<sup>44,45</sup>. Fusarium nivale furnished two metabolites, nivalenol (88)<sup>46</sup> and fusarenone (89)<sup>43</sup>. The structure of the latter was arrived at independently by Tatsuno<sup>47</sup> and Grove<sup>40</sup>. The latter has suggested that the lengthy procedure and the relatively severe conditions used for the isolation of nivalenol (88) and its monoacetate (89), in conjunction with the lability of the ester groups in the previously isolated enone (84), pointed to the possibility of both (88) and (89) being artifacts of the work-up procedure<sup>40</sup>. A recent communication by Tatsuno<sup>48</sup>, however, has suggested that the conditions of isolation of fusarenone and nivalenol were unlikely to bring about hydrolysis of the diacetate (84) and that they are true metabolites of the microorganisms.

The last member of the trichothecane family to be mentioned is crotocin (90) isolated from Cephalesporium crotocinigenum<sup>13</sup>.

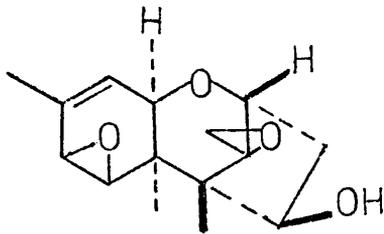
The isolation and characterisation of these metabolites illustrates the remarkable facility of some Fusaria species to oxidise the trichothecane nucleus. It is hard to imagine that the hitherto isolated compounds have exhausted Nature's ingenuity for functionalising the trichothecane skeleton and the future will, no doubt, expose many more of these intriguing products.

Chemical reactivity of the trichothecanes

The close structural similarity between the different members of the trichothecane family is manifestly reflected in the parallels of their chemical reactivity. For molecules as complex in their carboxylic ring system and as variegated in their functionality as the trichothecane group of sesquiterpenoids, they display a disappointing degree of diversity in their chemical behaviour.

One should, however, qualify the above statement by adding that most of the reactions recorded in this introduction have been culled from a hitherto young and consequently narrow field of chemistry, where most of the investigators were only concerned with elucidating the structures of this novel group of sesquiterpenoids. As a result of this the chemistry has been confined to those standard reactions which the organic chemist has found to be of maximum use to him in his century-long battle with biologically active and intellectually challenging organic molecules. One is referring, of course, to acid-base type reaction conditions and the effects of oxidising and reducing agent upon the trichothecanes. It is the interaction of the trichothecanes with these reaction media which will now be illustrated and discussed.

The chemistry of the trichothecanes is essentially the chemistry of the spiro epoxide grouping. It is this strained



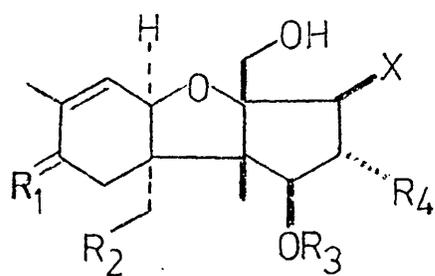
**91**

three membered oxide ring which serves as the fulcrum for most of the activity encountered in the trichothecane ring skeleton. More often than not its rupture appears to be the driving force for most chemical rearrangements to occur within the molecules and yet, at the same time, it provides a controlling influence upon the course of those chemical changes, for it is a remarkable coincidence that the vast majority of the profound rearrangements encountered, under fundamentally different experimental conditions, should all lead to one and the same APOTRICHOTHECANE ring skeleton.

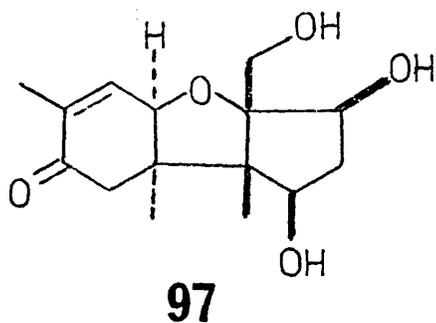
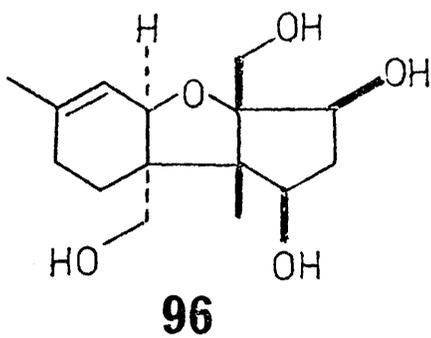
#### Reaction with acids

The oxirane moiety, in a number of circumstances, is susceptible to undergo intramolecular nucleophilic attack with accompanying skeletal rearrangement. Inspection of a model of a trichothecane reveals that the epoxide is sterically inaccessible to rearside nucleophilic attack by external anions. This shielding is reflected in the fact that trichodermin (26a)<sup>27</sup> and verrucarol (38)<sup>23</sup> for instance, are unaffected by hot aqueous base. Protonation of the epoxide ring in acidic medium, however, normally results in the formation of the apotrithothecane ring system (12). The notable exception to this is crotocol (91)<sup>13</sup> which will be discussed separately.

It should be pointed out that this facile formation of the apotrithothecane skeleton was not recognised during early structural elucidations of the trichothecanes and as such an



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
<b>92</b>	O	H	H	H
<b>93</b>	2H	OH	H	H
<b>94</b>	2H	H	H	H
<b>95</b>	2H	OAc	H	OAc



oxetane moiety, annelated with a cyclopentane ring, was proposed as a partial feature of the trichothecanes.

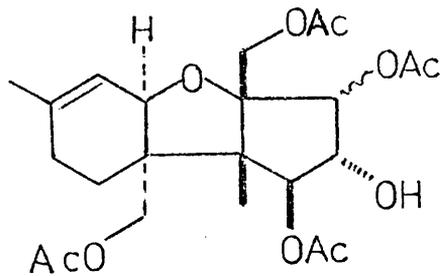
Hydrochloric or hydrobromic acids bring about the above mentioned skeletal reorganisation in the trichothecanes, resulting in the formation of chloro - or bromohydrins. Thus trichothecolone (27), verrucarol (38), trichodermin (26a) and diacetoxyscirpenol (72) all rearrange to furnish the halohydrins (92)<sup>17</sup>, (93)<sup>23</sup>, (94)<sup>24</sup> and (95)<sup>10</sup> respectively.

Treatment of the trichothecanes with dilute sulphuric acid normally results in the formation of glycols, as exemplified by the reaction of verrucarol (38) which affords (96)<sup>23</sup>.

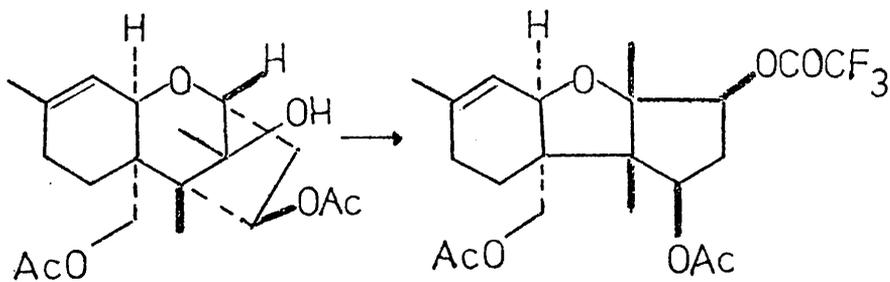
An analogous transformation is achieved by subjecting trichothecin (28) to hot 1N hydrochloric acid and subsequent hydrolysis of the product to give the triol (97)<sup>17</sup>.

These acid-catalysed rearrangements occur by initial protonation of the epoxide ring with accompanying 1,2 migration of the O<sub>1</sub>-C<sub>2</sub> bond resulting in a net inversion of configuration at C<sub>12</sub> and synchronous capture of the C<sub>2</sub> cation by an external nucleophile<sup>27</sup>. The steric requirements of this skeletal change are fully satisfied in as much as the O<sub>1</sub>-C<sub>2</sub> and C<sub>12</sub>-O bonds are antiperiplanar to each other. This postulated mechanism dictates the steric course of the rearrangement and allows a full stereochemical assignment to the final product.

It should be pointed out that whereas most trichothecanes

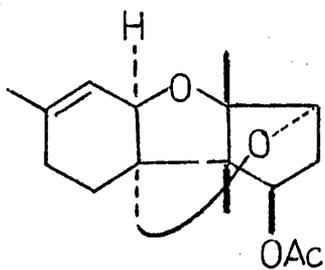


**98**

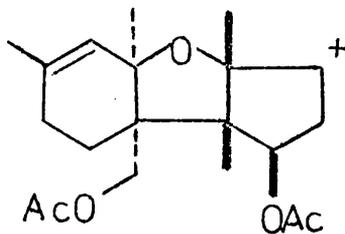


**76**

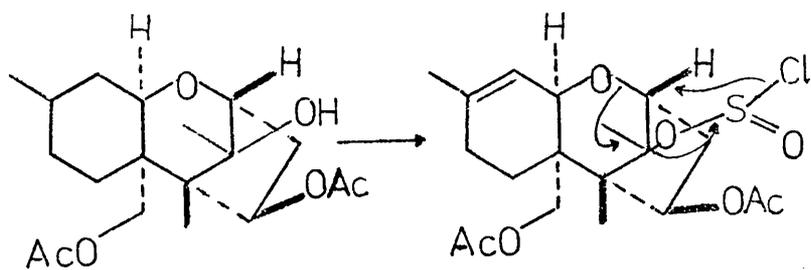
**99**



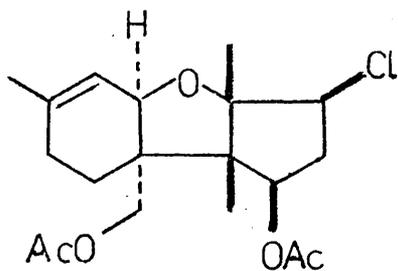
**100**



**101**



**76**



**102**

**Scheme 3**

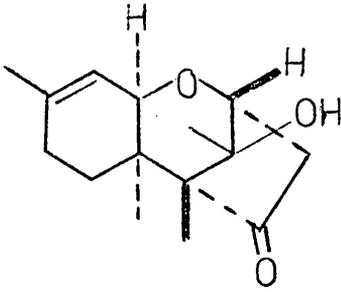
are acid-labile, diacetoxyscirpenol (72) remains unaffected by cold, dilute hydrochloric acid over a period of fourteen days and shows no tendency to rearrange on refluxing with acid resin for one hour. With zinc in acetic acid (72) is converted into the tetraacetoxy-alcohol (98)<sup>38</sup>.

Rearrangements to the apotrichothecane ring system are not confined to the parent trichothecanes. Their simple transformation products, wishing to rid themselves of the strain inherent in their carboxylic skeleton, are readily transformed into apotrichothecane derivatives.

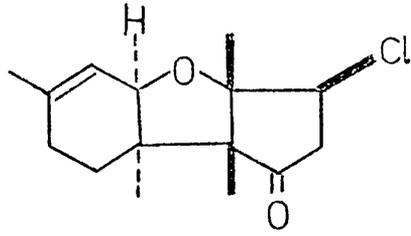
Thus diacetoxy-dihydroverrucarol (76) with trifluoroacetic acid is converted into (99). An interesting by-product of this rearrangement is the tetracyclic apotrichothecane derivative (100). This reaction has been postulated to proceed via the secondary carbonium ion (101) which is trapped either by external or internal nucleophile<sup>23</sup>.

Treatment of verrucarol (38) with thionyl chloride in pyridine gave a sulphite to which no structure has been assigned, but which, according to molecular weight measurements, is dimeric<sup>23</sup>. Diacetoxy-dihydroverrucarol (76), on the other hand, reacted in an entirely different manner. None of the anticipated dehydration product was encountered, instead the formation of the diacetoxy-chloride (102) was observed.

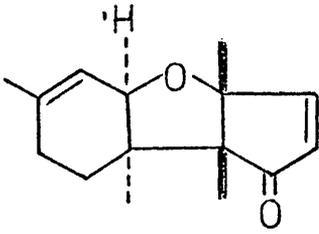
The mechanism indicated in Scheme 3 has been postulated to



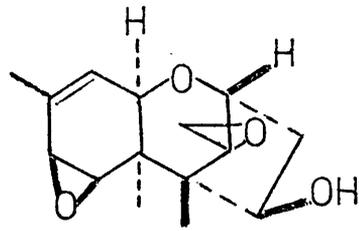
**103**



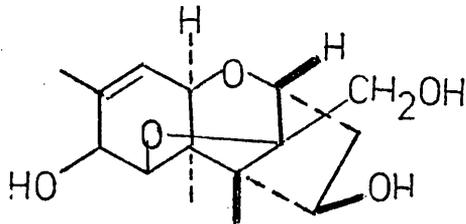
**104**



**105**



**106**



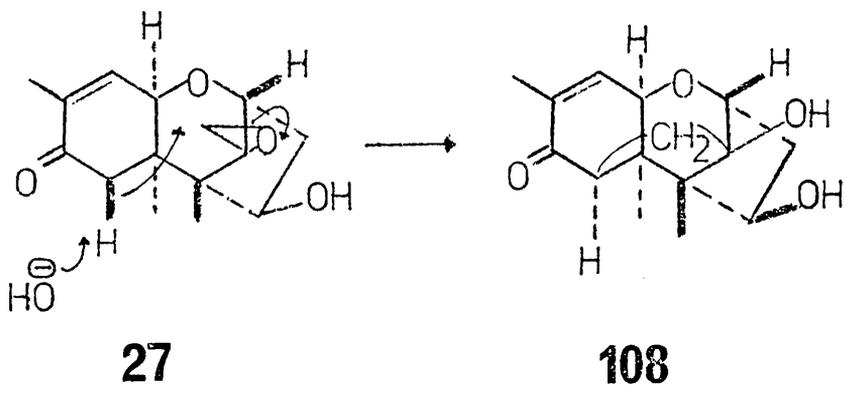
**107**

account for its formation<sup>23</sup>. Derivatives of trichodermin (26a) show a parallel behaviour with thionyl chloride in pyridine. When the ketone (103), obtained by chromium trioxide oxidation of dihydrotrichodermin (29), was treated with thionyl chloride in pyridine a chloro-ketone (104) was obtained, which readily eliminated hydrochloric acid to yield the  $\alpha, \beta$ -unsaturated ketone (105). The rearrangement has been rationalised by assuming an internal nucleophilic attack on an intermediate chlorosulphite ester by the tetrahydropyran oxygen<sup>27</sup>.

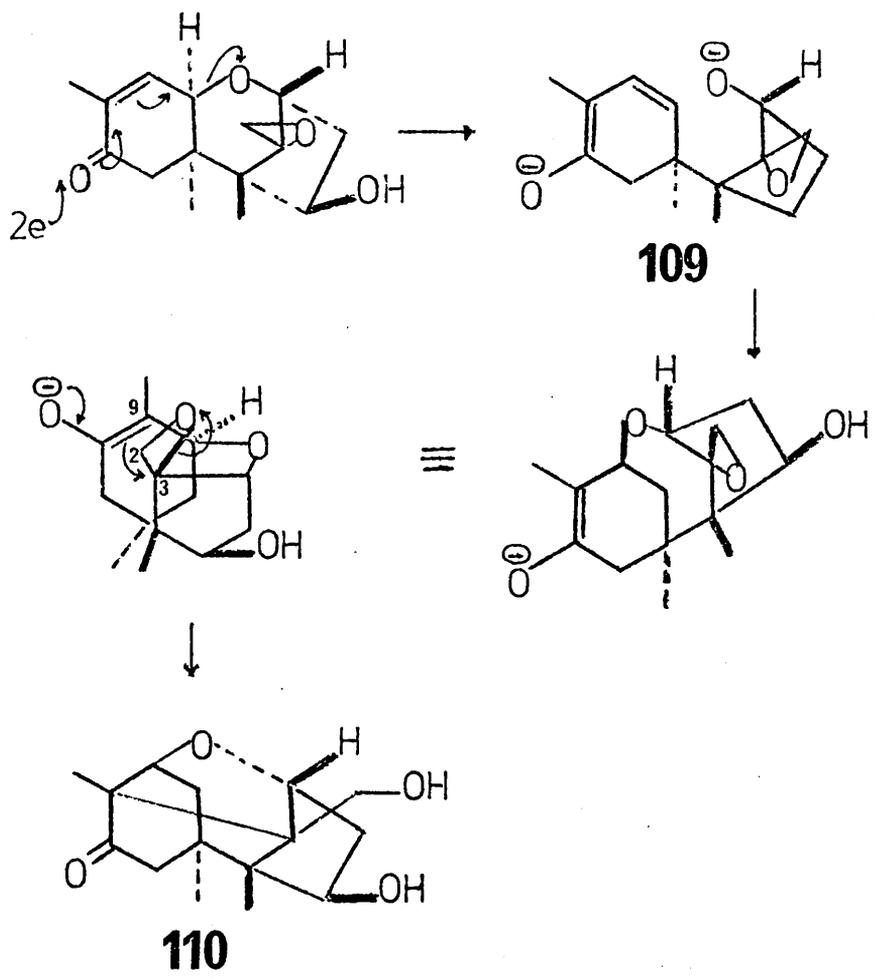
Crotocol (106) appears to be the most acid-labile member of the trichothecanes. 0.02N Sulphuric acid or 0.5N acetic acid, at room temperature, readily give rise to isocrotocol A (107)<sup>13</sup>. Whereas the protonated terminal epoxide is attacked by the tetrahydropyran oxygen in the other trichothecanes, in the case of crotocol (106) and crotocin (90), the oxirane ring mentioned above is more readily attacked by the heteroatom of the C<sub>7,8</sub> epoxide. This deviation from the normal trend is almost certainly due to a sterically favourable disposition of the diepoxide array.

#### Reaction with bases

The pronounced lability of the trichothecanes in acidic medium is severely curtailed by working under basic conditions. Only trichothecolone has been reported to undergo rearrangements in base. Isotrichothecolone (108) is formed by treating



Scheme 4

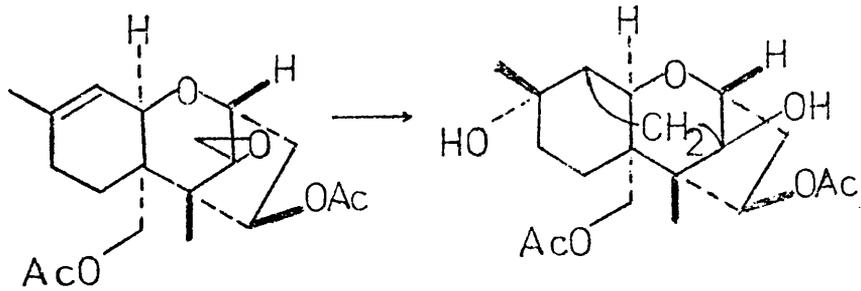


Scheme 5

trichothecolone (27) with hot, aqueous sodium hydroxide<sup>17,18</sup>, whereas treatment of (27) with zinc in base brings about its reduction to allodihydrotrichothecolone (110). Whereas the majority of reactions of trichothecolone, described by Freeman<sup>17</sup> and Jones<sup>18</sup>, can be interpreted readily in terms of both the old (13) and the revised formulae for this sesquiterpenoid alcohol, neither of the above mentioned authors was able to assign unequivocal structures to the two reaction products (108) and (110) on the basis of the evidence available to them. This unsatisfactory state of affairs prompted Tamm and coworkers to re-investigate these compounds<sup>49</sup>, allowing them, on the basis of n.m.r. data, to postulate structure (108) for isotrichothecolone.

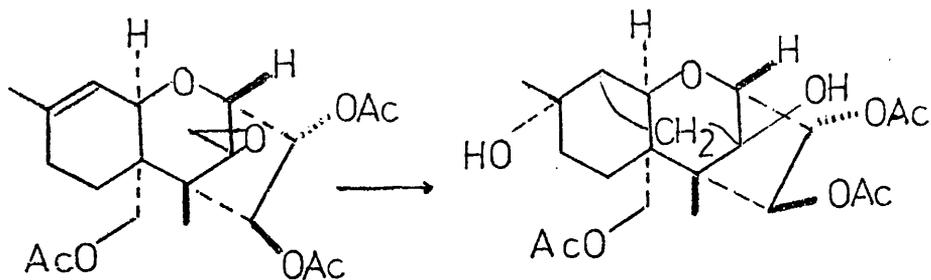
Since neither verrucarol (38) nor diacetoxyscirpenol (72) showed the same type of transformation, the keto group at C<sub>8</sub> was assumed to be responsible for the observed reaction via the mechanism depicted in Scheme 4. Isotrichothecolone formation was thus interpreted as an attack of base at the activated 7 $\beta$  hydrogen atom, followed by attack of the carbanion at C<sub>13</sub><sup>49</sup>.

Structure (110) has been assigned to allodihydrotrichothecolone<sup>49</sup>. The first step in its formation is assumed to be the well authenticated reductive cleavage of the  $\alpha, \beta$  unsaturated  $\gamma$ -alkoxy system<sup>50</sup> to give the intermediate (109), whose subsequent transformations are as shown in the appended



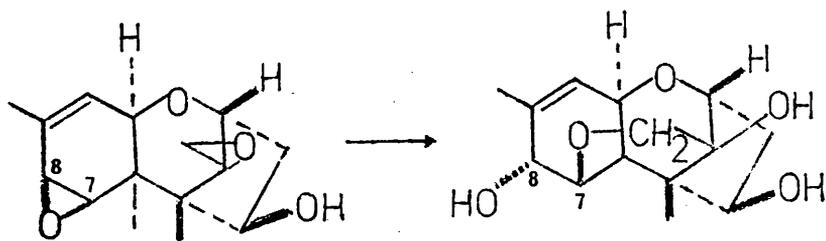
**111**

**112**



**79**

**113**



**106**

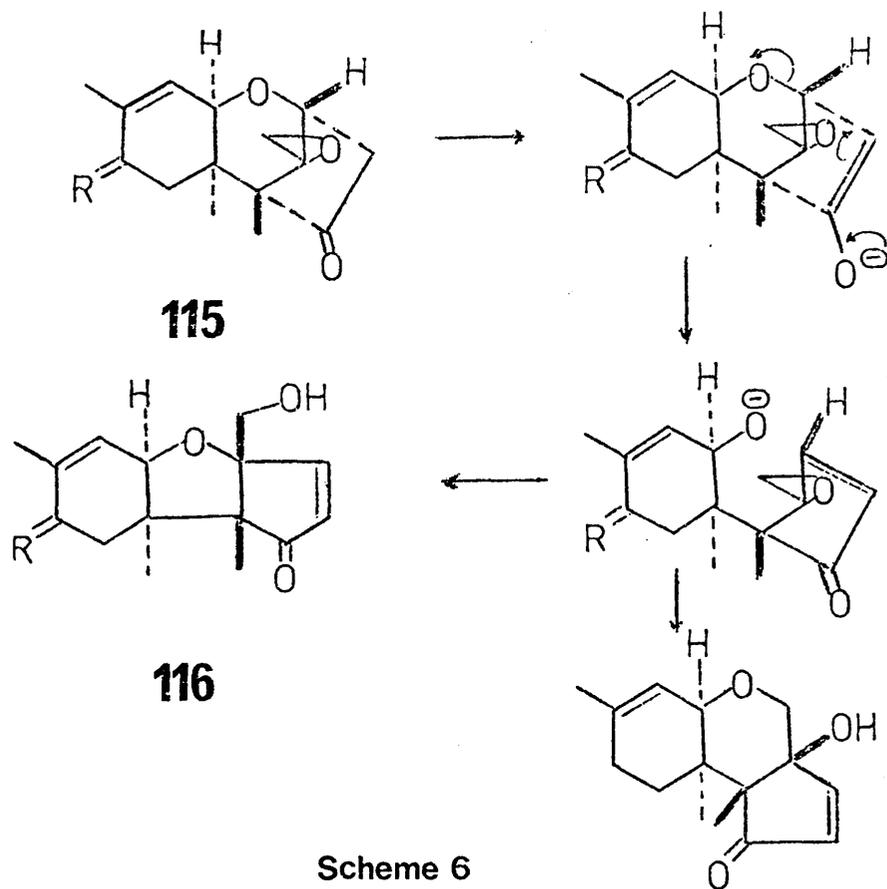
**114**

Scheme 5. This mechanistic interpretation explains product formation, but does not offer any reason as to why the nucleophilic attack of the C<sub>9</sub> carbanion on the oxirane moiety should occur in an abnormal manner. Indeed, an inspection of models would imply that nucleophilic substitution could occur with equal facility at C<sub>2</sub> and C<sub>3</sub>, the secondary carbon atom, if anything, being the sterically favoured site.

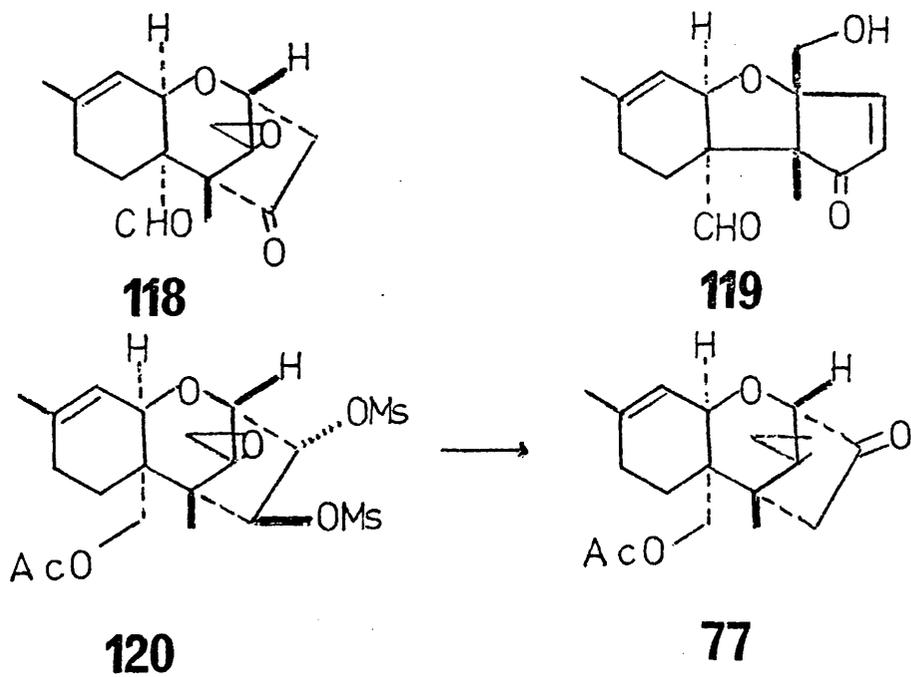
The susceptibility of the terminal epoxide to intramolecular nucleophilic attacks is perhaps best reflected in the fact that diacetoxyverrucarol (111), in boiling water, readily forms the hydrate (112) with participation of the ring A  $\pi$  electrons<sup>23</sup>. Analogously, triacetoxyscirpenol (79) rearranges to the triacetoxydiol (113)<sup>10</sup>.

Quite similar to these reactions is the interaction of crotocol (106) with base. Aqueous 5% sodium hydroxide brings about a smooth rearrangement to the di-tetrahydropyran (114)<sup>13</sup>. Although the authors do not assign any definite stereochemistry to the hydroxyl at C<sub>8</sub>, it is reasonable to attach the  $\alpha$  configuration to it if one assumes a synchronous reaction mechanism initiated by C<sub>7,8</sub> epoxide ring opening with hydroxide anion.

Rearrangement to the apotrichothecane skeleton, a dominant feature of the chemistry of the trichothecanes in acidic medium, is also encountered when some transformation products of this group of sesquiterpenoids are treated with base.



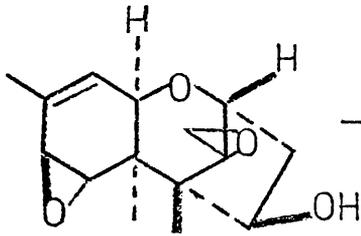
Scheme 6



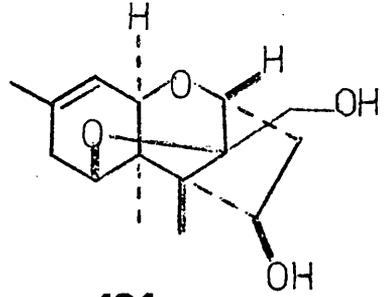
Thus trichodermane (115, R=2H), the oxidation product of trichodermol, isomerises readily, on treatment with aqueous sodium carbonate, to an  $\alpha, \beta$  unsaturated ketone<sup>27</sup>. This behaviour is quite analogous to the formation of neotrichothecodione from trichothecodione (116, R=0) under similar conditions. On the basis of extensive experimentation neotrichothecodione has been assigned structure (116, R=0)<sup>17,18</sup> and neotrichodermane should accordingly be represented by (116, R=2H), see Scheme 6. A plausible mechanism for the conversion of trichodermane (115, R=2H) into neotrichodermane (116, R=2H) has been suggested to involve initial opening of the tetrahydropyrane ring, facilitated through enolisation of the ketone, followed by internal epoxide ring opening. The direction of the epoxide opening in this reaction is abnormal and since no satisfactory steric explanation of this phenomenon is offered by an inspection of models, the reason must be that formation of the tetrahydrofuran in (116, R=2H) proceeds with a much greater velocity than the formation of the tetrahydropyrane moiety in the alternate product (117)<sup>27</sup>.

The keto-aldehyde (118), an oxidation product of verrucarol (38), similarly is converted to the apotrichothecane (119)<sup>23</sup>.

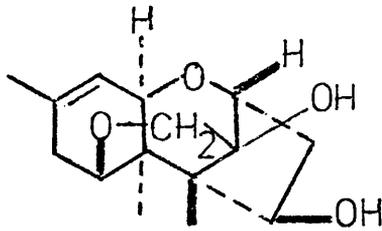
An intriguing reaction is given by 15-acetoxyscirpen-3 $\alpha$ , 4 $\beta$ -mesylate (120). Quite unexpectedly, treatment with sodium methoxide furnished the acetoxy-ketone (77). In order to



**106**



**121**



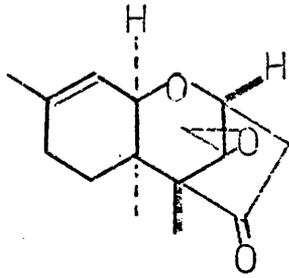
**122**

account for the reaction product, the authors<sup>10</sup> have suggested elimination of methane sulphonic acid and subsequent hydrolysis of the enol-mesylate under work-up conditions. The case with which methane sulphonic acid is eliminated would appear to throw doubt on the 3,4 trans hydroxyl configuration in scirpentriol (73), since one normally requires a trans arrangement of the departing substituents for an elimination to occur as smoothly as it does in this case. However, it has been shown by Cristol<sup>51</sup> and Hine<sup>52</sup> that in certain rigid carbocyclic systems cis elimination can and does occur more readily than trans elimination, thus rationalising the apparent anomaly.

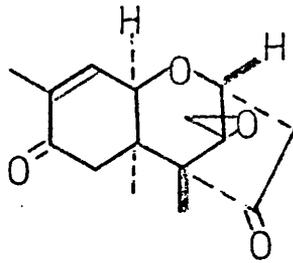
#### Reaction with reducing agents

The trichothecanes readily hydrogenate under standard conditions, taking up one mole of hydrogen with saturation of the  $\Delta^{9,10}$  double bond. A degree of variation is introduced by crococol (106), the sole exception to the above generalisation, which in the presence of palladium/carbon absorbs one mole of hydrogen to give rise to a mixture of dihydroisocrococol A (121) and dihydroisocrococol B (122)<sup>13</sup>. The olefinic bond is only saturated after a period of 1-2 hours.

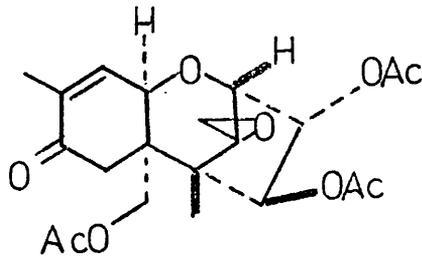
The more forcing conditions of lithium aluminium hydride uniformly yield dihydrotrichothecanes as a result of reductive epoxide cleavage. Crococol affords (122)<sup>13</sup>.



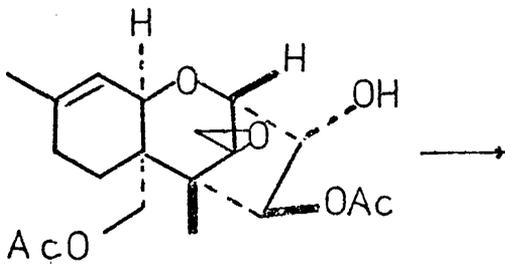
**123**



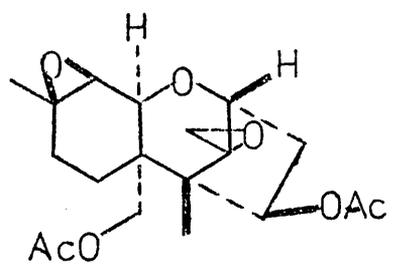
**124**



**125**



**72**



**126**

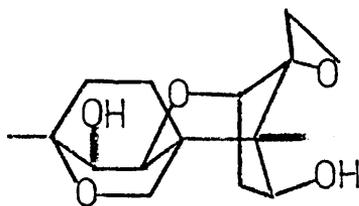
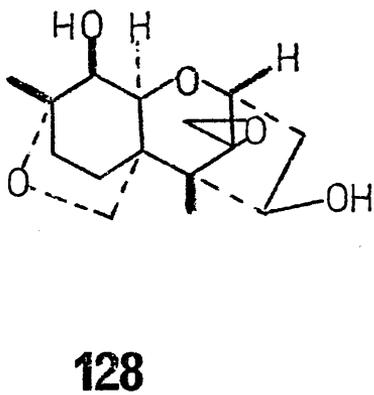
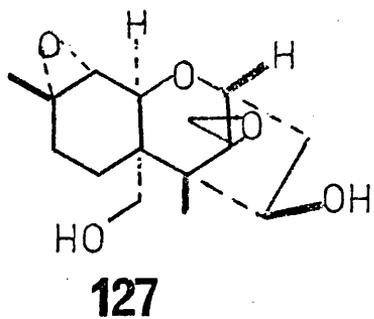
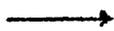
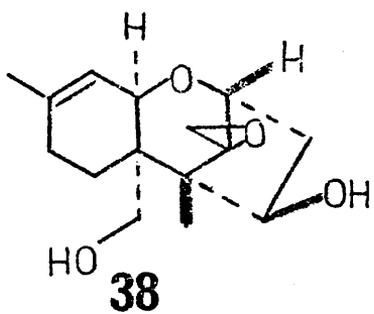
### Reaction with oxidising agents

An oxo grouping may be introduced into the C<sub>8</sub> secondary allylic position of the trichothecanes, in some instances, but only with difficulty. Thus trichodermane (123), in the medium chromic oxide/acetic acid, furnishes trichothecodione (124) in only 5% yield<sup>27</sup>. An analogous transformation is achieved with selenium dioxide in dioxan. Similarly triacetoxyscirpenol, with tert.butyl chromate, gives rise to the  $\alpha, \beta$ unsaturated ketone (125)<sup>10</sup>.

The directing influence of a suitably disposed hydroxyl, in epoxidation reactions with peracid, is strikingly illustrated by the oxygenations of verrucarol and its derivatives<sup>32</sup>. Diacetoxysterigmatocystin (72), on treatment with perbenzoic acid gives rise to  $\beta$  epoxy-diacetoxysterigmatocystin (126). The  $\alpha$  isomer is generated in only small quantities. The almost exclusive top-side attack of the double bond has been rationalised on steric grounds, the C<sub>15</sub> acetoxy substituent presumably preventing an easy access to the peracid on the  $\alpha$  side.

Verrucarol (38), when subjected to such oxidising conditions, was converted to an approximate 1:1 mixture of  $\alpha$  epoxyverrucarol (127) and the diol (128).

The rate enhancing effect of hydroxyls upon epoxidations of double bonds is a well authenticated phenomenon<sup>53</sup>. The interaction of peracid and primary hydroxyl function in verrucarol (38) presumably gives rise to a complex, the overall



rate of attack upon the double bond then becoming comparable to the speed of epoxidation of the unsaturated linkage, by peracid, from the less crowded face of the molecule. The diol (128) is the result of intramolecular nucleophilic ring opening of  $\beta$ -epoxyverrucarol (126) by the C<sub>15</sub> hydroxyl.

## Biological activity

The trichothecanes show a marked selectivity and specificity of biological activity. Selective toxicity is an outstanding property of this group of sesquiterpenoids.

All the naturally-occurring esters inhibit, in fairly small concentrations, growth of various cells in tissue culture, whilst displaying weak antibacterial activity.

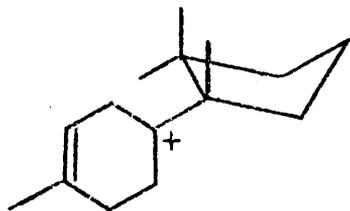
Nearly all trichothecanes show antifungal activity, the exception being diacetoxyscirpenol (72) which, together with trichothecin (28), is manifestly phytotoxic.

High mammalian toxicity, coupled with powerful local irritant action has been reported for trichothecin (28) and verrucarin A (61) in mice and for the former also in rats<sup>54</sup>.

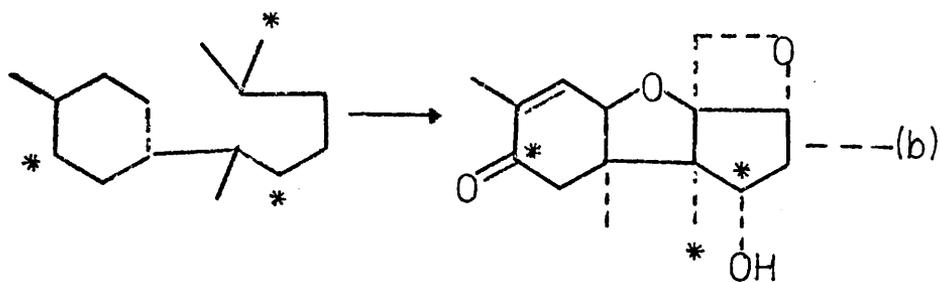
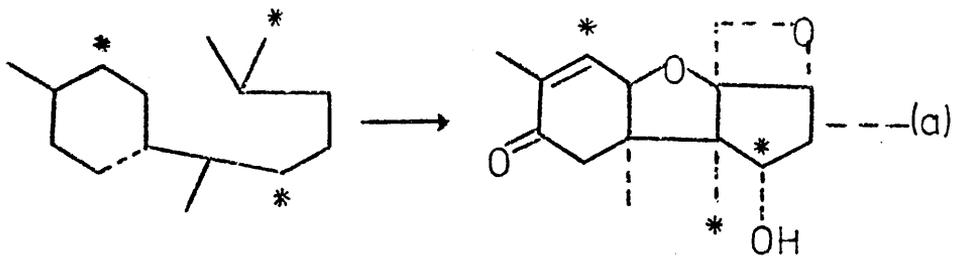
Verrucarin A is somewhat exceptional in this class of sesquiterpenoids, showing insecticidal properties<sup>55</sup>.

High antifungal activity against Trichophyton asteroides is exhibited by diacetoxyscirpenol (72)<sup>56</sup>. Specificity of antifungal activity is also shown by trichothecin (28) which shows strong antagonism to Penicillium digitatum<sup>57</sup> and to a lesser degree to Fungi imperfecti, Zygomycetes and Ascomycetes<sup>12</sup>.

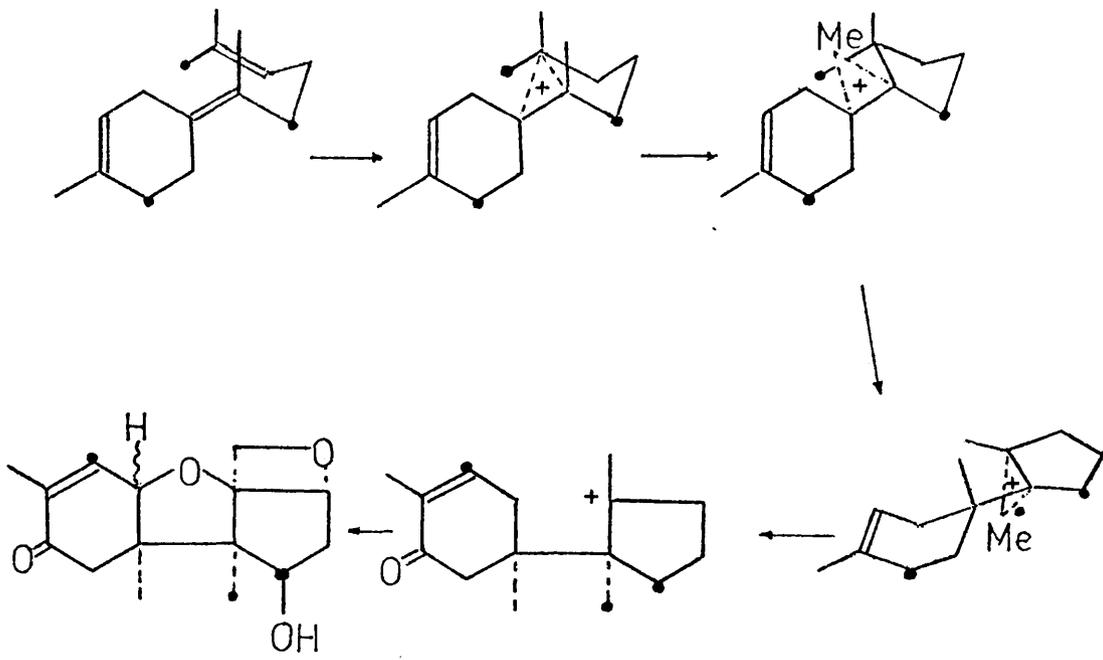
Diacetoxyscirpenol (72)<sup>11</sup>, nivalenol (88)<sup>46</sup> and fusarenone (89)<sup>43</sup> have been implicated in mouldy corn toxicosis and foot disease in cattle.



129



Scheme 7



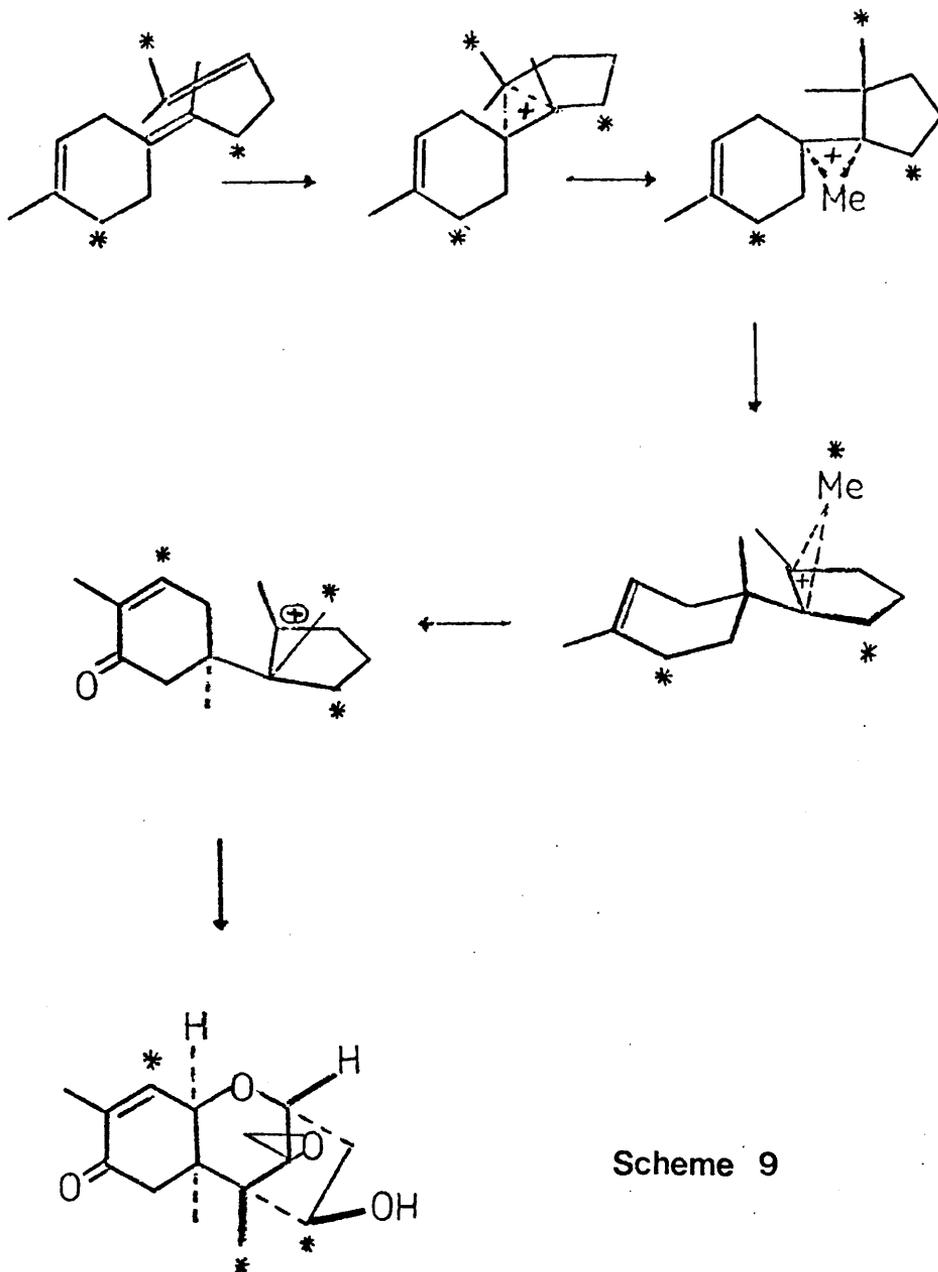
**Scheme 8**

## Biogenesis of the trichothecanes

The biogenesis of the trichothecanes is as open-ended today as it was when Jones and coworkers carried out their initial tracer experiments more than a decade ago. The early work, using [1-<sup>14</sup>C] acetate and [2-<sup>14</sup>C] mevalonate suggested the cationic intermediate (129) as the precursor of this group of sesquiterpenoids, the proposed genesis involving  $\gamma$ -bisabolene. Jones, in his formulation of a possible biosynthetic pathway, did not specify which of the four possible farnesyl pyrophosphates would serve as a pregenitor for the trichothecanes, merely indicating two possible modes by which the isoprene units of the farnesyl chain could undergo cyclisation in order to form a bisabolene (Scheme 7)<sup>58</sup>. These two different modes of cyclisation, (b) and (a), have been interpreted as involving cis, trans and cis, cis farnesyl pyrophosphate respectively<sup>59</sup>.

Elegant experimentation allowed Jones and coworkers to show that only mode (a), involving cis,cis farnesyl pyrophosphate, would allow activity to be incorporated into the trichothecin molecule in a manner consistent with experimental evidence<sup>58</sup>. On the basis of this Ruzcika proposed a possible biosynthetic pathway to trichothecin and the trichothecanes generally (Scheme 8)<sup>59</sup>.

Since this early work chemical and X-ray evidence has revised the structure of trichothecin to (28)<sup>28,27,26</sup>.



Scheme 9

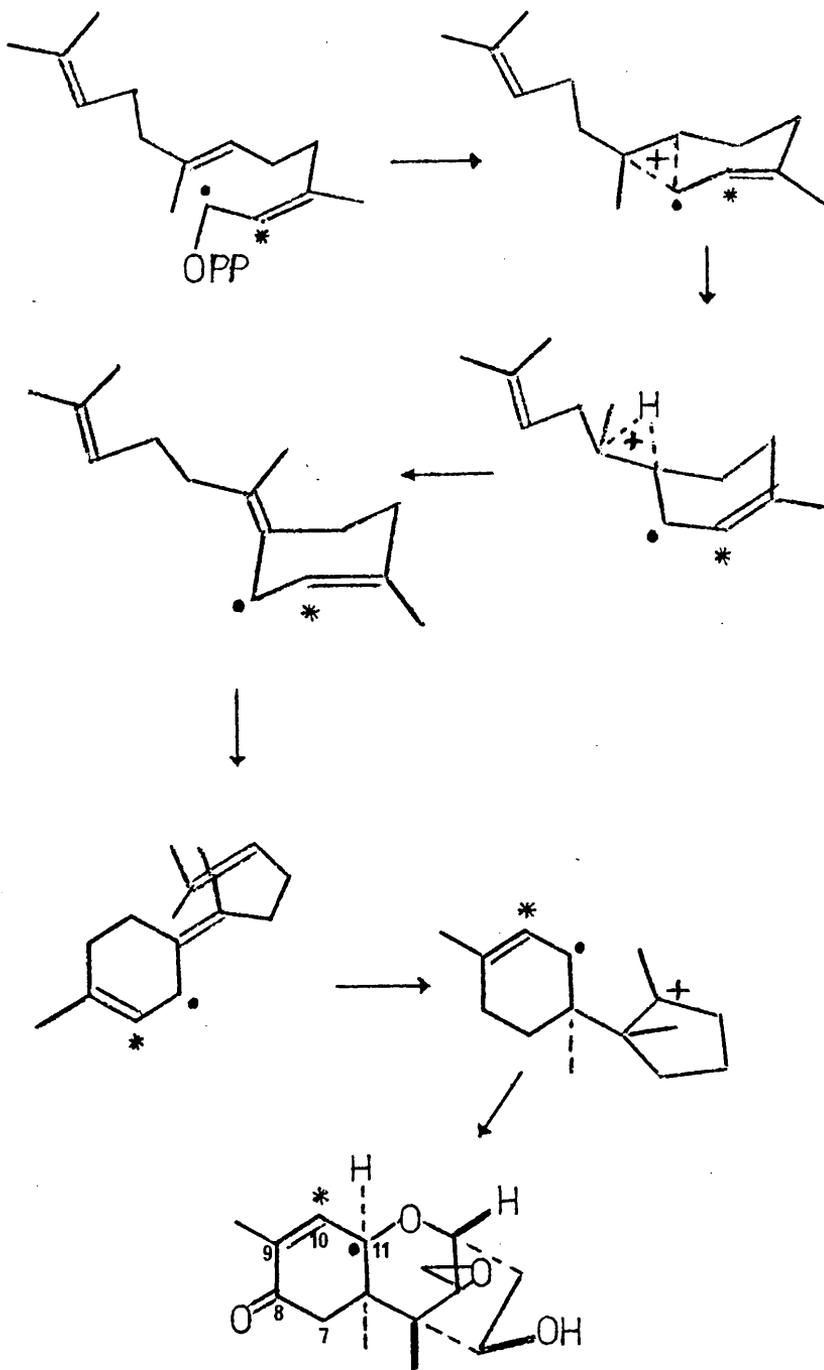
130

The revision of the formula does not, however, invalidate the early biogenetic conclusions and it seems reasonable to assume that the activity distribution, in the light of the new structure, is as shown in (130). A boat-type folding of the side-chain in  $\gamma$ -bisabolene has been postulated to accommodate both the labelling pattern and stereochemistry in the revised trichothecin structure (Scheme 9)<sup>27</sup>.

After a ten year lull new biogenetic evidence has appeared which has thrown serious doubt upon the above-formulated biosynthetic pathway to the trichothecanes.

Whereas earlier work suggested that the cis- $\Delta^6$ -farnesyl pyrophosphate gave rise to the trichothecane skeleton, Hanson and coworkers<sup>60</sup>, in an initial communication, obtained evidence supporting the involvement of trans- $\Delta^6$ -farnesyl pyrophosphate. The two ways of folding the farnesyl unit may be distinguished by the labelling pattern encountered in ring A of the trichothecanes. Both <sup>14</sup>C and tritium labelled mevalonic acid was fed to Trichoderma spa. and the tritium labelling pattern investigated. A direct piece of evidence was derived from [(4R), 4 <sup>3</sup>H<sub>1</sub>] mevalonic acid derived trichodermol (26). The isotopic ratio corresponded to the retention of two tritium atoms and it was shown by direct degradation that one of these resided at C<sub>10</sub>.

The two possible farnesyl pyrophosphates may also be differentiated by the number of (1-<sup>3</sup>H<sub>1</sub>) and (2-<sup>3</sup>H<sub>1</sub>) hydrogens

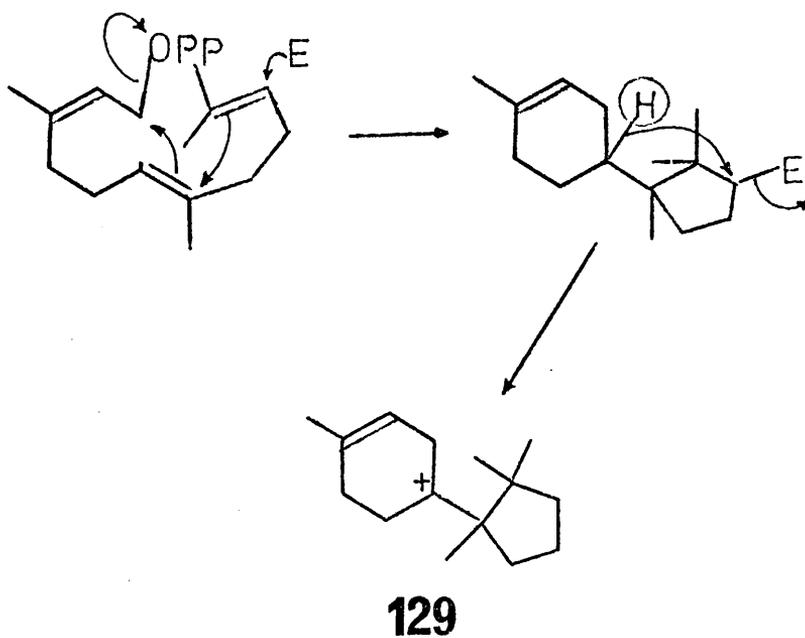


Scheme 10

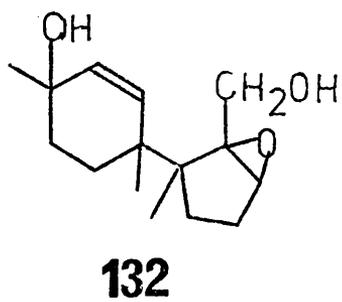
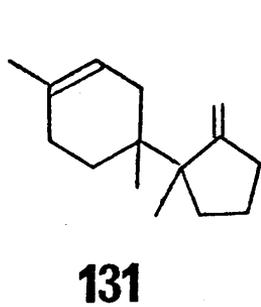
which are retained in the isolated trichothecane. Trans- $\Delta^6$ -farnesyl pyrophosphate would lead to labels at C<sub>10</sub> and C<sub>11</sub>, as shown in Scheme 10, invoking the intermediacy of a bisabolene intermediate. The cis- $\Delta^6$ -farnesyl isomer, in an analogous manner, would carry activity at C<sub>7</sub> and C<sub>8</sub>.

When [1-<sup>3</sup>H<sub>1</sub>, 2-<sup>14</sup>C] farnesyl pyrophosphate was fed to Trichothecium roseum, the isolated trichothecolone (27) showed the loss of one tritium label. [2-<sup>3</sup>H<sub>1</sub>, 2-<sup>14</sup>C] Farnesyl pyrophosphate, on the other hand, showed no loss of label in the final product, lending further credence to a trans folding of the central farnesyl bond<sup>60</sup>. This evidence, seriously conflicting with Jones's earlier findings, was soon thrown into further disarray, however.

In order to establish which prenyl fragment of the farnesyl pyrophosphate contributed to the C<sub>2</sub> label, Hanson and coworkers fed [2-<sup>3</sup>H<sub>1</sub>, 2-<sup>14</sup>C] geranyl pyrophosphate to Trichothecium roseum, Trichoderma polysporum and T. sporulosium<sup>61</sup>. Both trichothecin (28) and the isolated trichodermol (26) retained the [2-<sup>3</sup>H<sub>1</sub>] geranyl label, showing that the C<sub>2</sub> label is derived from the second [(4R)-4 <sup>3</sup>H<sub>1</sub>] mevalonoid hydrogen. These results clearly preclude the possibility of a bisabolene intermediate since such a biogenetic pathway, as Scheme 10 clearly shows, would involve the loss of the central mevalonate label. The authors<sup>61</sup> have suggested an alternate route involving a concerted cyclisation sequence (Scheme 11), in



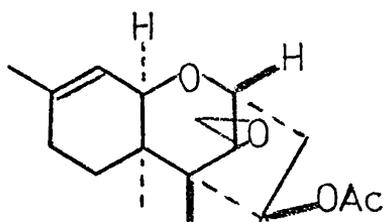
Scheme 11



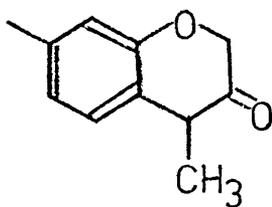
which a 1,5 hydrogen transfer occurs in the enzyme displacement step, the resulting cation then serving as an initiator for the subsequent methyl migrations leading to a trichothecane intermediate (129).

The stereochemistry of the hydroxylation step, at C<sub>4</sub>, in verrucarol was determined using the tritiated preparations obtained after feeding (3R)-[(2S)-2-<sup>3</sup>H]/(3S)-[2R-2-<sup>3</sup>H] and (3S)-[(2S)-2-<sup>3</sup>H]/(3R)-[(2R)-2-<sup>3</sup>H] sodium mevalonate to Myrothecium in separate experiments<sup>62</sup>. From incorporation of (3R)-[5-<sup>14</sup>C] mevalonate it was anticipated that only the (3R) mevalonate would be incorporated into the sesquiterpenoid moiety, assuming the compounds to be farnesol derived. The hydroxylation at C<sub>4</sub> was found to proceed in a stereospecific manner with retention of configuration. The stereochemistry corresponded to the pro-2R hydrogen atom of mevalonate. These conclusions were in agreement with those for trichothecin (28) and trichodermol (26)<sup>63</sup>.

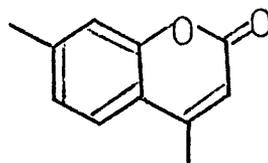
The isolation of trichodiene (131)<sup>64</sup> and trichodiol (132)<sup>65</sup> from Trichothecium roseum Link pointed strongly to the existence of the postulated intermediate (129) along the suggested biogenetic route to the trichothecanes. Specifically tritiated trichodiene (131) has, in fact, been shown to be incorporated into trichothecolone in a recent communication<sup>66</sup>.



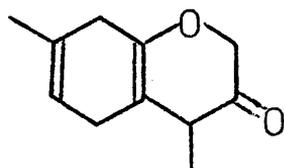
**26A**



**133**



**134**

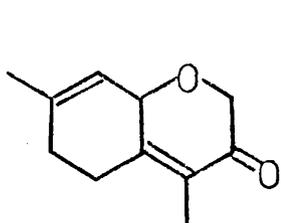


**135**

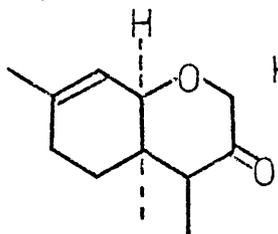
Synthetic approaches to the trichothecanes

Despite the growing interest in the trichothecane field little has hitherto been reported on synthetic ventures directed towards any member of this expanding group of biologically active mould metabolites. Their novel structural framework appears to have served both as a source of interest and, at the same time, a deterrent to the synthetic organic chemist.

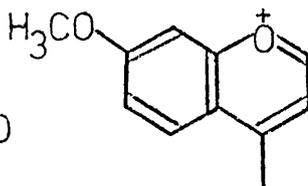
Two approaches towards trichodermin (26a) have been recorded in the literature. Thus Stills and coworkers<sup>67</sup> described the synthesis of a methylated chroman-3-one (133) a potential yet remote precursor to trichodermin. This compound (133) is readily available by hydroboration-oxidation of 4,7 dimethyl coumarin (134), the reaction being of a fairly general nature. The similarity between (133) and trichodermin (26a) is a perfunctory one indeed and no further communication concerning the elaboration of the intermediate (133) has been forthcoming. While an approach of this nature readily gives rise to ring B of trichodermin, it carries with it considerable stereochemical difficulties and in the presence of the aromatic ring possibly its own seeds of destruction. An elaboration of the aromatic ring to the structural moiety encountered in trichodermin is conceivable but not without many complications. Thus Birch reduction should give rise to the dihydro-derivative (135) which would have to



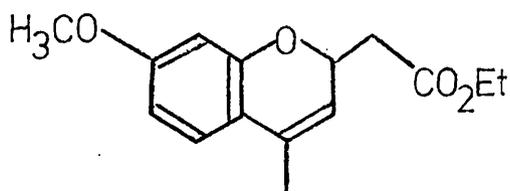
**136**



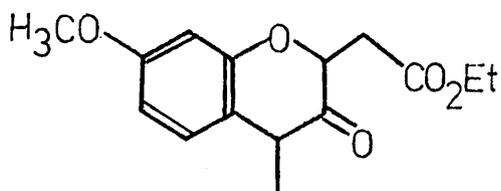
**137**



**138**



**139**



**140**

be isomerised to the enone (136). Isomerisations of such tetrasubstituted enol ethers are difficult, nor is there any guarantee about the migration of the trisubstituted double bond into its desired position. In the event of the successful accomplishment of all the described transformations, (137) may be viewed as an important building block towards the total synthesis of trichodermin.

An alternate approach has been described by Helmes<sup>68</sup>: The crux of this method hinged upon the successful addition of ethyl lithio acetate to the pyrylium salt (138). With the obtention of (139) the molecule was readily modified to the keto-ester (140). No further advances have been communicated. A third synthetic study in the trichothecane field, under R.A.Raphael at Glasgow<sup>69</sup>, culminated in the total synthesis of ( $\pm$ ) trichodermin (26a). The methodology and detailed strategy employed in this synthesis will not be elaborated upon at this stage, but will be discussed fully at a later stage.

While this introduction was in preparation a review of the trichothecanes was published<sup>70</sup>.

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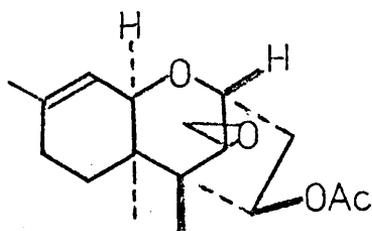
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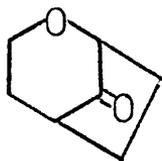
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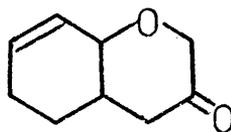
## Discussion



**1**



**2**



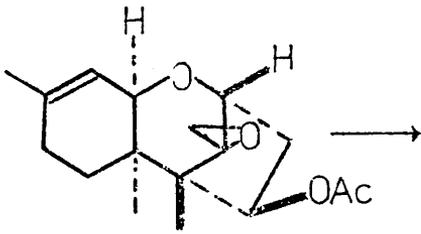
**3**

The overall objective described in this thesis is an approach towards the synthesis of two members of the trichothecane group of sesquiterpenoids. At the outset attention was focused on trichodermin (1)<sup>1</sup>, since this compound embodies the complex carbocyclic skeleton common to all members of this group of natural products but is less generously endowed with the multifarious functionality associated with the other, more highly-oxygenated trichothecanes. Although the complexities were thus reduced, the synthetic problem still remained a formidable one.

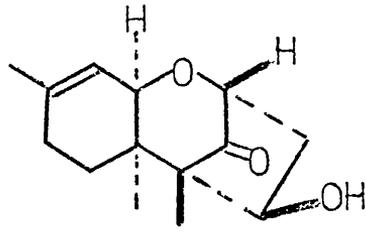
The trichothecane nucleus may be considered as either a derivative of 2-oxa-bicyclo[3,2,1]octan-8-one (2) or a reduced chroman-3-one (3). Since neither of these structural units is well-documented in the literature a projected synthesis along these lines can not take advantage of well-founded analogies. Thus any approach modelled upon the above two systems necessitates the synthesis of a new structural framework containing functional appendages capable of ultimate transformation to the synthetic objective.

Stereochemically the trichothecanes present a far from trivial problem with the presence of no less than six contiguous chiral centres. A potential source of further difficulty is the presence of the thermodynamically less favourable cis ring A/B junction.

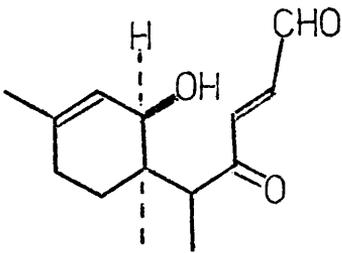
An efficient method for the construction of a synthetic



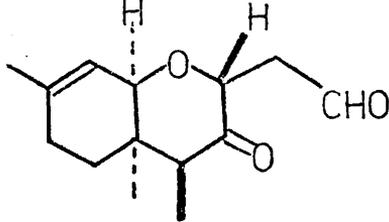
**1**



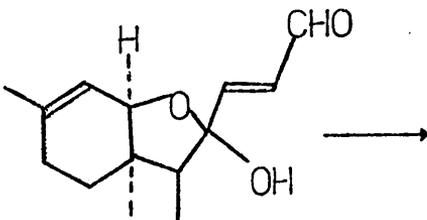
**4**



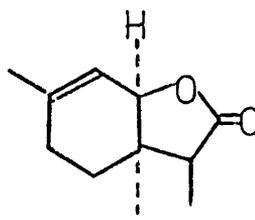
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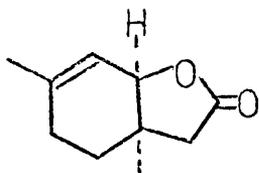
**7**



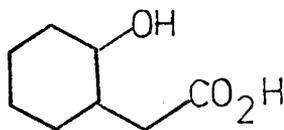
**8**

strategy is to reduce the complex molecular pattern into synthons<sup>2</sup> - suitably activated molecular fragments capable of assembly to the parent molecule. The logical pursuit in delineating the course of a synthesis towards trichodermin (1), or any trichothecane for that matter, is therefore to pinpoint both structural moieties which are capable of transformation to easily recognisable pregenitors and carbon-carbon bonds sufficiently activated to allow rupture and, necessarily, reassembly in accord with the principles of synthetic organic chemistry.

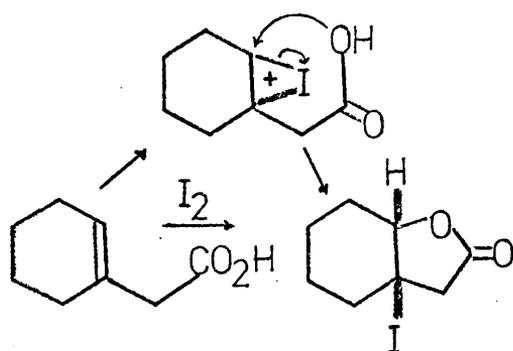
In a retro-synthetic sense trichodermin (1) is capable of two trivial functional group manipulations which allow its transformation into the ketol (4). This ketol (1), in turn, by retro-aldolisation is seen to be derivable from the tetrahydrochroman-3-one (5). These three simplifications have already defined a clear synthetic goal and a crucial intermediate in the synthesis of trichodermin. The molecule (5), however, graciously lends itself to further simplifications. It is easily recognised as a possible product of an intramolecular Michael reaction of the cross-conjugated keto-aldehyde (6). A simple tautomeric change, in turn, transforms the keto-aldehyde (6) into the ketal (7) and allows immediate speculation as to a potential synthesis of this latter compound. It is not unreasonable to propose for this the addition and modification of a suit-



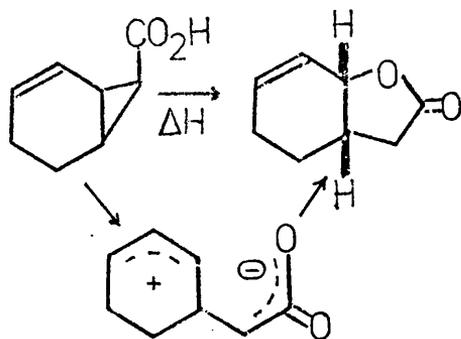
**9**



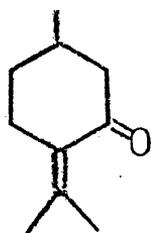
**10**



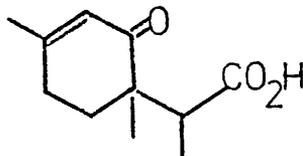
**Scheme 1**



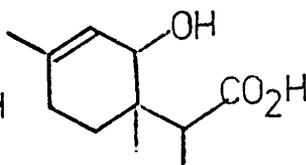
**Scheme 2**



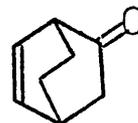
**11**



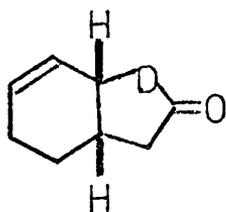
**12**



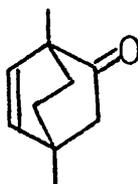
**13**



**14**



**15**



**16**



**17**

ably masked three-carbon unit to the cis  $\gamma$ -lactone (8).

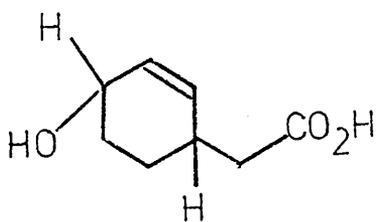
The initial problem, as a result of this series of clearly defined transformations, has thus been reduced to that of the synthesis of the  $\gamma$ -lactone (8), or its nor-methyl derivative (9). Indeed, all hopes were pinned upon the successful and synthetically viable formation of the relatively simple organic molecule (9). This compound was germane to all further chemical elaborations and was considered to be the crucial building block for trichodermin (1); not only does it embody the structural features of ring A, but it also contains the potential cis A/B ring fusion of trichodermin within its structural framework. It was hoped to utilise the thermodynamically more stable cis ring fusion of the  $\gamma$ -lactone (9) and to preserve its stereochemical integrity at the ring junction in all subsequent elaborations of the molecule along the lines discussed above.

With the overall synthetic strategy clearly delineated a large scale synthesis of the  $\gamma$ -lactone became the prime objective. While a number of approaches towards simple  $\gamma$ -lactones have been recorded in the literature<sup>3</sup>, there are few instances of stereospecific synthesis of butyrolactone moieties cis fused to cyclohexane rings. The available methods resolve themselves into two categories: those involving the synthesis of hydroxy-acids of type (10) with spontaneous lactonisation<sup>4</sup>, and the approaches utilising the

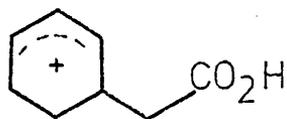
greater thermodynamic stability and ease of formation of formation of cis fused  $\gamma$ -lactones, employing a pendant carboxylic moiety to create an asymmetric centre at a neighbouring  $\gamma$ -carbon atom in a totally specific manner, as illustrated in Schemes 1 and 2<sup>5,6</sup>.

The former method of approach has been investigated in these laboratories<sup>7</sup>. Thus pulegone (11), by a series of relatively simple steps, has been converted into the enone-acid (12) in the anticipation of bringing about its reduction to the hydroxy-acid (13) and subsequent ring closure to the desired  $\gamma$ -lactone (8). Extensive experimentation, however, showed the carbonyl of the enone moiety to be severely hindered and 1,4 reduction to be a major competing process.

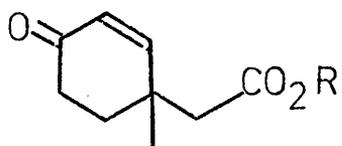
An important pointer to a potentially viable synthesis came from the work of Meinwald and Frauenglass<sup>8</sup> who found that peracid oxidation of bicyclo[2,2,2]oct-2-en-5-one (14) allowed isolation of the  $\gamma$ -lactone (15). The resemblance between (15) and the desired lactone (9) was striking. If two methyl substituents could be incorporated into the bicyclic nucleus at the bridgehead positions there was no obvious hindrance to the conversion of (16) into the  $\gamma$ -lactone (9). More fundamental, however, were the mechanistic implications of the observed rearrangement. The immediate Baeyer-Villiger product (17) presumably underwent lactone



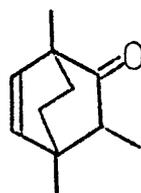
**18**



**19**



**20**



**21**



**22**

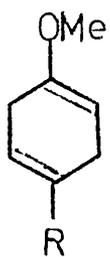


**23**

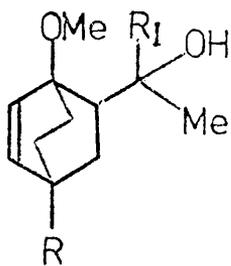
ring opening to the hydroxy-acid (18), which furnished the lactone (15) by intramolecular cation capture via the allylic cation (19). The implied intermediacy of the hydroxy-acid (18) had its immediate ramifications; it suggested that the 4,4-disubstituted cyclohexenone (20), after selective Grignard addition, hydrolysis and acidification might yield the sought-after lactone. It was, as a consequence of this reasoning, that the enone (20) assumed a position of considerable importance in all synthetic plans.

Initially, however, attempts were directed towards the obtention of the bicyclic ketone (21). By analogy with previously described work this may have provided an economical route to the methylated lactone (8). Such an approach demanded the synthesis of the diene (22). All efforts, however, were thwarted at the embryonic stage, since attempts to reproduce Alder's original synthesis of (22)<sup>9</sup> proved to be futile. The problem found a partial solution in the dehydration of the carbinol (23). A mixture of dienes was obtained, with the requisite one (22) predominating. However, all attempts to induce the molecule to undergo a Diels-Alder reaction with nitropropene met with failure.

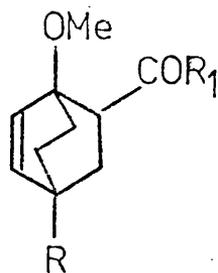
The synthesis of a number of 4-substituted cyclohex-2-enones has been reported by Birch<sup>10,11</sup>. The method rests upon the Diels-Alder addition between the dienes (24, R=H, Me) and a suitable dienophile. The carbinols (26, R=R<sub>1</sub>=Me;



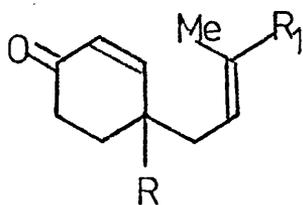
**24**



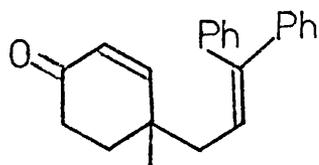
**26**



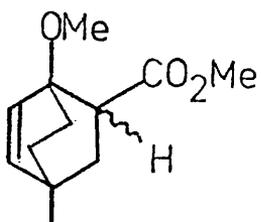
**25**



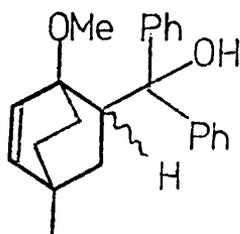
**27**



**28**



**29**

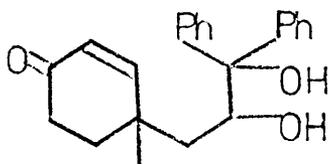


**30**

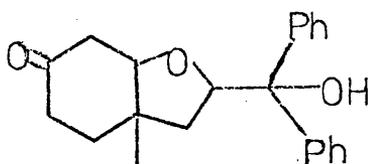
R=R=H) derived from the bridgehead substituted bicyclo-[2,2,2]octenes (25, R=Me, R<sub>1</sub>=OMe; R=H, R<sub>1</sub>=Me) undergo acid-induced fragmentation to furnish the enone-olefins (27, R=Me, R<sub>1</sub>=Me; R=R<sub>1</sub>=H). Their ease of formation appears to be a function of the stabilisation of the positive charge at the exocyclic tertiary position. In order to maximise stabilisation of the developing cationic charge at this site, it was decided to employ phenyl substituents and prepare the enone (28), a promising precursor of the desired keto-ester (20).

Diels-Alder addition of methyl acrylate to dihydro-4-methyl anisole (24, R=Me)<sup>12</sup> gave the bicyclic ester (29) as a mixture of epimers, the reaction proceeding only at elevated pressure and in a totally regiospecific manner. This finding is in accord with Birch's work on analogous systems<sup>10,11</sup> and, no doubt, is a direct consequence of the more favourable alignment of the reacting components in the transition state. Phenyl magnesium bromide addition to the ester (29) gave the diphenyl carbinol (30) which, on treatment with a mixture of perchloric and acetic acids, smoothly and in 65% yield afforded the enone-olefin (28).

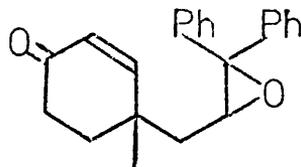
The phenyl substituents were intended to serve a second function. It was planned, at this stage, to oxidise the olefinic side chain in (28) to the corresponding carboxylic acid residue and thence to the desired enone-ester (20).



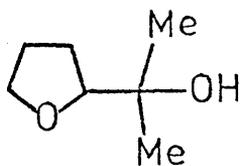
**31**



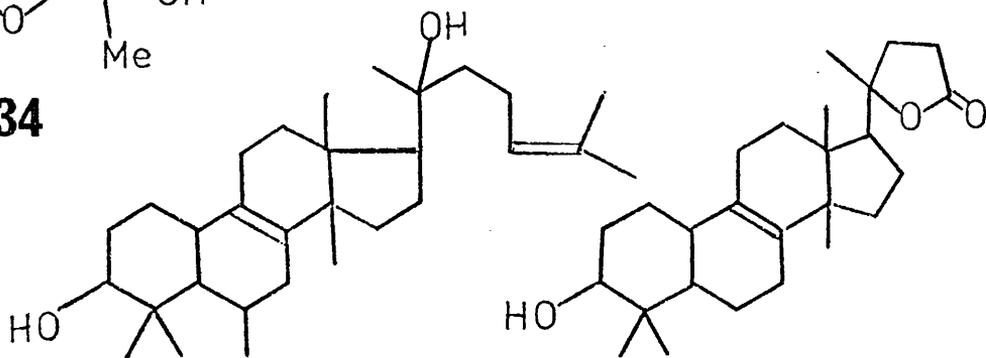
**32**



**33**

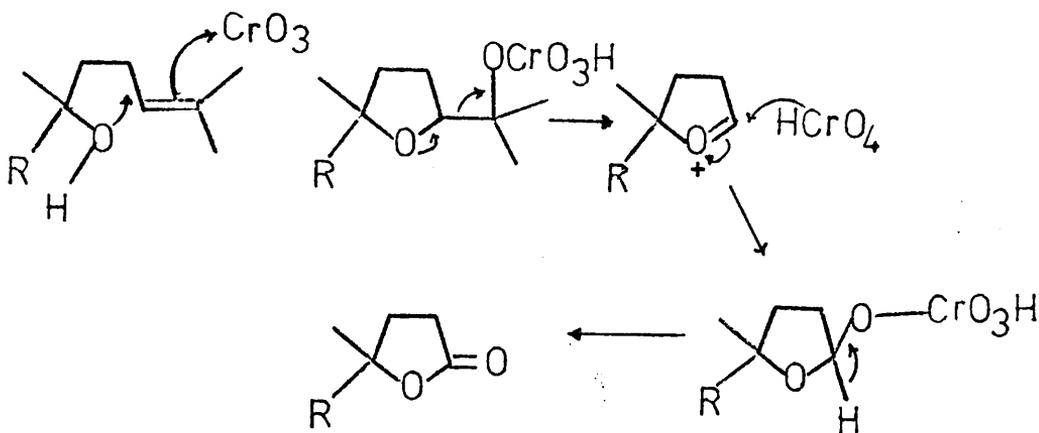


**34**

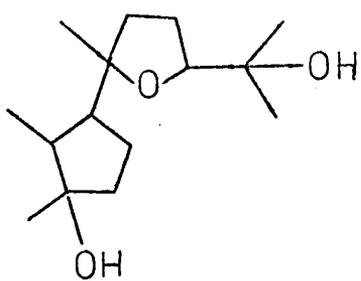


**35**

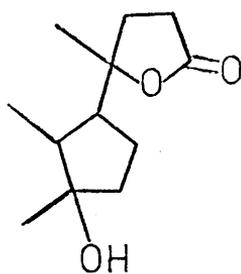
**36**



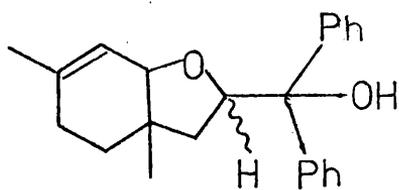
**Scheme 3**



**37**



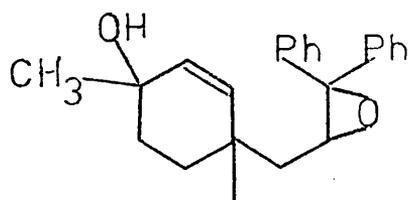
**38**



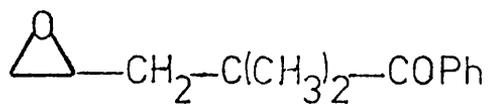
**39**

All hopes rested on the selective oxidation of the trisubstituted olefinic moiety contained in (28). It was felt that the requisite degree of selectivity could be achieved with osmium tetroxide<sup>13</sup>; it was dubious whether the more electrophilic and powerful oxidising conditions of ozone<sup>14</sup> could achieve the same objective. In the event, osmylation of the olefinic-enone (28) did not allow the isolation of the anticipated diol (31), the bicyclic ketone (32) being obtained instead as the outcome of an intramolecular Michael addition; this product was also isolated by acid treatment of the epoxy-enone (33). Failure at this juncture necessitated a deviation from the initially-conceived plan towards the lactone (9) and the tetrahydrofuranyl carbinol (34) served as an important guide in this connection.

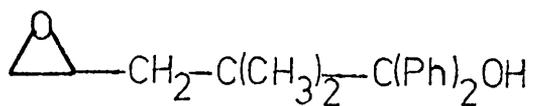
Mills<sup>15</sup>, working on tetracyclic triterpenoids, has described an interesting oxidative cleavage of a three-carbon unit in dammarenodiol (35). Thus (35), on treatment with chromic oxide in sulphuric acid, furnished acetone and the  $\delta$ -lactone (36). This result has been rationalised by de Mayo<sup>16</sup>, who has postulated the mechanism shown in Scheme 3. The implication of a tetrahydrofuranyl carbinol was vindicated by the findings of Morisaki et. al.<sup>17</sup>, who derived the lactone (38) from the diol (37) under similar oxidising conditions. It was, therefore, conceivable that the diphenyl carbinol (39), under conditions akin to those described



**40**



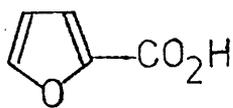
**41**



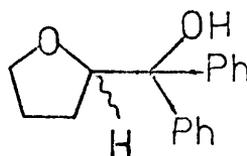
**42**

above, would afford the requisite  $\delta$ -lactone (9). With this end in view three distinct, successive transformations of the enone (28) had to be achieved, viz., selective epoxidation of the trisubstituted double bond, selective Grignard addition to the ketonic moiety and acid-catalysed transformation of the epoxy-carbinol (40) to the tetrahydrofuran (39).

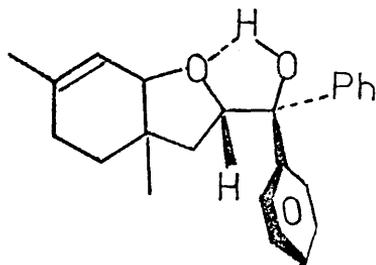
No difficulty was anticipated in the epoxidation step nor, indeed, was any encountered. The electron-rich ethylenic linkage furnished the epoxy-enone (33) readily and in high yield on treatment with m-chloroperbenzoic acid in methylene chloride. Selective addition of Grignard reagents to the ketonic function of keto-epoxides has been recorded<sup>18</sup>. Thus Grignard<sup>19</sup> was able to convert the epoxy-ketone (41) to the epoxy-alcohol (42) in good yield. Analogously, using equimolar quantities of methyl magnesium chloride and the epoxy-ketone (33) and working rapidly at 0°, the epoxy-carbinol (40) was obtained smoothly and in high yield. When (40) was treated with aqueous 60% perchloric acid in ether three products were isolated by preparative t.l.c. Two of these were the epimeric carbinols (39), whose presence, although anticipated, was seriously questioned for a period of time. The difficulty arose as a result of the chemical shift of the C<sub>2</sub> methine proton in (39), being about 1 $\tau$  below the value normally associated with protons in similar chemical environments<sup>20</sup>. Unless one postulated restricted rota-



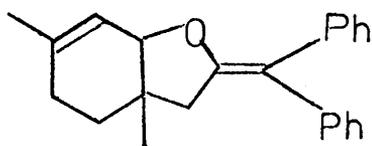
**45**



**44**



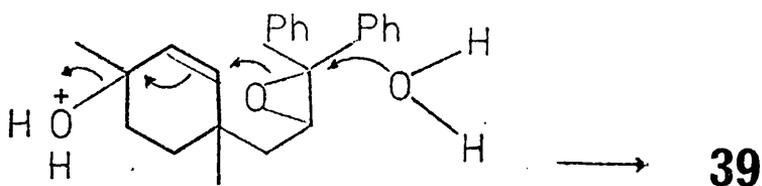
**43**



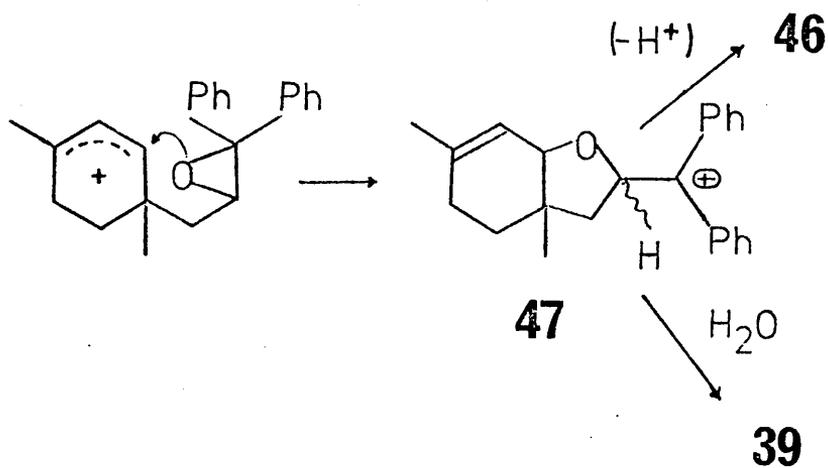
**46**

tion of the  $C(Ph)_2OH$  fragment, and a subsequent deshielding by the aromatic rings, it was difficult to rationalise the observed spectral anomaly. A potential source of such hindered rotation was the possibility of strong intramolecular hydrogen bonding between the tert. hydroxyl group and the ethereal oxygen as shown in structure (43). The molecule did, indeed, show a strong intramolecular hydrogen bond in the i.r. spectrum at  $3570\text{ cm}^{-1}$ . In order to dismiss any ambiguity associated with the structural assignment to the compound (43), it was decided to investigate the spectral properties of a simple model system - the tetrahydrofuran (44). Fortuitously, its preparation had been recorded in the literature; furoic acid (45) on catalytic hydrogenation, esterification and treatment with phenyl magnesium bromide, readily allowed the isolation of crystalline alcohol (44). It was gratifying to observe that the methine proton at  $C_2$  did, indeed, show an unusually low chemical shift at  $\tau$  5.11 in the n.m.r. spectrum. Furthermore, its solution i.r. spectrum clearly demonstrated strong intramolecular hydrogen bonding ( $\nu_{\text{max}}^{CCl_4}$   $3567\text{ cm}^{-1}$ , unaffected by dilution) lending credence to the concept of restricted rotation of the diphenyl carbinol moiety and its subsequent effect upon the n.m.r. spectrum.

The third, unexpected product arising from the acid rearrangement of the carbinol (40) was the enol ether (46).



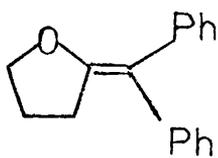
Scheme 4



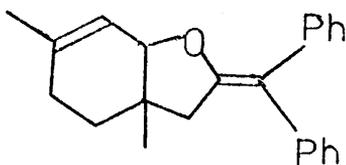
Scheme 5

It was initially assumed to arise by simple dehydration of the bicyclic carbinol (39). That this was erroneous was established very readily; not only did the alcohol (39) prove to be stable under the conditions employed in the acid rearrangement, but it also proved to be remarkably inert to normal dehydrating conditions. Thus thionyl chloride - pyridine, phosphorus oxychloride - pyridine and acetic acid-acetic anhydride were ineffective and only the more forcing conditions of magnesium sulphate, high temperature and reduced pressure resulted in loss of water leading to the obtention of the enol ether (46). Mechanistically this implied that the carbinols (39) did not arise by a concerted nucleophilic epoxide ring opening followed by an intramolecularly-induced anionotropic rearrangement of the tertiary allylic carbinol (Scheme 4). The products may be accounted for by invoking the capture of an allylic carbonium ion by the oxirane heteroatom (Scheme 5), the resulting tertiary carbonium ion (47) then either losing a proton to furnish the enol ether (46), or else undergoing intermolecular capture by water to yield the epimeric carbinols (39). Irrespective of their mode of formation, however, both the enol ether (46) and the carbinols (39) were considered to be of synthetic utility in the final step towards the  $\gamma$ -lactone (9).

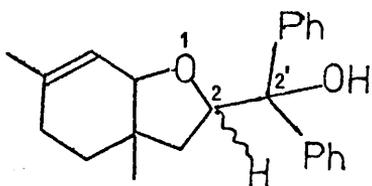
Huffman and coworkers<sup>23</sup> have been able to effect



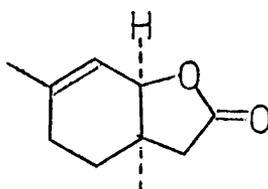
**48**



**46**



**39**



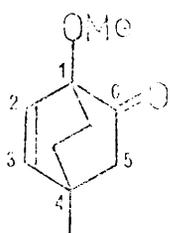
**9**

oxidative cleavage of the enol ether (48) with peracid to furnish  $\gamma$ -butyrolactone. The close structural similarity between (48) and the bicyclic enol ether (46) prompted an immediate extrapolation of their reported reaction.

m-Chloroperbenzoic acid did bring about oxidative cleavage of the enol ether moiety in (46); however, whereas benzophenone could be isolated by preparative t.l.c., the other reaction products were devoid of the high carbonyl stretching frequency associated with  $\gamma$ -lactones<sup>24</sup> and their complex n.m.r. spectra did not permit structural assignments. It was clear that no  $\gamma$ -lactone was in evidence and varying reaction conditions failed to remedy this synthetic stalemate.

Attention was therefore focused upon the carbinols (39) in the hope of achieving oxidation of the diphenyl carbinol fragment. Whereas literature analogies<sup>17,15</sup> were strikingly good, success was by no means guaranteed, as the enol ether oxidation had forcibly demonstrated.

Initial attempts to oxidatively cleave the  $C_2-C'_2$  carbon bond in (39) resulted in the isolation of starting material only. Thus two molar equivalents of 8N Jones reagent for short but varying periods of time failed to induce the desired transformation. Eventually it was found that an excess of oxidising agent, for a period of 72 hours, resulted in the formation of the  $\gamma$ -lactone (9) in a poor yield of 15%,

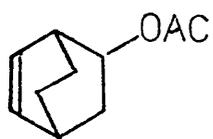


40

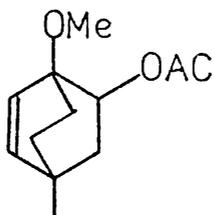
spectral and analytical data being completely in accord with the assigned structure.

While this approach, finally, afforded the desired material, the yields over the last two stages were disappointing, thus relegating this construction of the  $\gamma$ -lactone (9) from a possible synthetically viable route to a mere mode of formation. It was important, however, to achieve a high yield synthesis of the  $\gamma$ -lactone (9) and consequently a different approach was adopted.

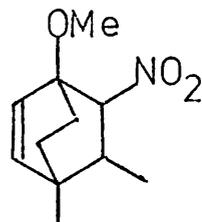
Conceptually the second method did not differ significantly from the one described above. It modelled itself closely on the work of Meinwald and Frauenglass<sup>8</sup>, the initial aim being the synthesis of the bicyclic ketone (49). In the event of a successful synthesis of (49) it was hoped to effect an oxidative cleavage of the C<sub>1</sub>-C<sub>6</sub> bond and thus obtain a 4,4-disubstituted cyclohexenone capable of further transformations to the  $\gamma$ -lactone along previously discussed lines. Since the reaction of ketenes with 1,3-dienes leads to cyclobutanone formation<sup>25</sup> rather than Diels-Alder addition, other approaches were required for the synthesis of structures corresponding to the 1,4 cycloaddition of a -CH<sub>2</sub>CO- unit to 1,3 dienes. The utilisation of  $\alpha$ -acetoxyacrylonitrile<sup>26,27</sup>, 2-chloroacrylonitrile<sup>28,29</sup>, vinyl acetate<sup>30,31</sup> and, more recently, 2-chloroacryl chloride<sup>32</sup> have been described for both cyclopentadienes and cyclohexa-



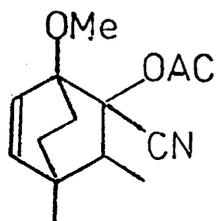
**50**



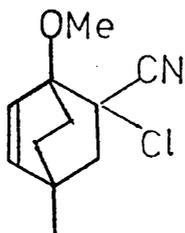
**51**



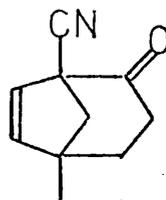
**52**



**53**



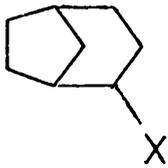
**54**



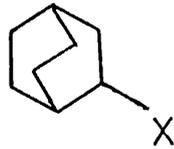
**55**

dienes. Mislou<sup>30</sup> had employed vinyl acetate and cyclohexa-1,3-diene in the synthesis of the bicyclic acetate (50). The yields for the cycloaddition were poor, but since the starting materials for the projected route towards the bicyclic ketone (49), viz. the diene (24, R=Me) and vinyl acetate, are readily available in large quantities, an attempt was made to effect the desired Diels-Alder addition in the hope of isolating the acetate (51). Varying reagent quantities and both temperature and pressure failed to produce the required transformation. The presence of 1,4-substituents in the diene component, coupled with the poor electrophilicity of vinyl acetate, no doubt contributed to the reluctance of the molecules to combine. Equally unsuccessful were the attempts to bring about  $4+2\pi$  cycloadditions between the diene (24, R=Me) and nitropropene or 2-acetoxy-1-butenitrile in an effort to synthesise the bicyclic compounds (52) and (53) respectively. Intractible mixtures of products were invariably isolated.

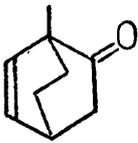
Eventually the successful route utilised 2-chloroacrylonitrile as the dienophilic component. Initial runs were conducted employing neat reagents and hydroquinone as stabiliser at 135°. This did, indeed, furnish the desired bicyclic chloro-nitrile (54), albeit in only 14% yield. A secondary product of the Diels-Alder addition was the bicyclo[3,2,1]octenone (55). Experiments under thermodynamic conditions



**56**



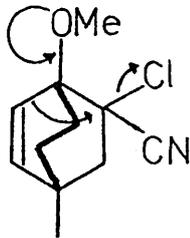
**57**



**58**



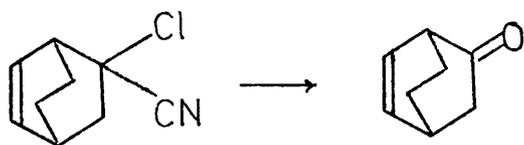
**59**



**60**

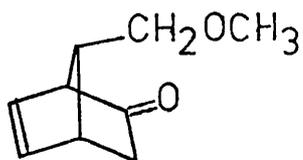
have confirmed the generally-held belief that derivatives of type (56) are more stable than (57); an approximate free energy of isomerisation of 0.5 kcal./mole having been estimated by Goering and Sloan<sup>33</sup>. Schleyer and coworkers<sup>34</sup>, investigating the isomerisation of bicyclo [2,2,2] octane and bicyclo [3,2,1] octane found the latter to be thermodynamically more stable and ascribed its stability entirely to its more favourable entropy content, a consequence of the greater symmetry associated with the bicyclo[2,2,2]octane skeleton. Rogers et. al.<sup>35</sup>, conducting similar investigations of the bicyclic ketones (58) and (59) found the equilibrium to lie on the side of the bicyclo[2,2,2]octenone (58). Entropy factors have no doubt ceased to play a significant role and the thermodynamic equilibrium reflects the fine balance of enthalpy content between the bicyclic ketones (58) and (59). Isolation of the bicyclo[3,2,1]octenone (55) demonstrates the relative instability of the bicyclo[2,2,2]octene (54) and its ability to rearrange under thermal conditions. The appended mechanism (60) is proposed to account for its formation.

Hydrolysis of the chloro-nitrile (54) to the ketone (49) proved to be an unexpected stumbling block for a considerable period of time. Two analogous transformations have been recorded; Freeman et. al.<sup>29</sup>, using aqueous potassium hydroxide in methanol/tetrahydrofuran, have been able to



**61**

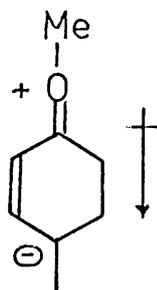
**14**



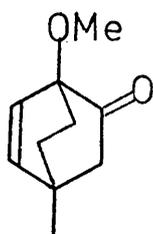
**62**

convert (61) into the ketone (14). Corey *et. al.*<sup>36</sup>, employing aqueous potassium hydroxide in dimethylsulphoxide, has achieved a similar transformation in the synthesis of the bicyclo[2,2,1]heptanone (62). Neither of these experimental conditions, however, achieved the desired effect with the chloro-nitrile (54); invariably starting material was recovered. Fortunately, an alternate method of transforming geminal chloro-nitriles to the corresponding ketones was described by Evans and coworkers<sup>37</sup>. The chloro-nitrile (54), on heating with sodium sulphide in ethanol, readily furnished the ketone (49). Furthermore, the authors found equimolar quantities of 2-chloroacrylonitrile and the diene (24, R=Me), on refluxing in benzene and utilising phenothiazine as stabiliser, not only circumvented the occurrence of the synthetically useless bicyclo[3,2,1]octenone (55), but also resulted in considerably improved yields of the bicyclic chloro-nitrile (54). Using this method (54) was obtained in a high state of purity in 60% yield.

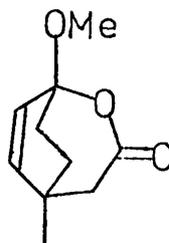
A point not commented upon, and perhaps deserving explanation, is the high regioselectivity of the Diels-Alder addition. This problem has received considerable attention for a number of years<sup>38</sup>, but even now has considerable vagueness associated with it. As ever, steric and electronic factors have been cited with varying degrees of emphasis. Electronic effects, manifesting themselves in the



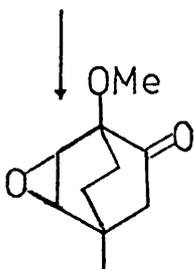
**63**



**49**



**64**

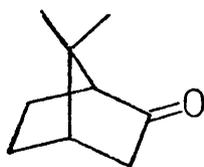


**65**

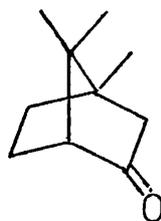
polarisation of the diene and dienophile components, no doubt play a pivotal role in the formation of (54). The involvement of dipolar character associated with the diene (24, R=Me) ties in with the present-day concepts of electron-releasing abilities of methyl and methoxyl substituents<sup>39</sup>. Thus the methoxy moiety, in view of its superior electron releasing power, polarises the molecule in the indicated manner (63) and aligns itself with 2-chloroacrylonitrile with a minimum of repulsions in the transition state.

A number of ways of rupturing the C<sub>1</sub>-C<sub>6</sub> bond in the ketone (49) were considered, the initial approach simply involving Baeyer-Villiger<sup>40</sup> oxidation to the lactone (64). The presence of the olefinic moiety in the molecule did not detract from the merit of this scheme since a number of workers have achieved the required selectivity in related oxidative transformations<sup>8,36</sup>. However, the result of treatment of the ketone (49) with m-chloroperbenzoic or trifluoroperacetic acids did not accord with previous experimental findings and the product isolated was the epoxy-ketone (65). This result was a clear reflection of the relative rates of the two reactions which the molecule could undergo and suggested that the introduction of a bridgehead methoxyl substituent severely retarded the rate of peracid attack upon the ketonic moiety.

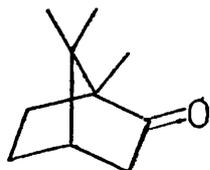
As has been previously mentioned, the bicyclic ketone



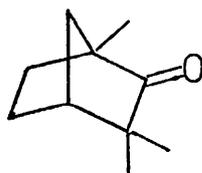
**66**



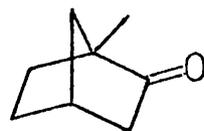
**67**



**68**



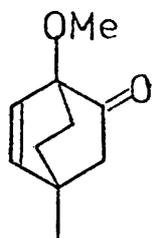
**69**



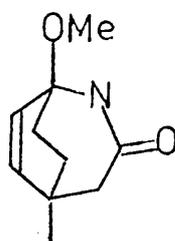
**70**

(14) readily and selectively underwent Baeyer-Villiger oxidation<sup>8</sup>. The question of relative migratory aptitudes of substituents in Baeyer-Villiger oxidation has been extensively investigated, the order of preference being tert. > sec. > prim.<sup>41</sup> Furthermore, the effect of para substitution upon phenyl migration has suggested the preferred order of migration  $\text{CH}_3\text{O} > \text{CH}_3 > \text{H}$ <sup>41</sup>. It may therefore be concluded from these findings that the group which migrates preferentially is the one best able to sustain a positive charge in the transition state.

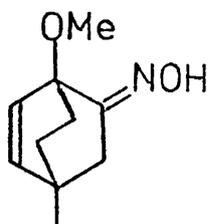
This paradox between experimental result and theoretical prediction is more apparent than real. Firstly one must evaluate the true electronic role of the bridgehead methoxyl group. The pronounced mesomeric phenomenon common to methoxyl substituted aromatic systems<sup>42</sup> may be of secondary importance in comparison with the -I effect of the substituent in aliphatic systems<sup>43</sup>. Its function may therefore be one of destabilising the transition state. Furthermore, Sauers and Ahearn<sup>44</sup> made the interesting observation that nor-camphor (66) and epi-camphor (67) are oxidized considerably more readily to the corresponding lactones than either camphor (68), fenchone (69) or 1-methyl nor-camphor (70). These results suggest that a methyl bridgehead substituent introduces a substantial amount of steric hindrance about the carbonyl group of bicyclic ketones and that the



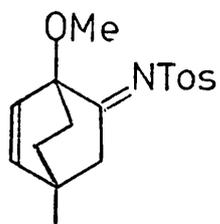
**49**



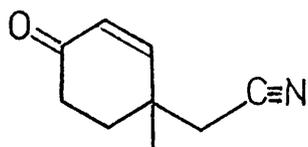
**71**



**72**



**73**

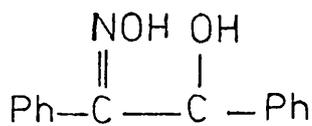


**74**

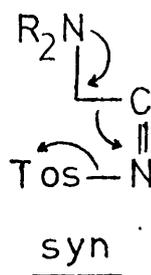
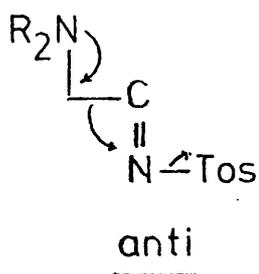
decreases in rates are caused by a decreased concentration of adducts due to pseudo-eclipsing of addend with the methyl group. This rationale may be extended to the bicyclic ketone (49), steric and conceivably electronic factors working hand in hand to render Baeyer-Villiger oxidation sufficiently unfavourable for the epoxy-ketone (65) to become the kinetically-favoured product.

An alternative to the Baeyer-Villiger oxidation which had been envisaged was a Beckmann transformation<sup>45</sup> of the ketone (49) to the bicyclic amide (71). The conceptual motivation for this reaction did not differ significantly from that described for the unsuccessful Baeyer-Villiger oxidation.

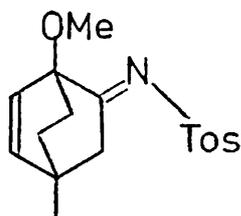
Refluxing the bicyclic ketone (49) with sodium acetate and hydroxylamine hydrochloride in aqueous ethanol afforded the oxime (72) as a crystalline, sharply melting compound. Methods of effecting the Beckmann transformation are manifold<sup>46</sup>; the method of choice involved the initial formation of the toluene-p-sulphonate derivative (73). Kuhara and coworkers<sup>47</sup> have demonstrated the ease of rearrangement of such esters and since then the method has been extensively employed<sup>46</sup>. Treatment of the oxime (72) with sodium hydride in ether and subsequent addition of toluene-p-sulphonyl chloride at  $-78^{\circ}$  did not permit isolation of the anticipated tosylate (73); instead the enone-nitrile (74) was obtained



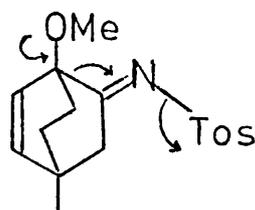
**75**



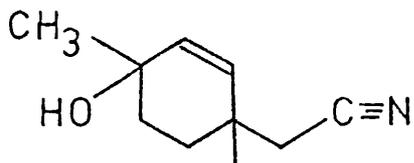
Scheme 6



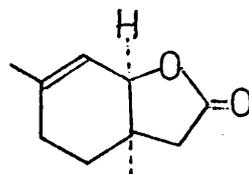
**76**



Scheme 7



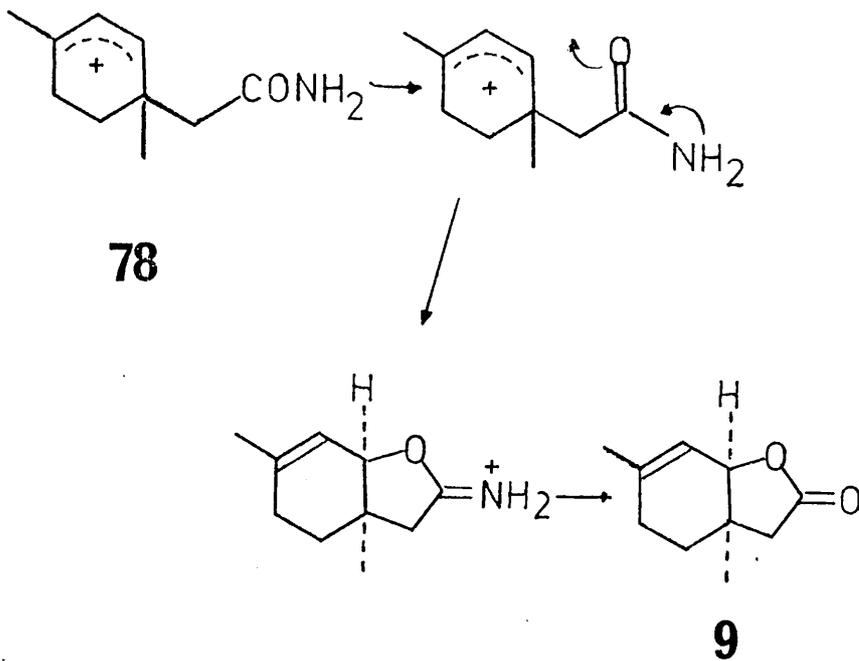
**77**



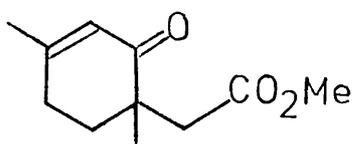
**9**

in 80% yield. The isolation of an abnormal Beckmann<sup>48</sup> product was not surprising. Werner et. al.<sup>49</sup> found benzoin oxime (75) to undergo a fragmentation under similar conditions to yield benzonitrile and benzaldehyde, the reaction being a fairly general one for  $\alpha$ -keto - and  $\alpha$ -hydroxy-oximes. The abnormal Beckmann rearrangement of  $\alpha$ -amino oximes has also been extensively investigated by Grob<sup>50</sup>, who found both syn and anti isomers capable of affording nitriles, the rates of fragmentation of the latter isomer being considerably greater than those of the former<sup>50</sup> as a consequence of the more favourable disposition of electrons in the transition state (Scheme 6) of the anti compound. It was not easy to assess the stereochemistry of the oxime (72). Solution i.r. data showed a hydroxyl band at  $3600\text{ cm.}^{-1}$  at high dilution, suggesting a free hydroxylic moiety<sup>51</sup> and the existence of the molecule in the anti configuration (76). The presence of one isomer was also consistent with the n.m.r. spectrum and the sharp melting point of the compound. It seems likely that a concerted mechanism of elimination is operational during the transformation (Scheme 7).

The enone-nitrile (74), on treatment with an equimolar quantity of methyl magnesium chloride at  $0^\circ$  readily and selectively furnished the allylic alcohol (77), which on treatment with concentrated hydrochloric acid in methanol afforded the desired  $\gamma$ -lactone (9) in 60% yield.



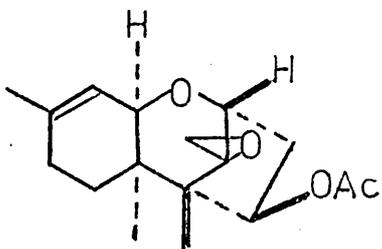
Scheme 8



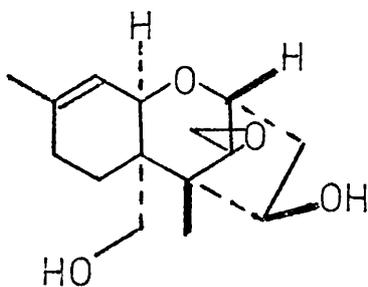
The mode of lactone formation presumably involves the intermediacy of the species (78), intramolecular capture of the secondary allylic carbonium ion by oxygen occurring in the manner shown in Scheme 8. The absence of any lactam no doubt reflects the greater nucleophilicity of the oxygen atom in the amide group, a feature illustrated by the ready conversion of amides to imino esters by trialkyloxonium fluoroborates<sup>52</sup>.

While this work was in progress an alternate and efficient route to the  $\gamma$ -lactone (9) had been explored in these laboratories. The considerable amount of effort devoted to the synthesis of the lactone (9) found ample justification in the total synthesis of trichodermin (1)<sup>53</sup>.

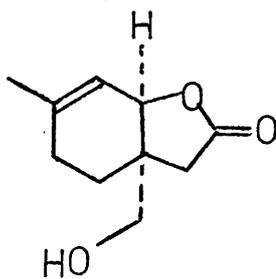
Recently yet another synthesis of (9) has been communicated<sup>54</sup>. The keto-ester (79) on selective reduction of the ketone moiety and subsequent acidification afforded the  $\gamma$ -lactone (9).



**1**



**80**



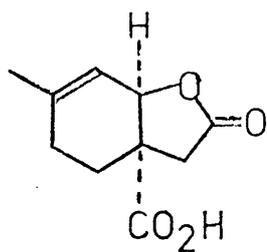
**81**

Approach towards Verrucarol

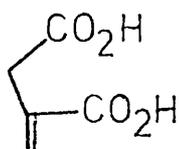
With the synthesis of trichodermin (1) entering an anticipatory phase of development at the hands of Dr. Colvin, a rationalisation of synthetic research was required.

Verrucarol (80), the basic sesquiterpenoid component of a large number of the trichothecane group of mould metabolites<sup>57</sup>, was considered a worthy target of synthetic enterprise. Its molecular architecture bears a close similarity to trichodermin (1), the difference residing in an innocuously appended hydroxylic function at C<sub>15</sub>. However, time and again apparently trivial structural modifications have belied the ultimate efforts required to bring about their incorporation into a synthetic route and the approach towards verrucarol (80) is a case in point, strikingly illustrating the penalties and rewards of working by analogy.

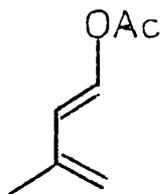
The general synthetic strategy towards the trichothecanes persevered. Indeed, there was no reason to doubt the synthetic utility of a cis-fused  $\gamma$ -lactone intermediate, the requisite precursor, in an extrapolated synthesis towards verrucarol (80), becoming the hydroxy-lactone (81). The angular hydroxymethyl group was initially conceived in the form of a tertiary carboxylic moiety which, at an opportune stage, could be transformed into the desired primary alcohol. Consequently, the initial approaches were directed



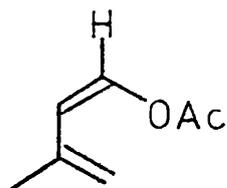
**82**



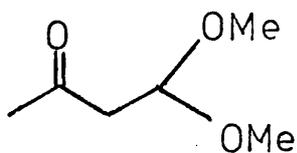
**83**



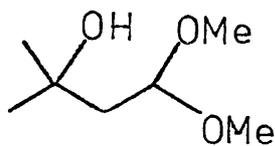
**84**



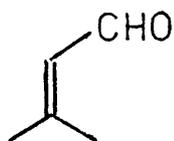
**84A**



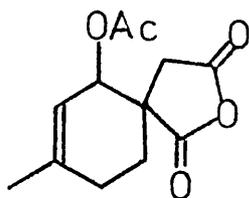
**85**



**86**

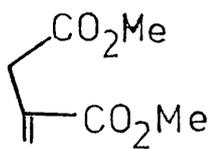


**87**

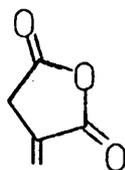


**88**

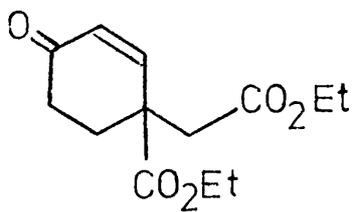
towards obtention of the cis-fused  $\gamma$ -lactone acid (82). The originally-conceived route had a pleasing simplicity, but suffered rather prematurely from its impracticability. The synthetic approach necessitated a Diels-Alder addition between itaconic acid (83) and 1-acetoxy-3-methylbuta-1,3-diene (84). The first operation consisted of the synthesis of the diene component. Price et al.<sup>58</sup> have paved the way towards the synthesis of a number of simple crotonaldehyde derivatives. Thus, methyl magnesium iodide addition to the keto-acetal (85) afforded the tertiary alcohol (86), which on treatment with aqueous sulphuric acid and subsequent steam-distillation of the reaction mixture allowed the isolation of 3,3-dimethylcrotonaldehyde (87). The  $\alpha,\beta$ -unsaturated aldehyde, on heating with potassium acetate-acetic anhydride at 140° for 6 hours, gave rise to a mixture of the isomeric acetoxydienes (84) and (84a) as indicated by n.m.r. spectroscopy. The stereochemical composition of the diene mixture was of no consequence to the subsequent Diels-Alder reaction. The only stereochemical control which was felt necessary was in the orientation of the reacting components with respect to each other. In the event of this prerequisite being met, a mixture of the diastereoisomeric cyclohexene derivatives (88) was anticipated, with the possibility of both cis and trans lactones being produced in the subsequent hydrolysis and acidification of the Diels-



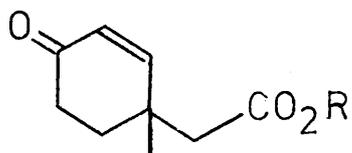
**89**



**90**



**91**

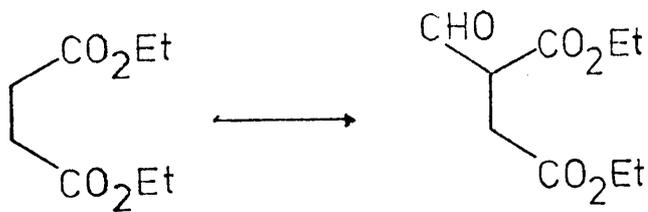


**20**

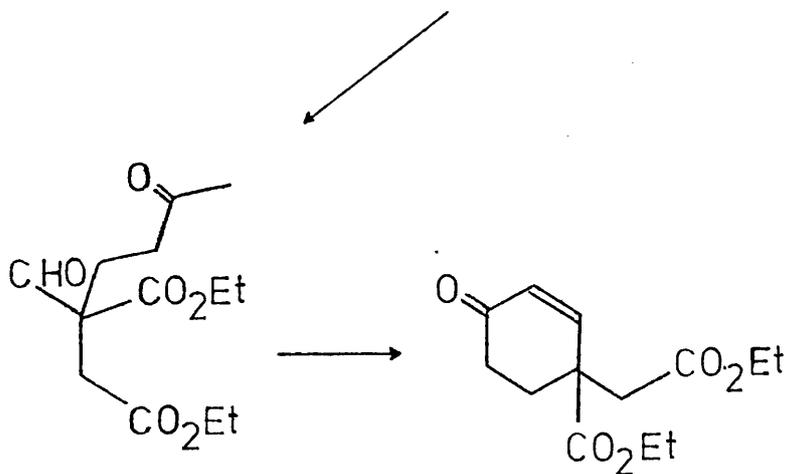
Alder adducts.  $\gamma$ -Hydroxy-acids, of course, undergo cyclisation to cis-fused lactones very readily<sup>4</sup>, in contrast to the sluggish mode of trans ring closure. The isolation of trans-fused material was not anticipated to be a major problem. The Diels-Alder addition, however, failed to materialise. Itaconic acid (83) and the dienes (84) and (84a) were subjected to a variety of reaction conditions without any adduct ever being in evidence. In hindsight, it is felt that justice was not done to the reaction, and that dimethyl itaconate (89) or itaconic anhydride (90) may have afforded the necessary degree of electrophilicity in the dienophilic component to bring about the desired cycloaddition.

Often in the course of synthetic work one or two key ideas provide the stimulus for further investigation. The ideas in question pertain to the mode of synthesis of the  $\gamma$ -lactone (9), thus elevating the enone diester (91) to a role of primary importance. The methodology of the subsequent transformative steps of this compound needs no reappraisal, having been discussed in the context of the enone ester (20).

Fortunately, the synthesis of the enone diester (91) had been recorded in the literature<sup>59</sup>. Thus, formylation of diethyl succinate with ethyl formate gave the formyl diester (91a), which on treatment with potassium tert. but-



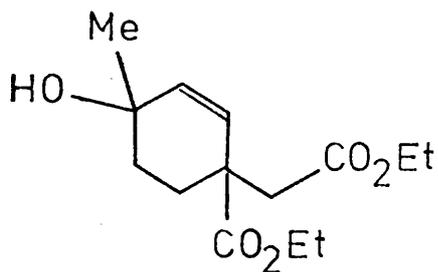
**91A**



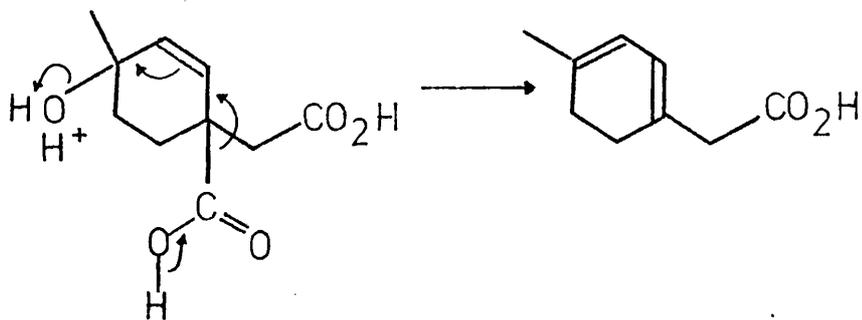
**93**

**91**

Scheme 9



**92**

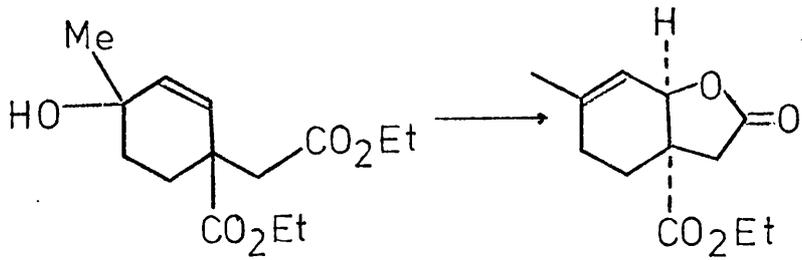


**94**

**Scheme 10**

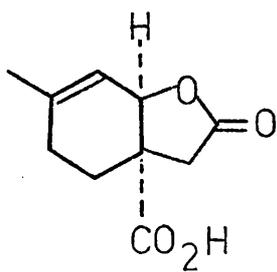
oxide in tert. butanol and benzene, followed by addition of methyl vinyl ketone, afforded the Michael adduct (93). This keto-ester (93) readily underwent intramolecular aldol condensation, allowing the isolation of the derived enone diester (91). It was the usual practice, at this juncture, to effect purification of the enone (91) via its semicarbazone derivative. These transformations are outlined in Scheme 9.

Exposure of the enone diester (91) to an equimolar amount of methyl magnesium iodide at 0° over a short period proceeded in the anticipated manner, the greater electrophilicity of the ketone carbonyl over the ester group ensuring a high yield conversion of (91) to the corresponding carbinol (92). The alcohol (92) proved to be a rather unstable compound and as a rule was employed in subsequent transformations without purification. The remaining tasks, in theory, were trivial; base hydrolysis followed by acidification was expected to yield the  $\gamma$ -lactone acid (82). A degree of caution was initially exercised: this arose from the recognition that the intermediate diacid (94) was  $\beta,\gamma$ -unsaturated and, from general experience, was capable of decarboxylating in acidic media (Scheme 10)<sup>60</sup>. In an attempt to circumvent this potential difficulty, studies were initiated to achieve a selective hydrolysis of the primary ester linkage in (92). While aqueous methanolic



**92**

**95**

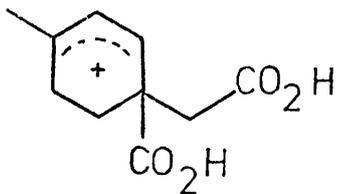


**82**

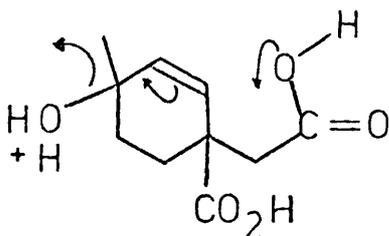
potassium carbonate in varying degrees of concentration failed to achieve this objective, aqueous 1N sodium hydroxide proved successful, and on acidification, the  $\gamma$ -lactone ester (95) was obtained. The same product was also the outcome of 60% aqueous perchloric acid-ethanol treatment of the alcohol ester (92).

This circumspect procedure, in the end, proved unnecessary. Vigorous hydrolysis of (92) with an excess of 4N sodium hydroxide and subsequent acidification afforded a brown mass, from which the  $\gamma$ -lactone acid (82) could be isolated as a colourless solid by crystallisation. The overall yield from the enone (91) was 40%, and allowed the lactone (82) to be procured in batches of 10 g. and more.

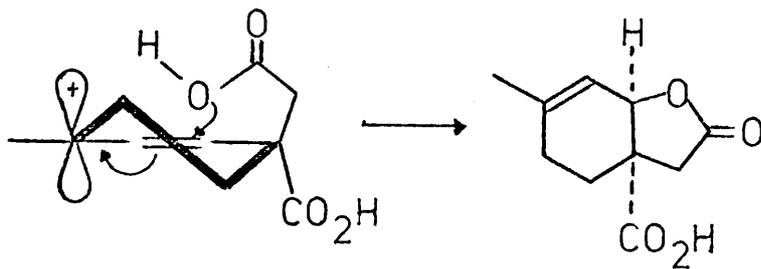
A point of considerable importance was the stereochemical composition of the isolated  $\gamma$ -lactone. The cis-fused nature of the previously synthesised lactone (9) has been alluded to in earlier discussions, without resorting to any justification for this assignment. It is true that the ultimate conversion of (9) into trichodermin (1)<sup>53</sup> removed all stereochemical dubiety. At the time in question, however, there was no rigorous way of establishing the pertinent stereochemistry in (9). The optimism associated with the assignment of a cis ring fusion was founded upon two pertinent facts. The  $\gamma$ -lactone acid (82) readily underwent base hydrolysis, and on acidification at 0° was almost



**96**

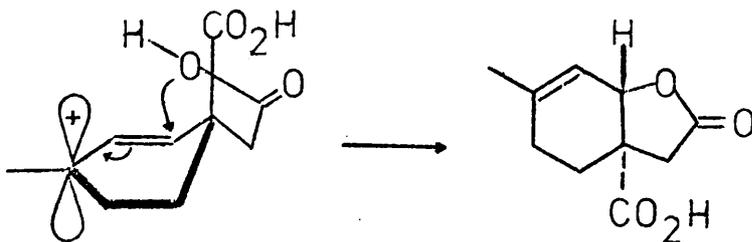


**Scheme 11**



**Scheme 12**

**82**

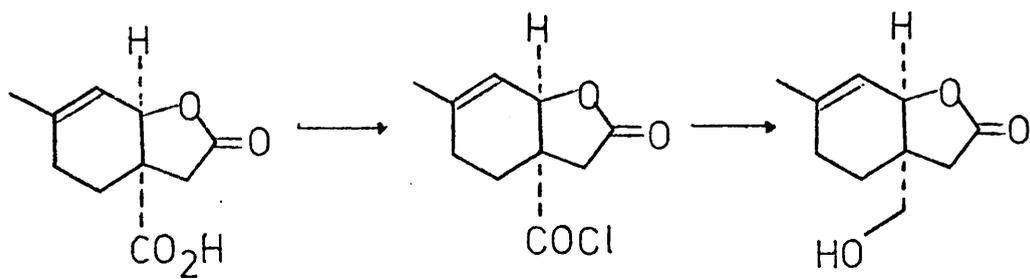


**Scheme 13**

**97**

spontaneously regenerated. This observation pointed to a cis disposition of hydroxylic and carboxylic moieties, in accord with previous experience. This deduction was reinforced by a consideration of the mechanism of lactonisation. It is of no consequence whether one assumes the  $\gamma$ -lactone to arise from the cationic intermediate (96), or as a result of an  $S_N2'$  process<sup>61</sup>, as shown in Scheme 11. A consideration of the two possible transition states, shown in Schemes 12 and 13, and manipulation of Dreiding models rapidly leads to the overwhelming conclusion that cis lactone formation should be the kinetically favoured pathway. The trans lactone (97) could of course be constructed from models, albeit with considerably more strain than was involved in the case of the cis isomer, and since an energy difference of only a few Kcal./mole suffices for specific product formation in kinetically competing reactions, it was felt that lactonisation had been accomplished affording the cis-fused  $\gamma$ -lactone (82), with complete exclusion of the trans isomer. N.m.r. data confirmed the homogeneity of the lactone acid (82) and subsequently g.l.c., spectral and ultimately X-ray evidence of its derivatives rigorously confirmed this contention. The incorporation of a carboxylic moiety into the molecular structure of (82) started to pay dividends in the subsequent reaction step.

A primary hydroxyl group had to be introduced at the

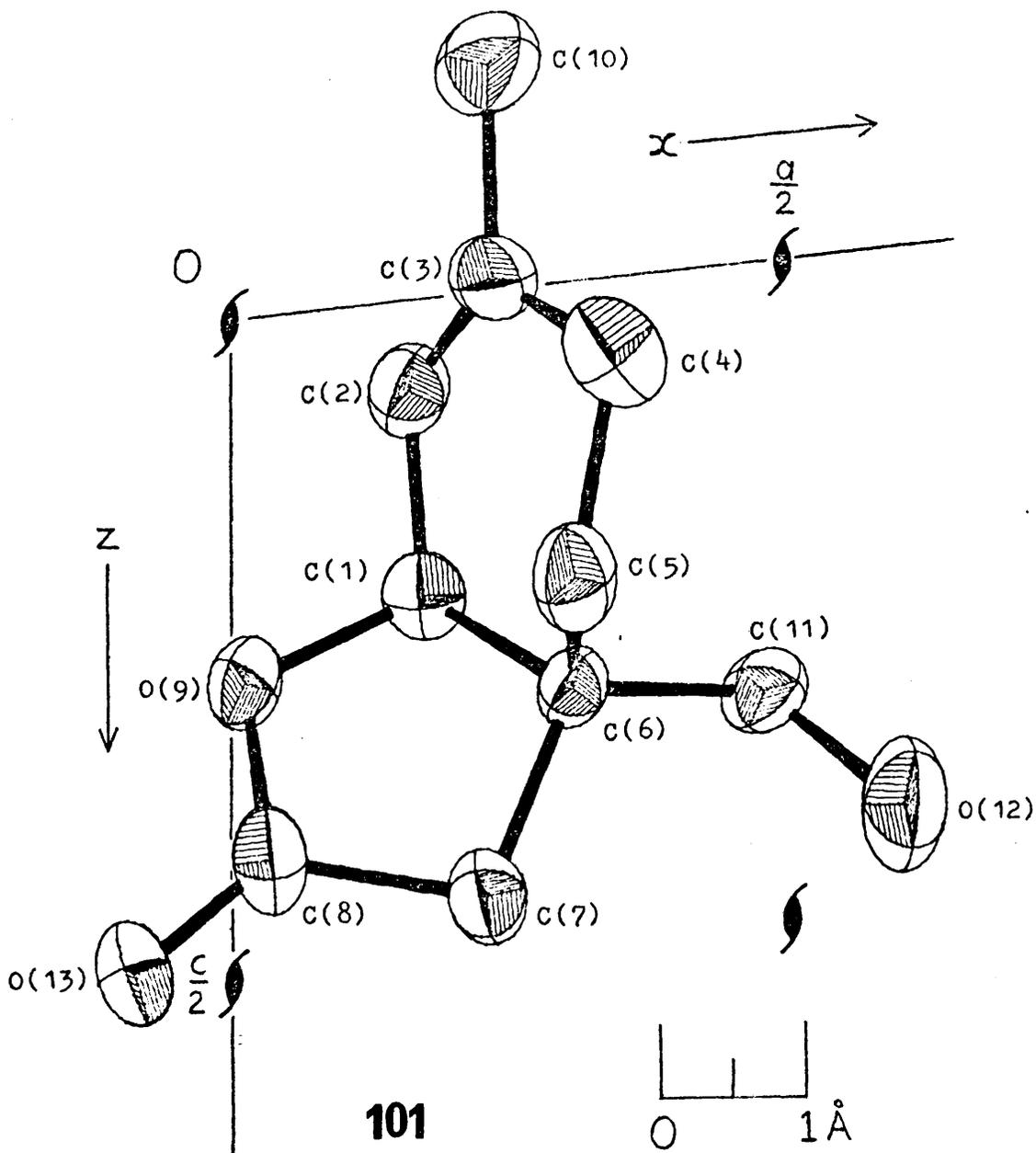


**82**

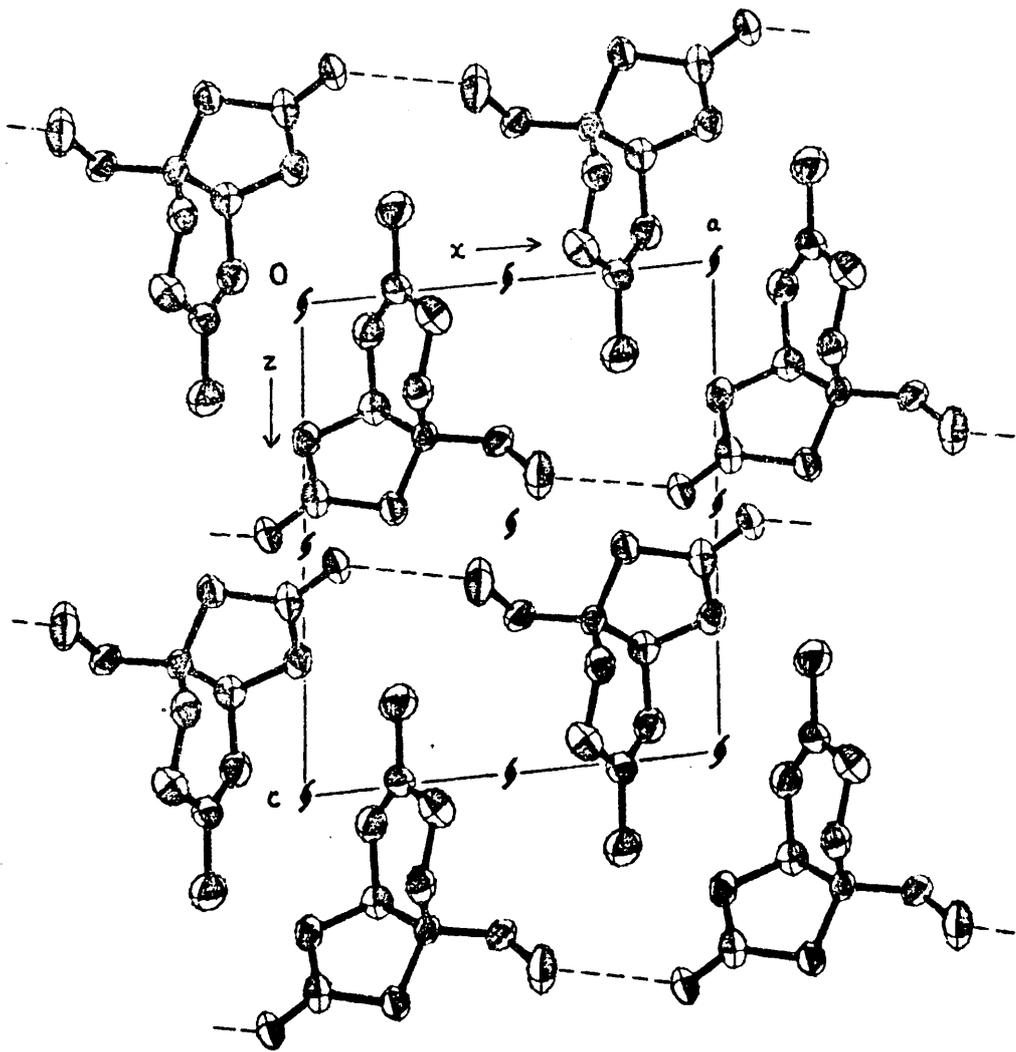
**98**

**99**

A/B ring junction in a sufficiently selective manner to take into account the highly electrophilic and sterically less congested  $\gamma$ -lactone carbonyl moiety. The method of choice utilised the acid chloride (98), which was readily available, as a highly hygroscopic solid, by exposure of of the  $\gamma$ -lactone acid (82) to oxalyl chloride in methylene chloride and dimethylformamide. Parenthetically, it may be noted that thionyl chloride proved a less effective reagent, even after prolonged reaction times. Reduction of acid chlorides with sodium borohydride is well-authenticated<sup>62</sup>, and generally has been found to proceed both rapidly and cleanly. Furthermore, sodium borohydride is not notably subject to ordinary steric effects, thus allaying any misgivings associated with the relative accessibility of the two reducible sites in the molecule (98). However, selective reduction proved to be decidedly troublesome. A large excess of reducing agent, in dry dioxan, over a period of 50 hours at room temperature resulted in over-reduction; i.r. data showed the absence of the  $\gamma$ -lactone carbonyl stretching frequency in the isolated product. On the other hand, the reaction of the acid chloride (98) with an equimolar quantity of sodium borohydride was extremely sluggish. It is superfluous to discuss the various reaction conditions employed in an attempt to achieve the requisite degree of selectivity;  $\gamma$ -lactone alcohol (99) was isolable in a number



The structure as seen in its b-axial projection



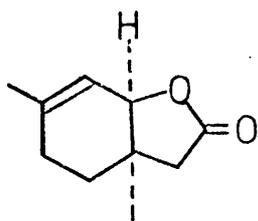
100

The arrangement of the molecules in the crystal

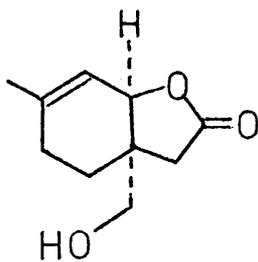
of runs, the yields never exceeding 30%. Optimum conditions were eventually hit upon. Thus, the acid chloride (98) was treated with a five-fold molar excess of sodium borohydride in dry dioxan for three hours at room temperature and then for a further 0.5 hour at 85°. Work-up afforded the  $\gamma$ -lactone alcohol (99) as a highly crystalline compound in an overall yield of 73% from the acid (82). This process was temperamental in nature, however, and was only consistently reproducible by adherence to rigorously formulated experimental conditions, and furthermore, it was only applicable on the 1-2 g. scale, since increases in reagent and reactant quantities resulted in correspondingly diminished yields. This result made a large scale synthesis of the alcohol (99) a tedious task, but since runs could be conducted simultaneously on several batches of the acid chloride (98), the speed of formation of (99) was not severely affected.

At this juncture, and in order to establish the stereochemistry of the  $\gamma$ -lactone alcohol (99) unequivocally, a direct method three-dimensional X-ray analysis was carried out on the molecule<sup>63</sup>. The results of this effort, shown in the appended diagrams (100) and (101), establish beyond any doubt the cis-fused nature of the ring skeleton, and confirm the earlier stereochemical speculations.

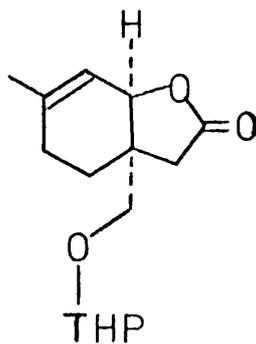
The satisfactory solution of the synthetic problem ass-



**9**



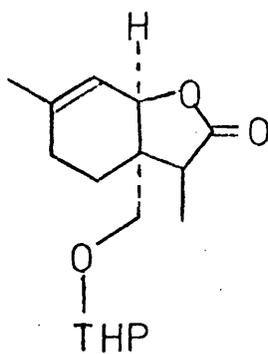
**99**



**102**

ociated with the alcohol (99) heralded a new phase in the approach towards verrucarol (80). The time had come to test the concepts alluded to in the initial appraisal of the overall synthetic strategy. Fundamental was the problem of  $\gamma$ -lactone ring expansion to a suitably functionalised oxadecalin derivative. The exploratory and encouraging work on the prototype, trichodermin (1), concurrently pursued in these laboratories, led to the reasonable belief that the  $\gamma$ -lactone alcohol (99) should be capable of analogous transformations.

The first task was the introduction of a methyl group adjacent to the  $\gamma$ -lactone carbonyl function in (99). An analogous alkylation had been achieved in the case of the corresponding lactone (9) in the trichodermin series<sup>53</sup>. The method of choice utilised lithium di-isopropylamide<sup>64</sup> and methyl iodide. Before proceeding with the methylation however, it was desirable to immunise the primary hydroxyl from the reaction conditions lest it should, in any way, interfere with the alkylation procedure. Consequently, treatment of (99) with dihydropyran in benzene and phosphorus oxychloride, over a period of 1.5 hours, allowed the isolation of the tetrahydropyranyl ether (102). Monoalkylation proceeded without difficulty. Thus, treatment of (102) with 1.1 equivalents of lithium di-isopropylamide in ether, followed by methyl iodide, afforded the methylated



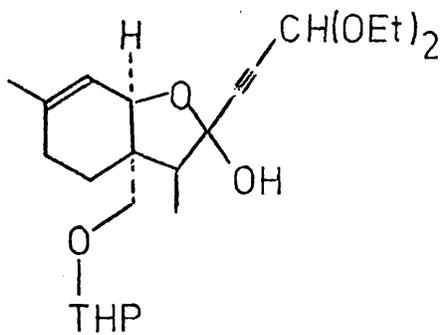
**103**



**104**



**105**

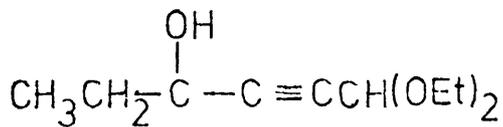


**106**

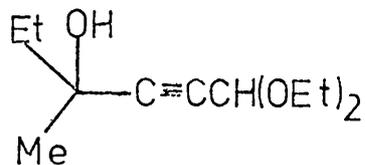
$\gamma$ -lactone (103), after column chromatographic purification, in an overall yield of 50% from (99). The alkylation warrants discussion from two standpoints. It was non-stereospecific and as such deviated from the analogous methylation in the trichodermin series. Whereas this in itself was of no consequence to the overall synthetic pursuit- the asymmetric centre was destined to be destroyed at a later stage- it had its ramifications in the t.l.c. behaviour of the compound. The material ran as a number of overlapping bands and gave prior warning that indiscriminate introduction of further asymmetry into the the molecule might present problems in the monitoring and isolation of reaction products. The use of a tetrahydropyranyl protecting group in the case at hand had two distinct drawbacks. It both created a new chiral centre and obscured a diagnostic region of the n.m.r. spectrum. These reservations appeared of minor significance with the realisation that the stage was set for a crucial elaboration of the lactone (103).

At the outset, it was intended to effect mono-addition of lithio 3,3-diethoxypropyne (105)<sup>65</sup> to the lactone (103) and subsequently elaborate the resulting hemi-acetal (106) to an oxadecalin system.

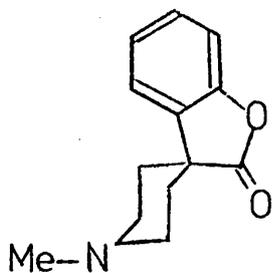
Lithio and magnesio salts of the acetylenic derivative (104) have, in the past, been employed in nucleophilic additions to both aldehyde and ketone functional groups.



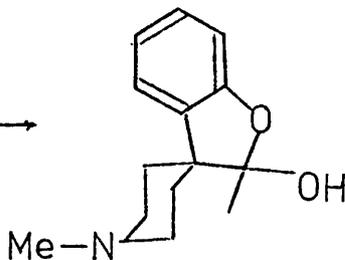
**107**



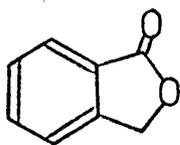
**108**



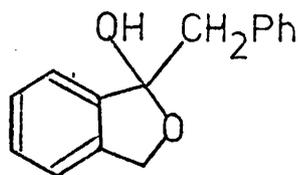
**109**



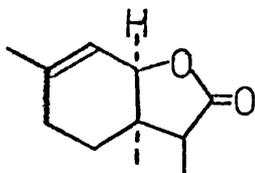
**111**



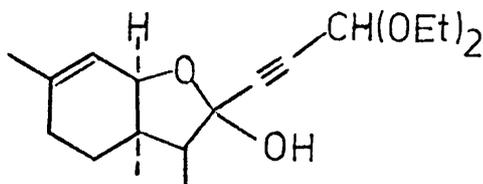
**110**



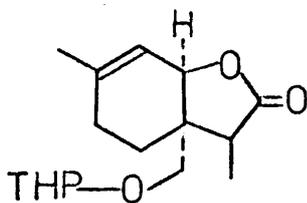
**112**



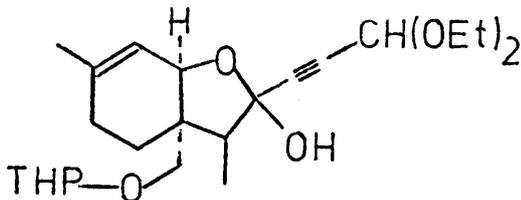
**8**



**113**



**103**

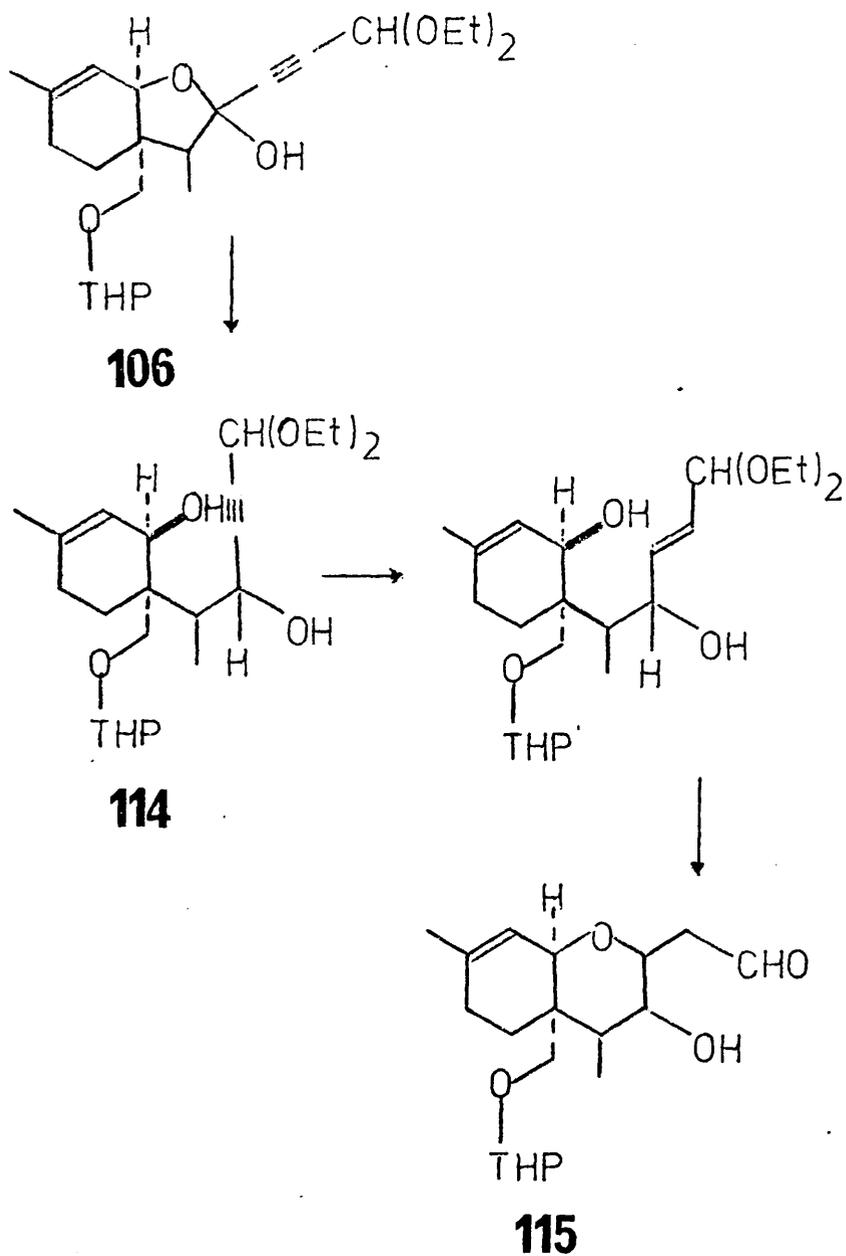


**106**

Thus Ward et. al.<sup>67</sup> achieved a 60% conversion of propionaldehyde to the corresponding secondary alcohol (107). Mauge and coworkers<sup>68</sup> similarly converted ethyl methyl ketone into the carbinol (108) and Corey et. al.<sup>65</sup> have employed this reagent in the synthesis of caryophyllene. No additions to lactones, however, have been recorded.

The choice of a  $\gamma$ -lactone as a synthetic intermediate was a discriminate one, however, arising from the knowledge that five-membered lactones tend to approximate to cyclohexanones in the behaviour of their carbonyl grouping towards some organometallic reagents. Grignard addition to the lactones (109) and (110) for instance, results in the incorporation of only one mole of reagent, affording the hemi-acetals (111)<sup>69</sup> and (112)<sup>70</sup> respectively. More reassuring was the knowledge that the lactone (8), on treatment with two molar equivalents of the lithio salt (105) furnished, in high yields, the hemi-acetal (113)<sup>53</sup>.

In the event, the  $\gamma$ -lactone-tetrahydropyranyl ether (103), under identical conditions, did not behave in the anticipated manner. T.l.c. and i.r. analysis of the reaction mixture pointed to the presence of both starting material and product (106) and preparative t.l.c., despite sacrificial cuts in the isolation of the newly-formed material, failed to remove the lactone contaminant (103). N.m.r. data was by no means unequivocal in a structural

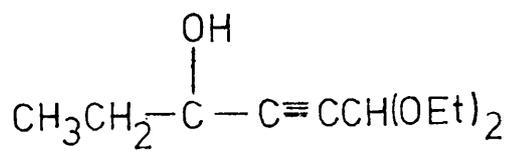


Scheme 14

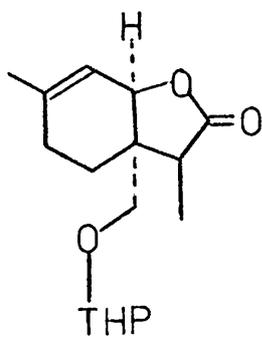
assignment of the isolated material but, nonetheless, had features compatible with the presence of the hemi-acetal (106). An extrapolation of the reaction sequence was called for with the crude material in hand, in the hope of achieving a satisfactory characterisation of the reaction products at a later stage.

Sodium borohydride reduction of (106) introduced another degree of complexity. This time the only tangible evidence which the reaction products offered as to their identity, was the high intensity hydroxyl bands in the i.r. In the forlorn hope that the crude mixture, nonetheless, contained the desired diol (114), two further reactions were carried out; sodium-liquid ammonia reduction of the acetylenic bond and subsequent acid catalysed rearrangement of any olefinic-diol to the chromanol (115) (Scheme 14). An examination of the multitude of products obtained at the end of this reaction sequence showed that this portmanteau approach had not been successful; no chromanol was in evidence.

A considerable amount of both time and effort was devoted to circumventing what was considered to be the prime-cause of all subsequent difficulties - the addition of the lithio salt (105) to the lactone (103). However, varying reagent quantities, reaction times and the utilisation of Grignard derivatives of the acetylene (104)



**107**

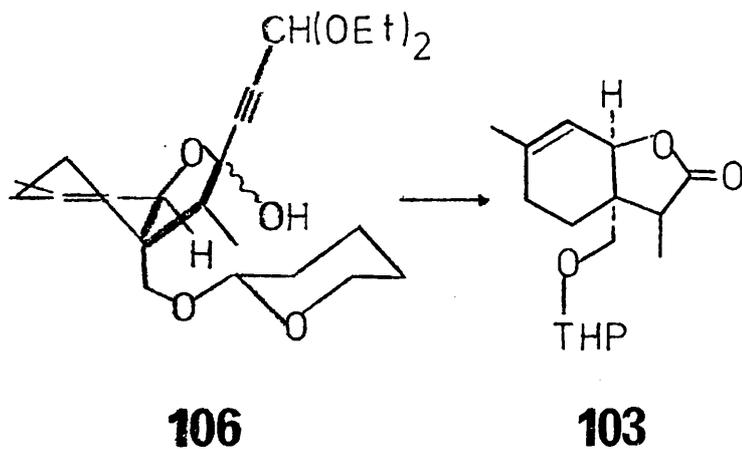


**103**

offered no solution to the problem.

A reappraisal of the verrucarol synthesis was called for in terms of overcoming the destructive influence of the tetrahydropyranyl protecting group. Wherein lay the inability of the lactone (103) to undergo complete conversion to the hemi-acetal? The evidence assembled in a large number of runs strongly suggested that the lithio-acetylide addition was capable of undergoing reversal, as was evidenced by the complete inability to isolate a reasonably pure sample of the hemi-acetal (106). This contention found justification in the work of Heilbron et. al.<sup>71</sup> who failed to obtain a pure sample of the alcohol (107) and whose results have been rationalised by Ward and coworkers<sup>67</sup>, suggesting decomposition of the compound (107) into its parent components. Mauge et. al.<sup>68</sup>, in fact, have demonstrated the instability of (107), showing it to be converted into propionaldehyde and 1,1-diethoxy-prop-2-yne (104) on heating to 140°.

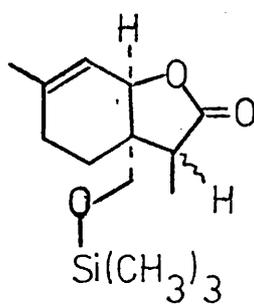
The function of the tetrahydropyranyl linkage can be but one therefore - to encourage the equilibrium to the side of the addends and thus render hemi-acetal formation a thermodynamically unfavourable process. It may well be that the steric bulk associated with the protecting group in (103) is such as to congest the proximity of the  $\delta$ -lactone carbonyl group. This congestion then reflects itself



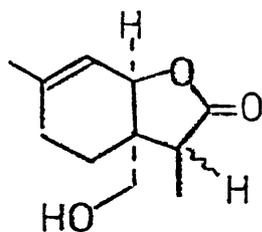
Scheme 15



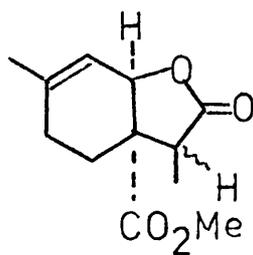
**116**



**117**



**118**



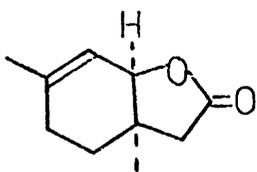
**119**

in a corresponding increase in the ground-state energy of the hemi-acetal (106) and its subsequent facility to extrude any nucleophilic addend in order to revert to its former state of  $sp^2$  hybridisation (Scheme 15).

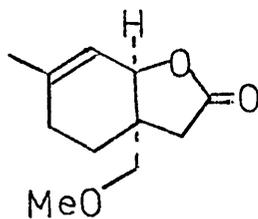
A different protecting group for the primary hydroxyl in (99) was required and the trimethylsilyl derivative (116) was readily available by treatment of the lactone-alcohol (99) with trimethylsilyl diethylamide in acetone.

Alkylation of (116) with lithio di-isopropylamide/methyl iodide again afforded a mixture (4:1) of epimeric lactones (117), as evidenced by n.m.r. and g.l.c. analysis. The trimethylsilyl group, however, did not engender the requisite degree of protection demanded by reaction conditions and on treatment with the lithio salt (105) underwent cleavage of the O-Si bond to afford the lactone (118). Stork and coworkers<sup>72</sup> have employed the addition of methyl lithium to trimethylsilyl enolates in their investigations of specific enolate formations of ketones and the above observation serves to demonstrate the high degree of nucleophilicity associated with the lithio-acetylide (105).

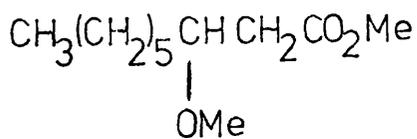
Equally unsuitable was the use of the lactone-ester (119). It had been obtained by alkylation, with lithio di-isopropylamide/methyl iodide, of the lactone acid (82) and subsequent esterification with ethereal diazomethane. Once more a mixture of epimeric lactones was isolated



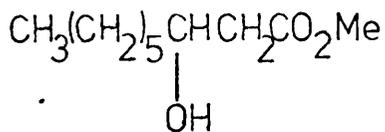
**9**



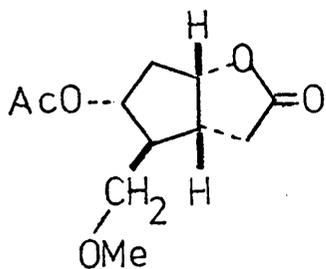
**120**



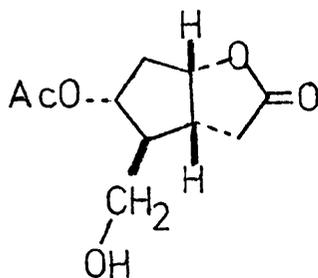
**121**



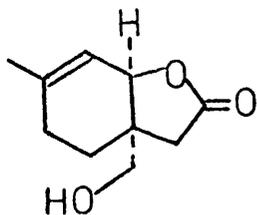
**122**



**123**



**124**



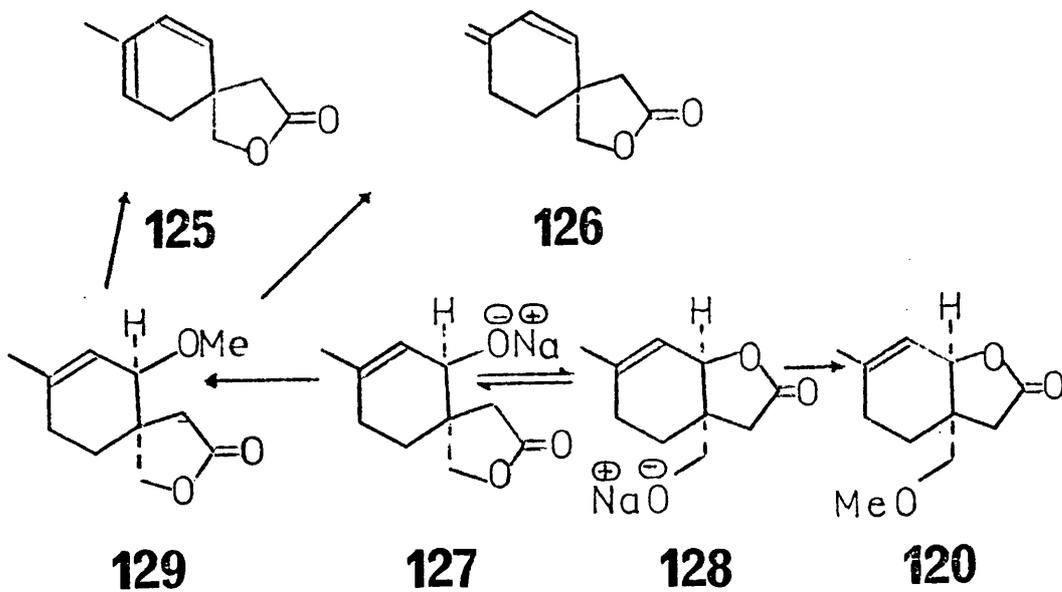
**99**

which on treatment with (105) led to a gamut of products resulting in the abandonment of the reaction.

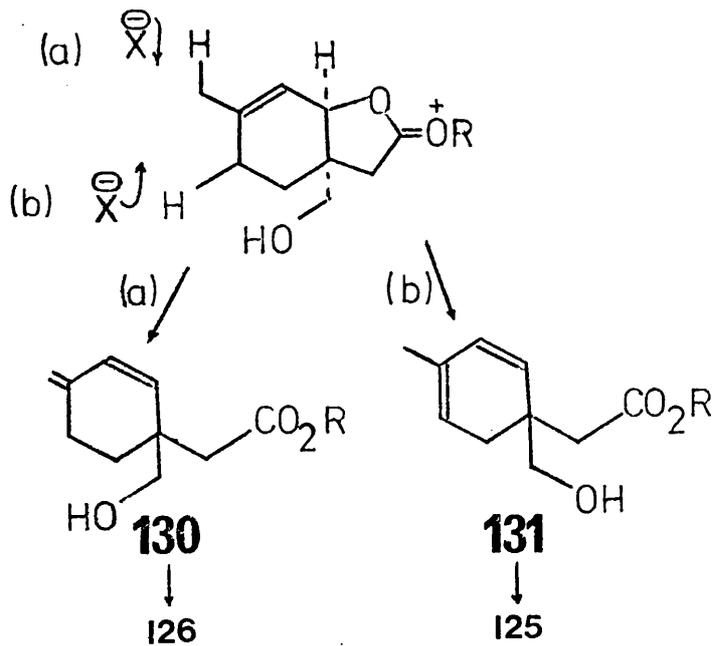
If steric reasons were germane to the difficulties observed in the previous discussion it was logical to concentrate on the use of a protecting group which closely approximated to the inoffensive, angular methyl group of the lactone (9). As a result studies were directed towards the obtention of the methyl ether (120).

Of late there have been a number of sufficiently mild methods developed for the cleavage of methyl ethers in aliphatic systems. Thus treatment of optically active ether (121) with carbon tetrachloride/iodine/sodium borohydride had allowed the isolation of the alcohol (122) without racemisation<sup>73</sup> and Corey et. al.<sup>36</sup> have employed boron tribromide in their conversion of the ether (123) into (124). In the event of a successful synthesis of (120) and subsequent elaboration of the molecule, it was anticipated that the use of either reagent would have allowed the methylated primary hydroxyl to be regenerated.

Unfortunately methylation of (99) was not easily achieved and, in the end, in 30% yield at best. The methods employed were manifold and made use of the many standard procedures recorded in the literature for achieving such objectives<sup>74</sup>. The reagents employed are recorded briefly in the experimental section and mostly were



Scheme 16

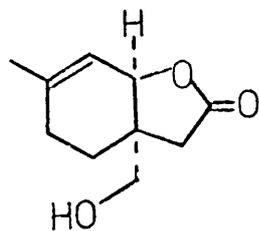


Scheme 17

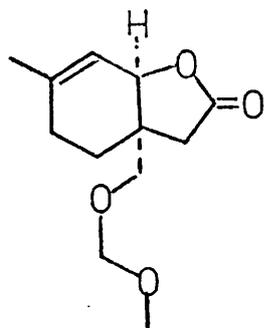
without effect, starting material invariably being recovered. However, when the  $\delta$ -lactone alcohol (99) was treated with an excess of sodium hydride in dimethylformamide<sup>75</sup> for 2 hrs. at 80°, followed by addition of methyl iodide and further heating for 15 hrs., the methyl ether (120) could be isolated by preparative t.l.c. in a depressingly low yield of 8%. The primary product of this reaction was a 2:1 mixture of the isomeric spiro-lactones (125) and (126) as indicated by n.m.r. This unexpected transformation may be explicable on the grounds of base induced equilibration of the lactone alkoxides (127) and (128), either of which is capable of being trapped by methyl iodide. The secondary allylic ether (129) then thermolytically extruding methanol with the formation of the dienes (125) and (126) (Scheme 16).

Formation of these spiro-lactones was not confined to the above-mentioned reaction, but was also observed on exposure of the  $\delta$ -lactone alcohol (99) to methyl fluoro-sulphonate<sup>76</sup> and triethyloxonium fluoroborate, in methylene chloride, at ambient temperature. Mechanistically the spiro-lactones may be considered to arise by fragmentation of the lactone ring to afford the esters (130) and (131), intramolecular esterification then leading to (126) and (125) respectively (Scheme 17).

By reducing the contact time between sodium hydride



**99**

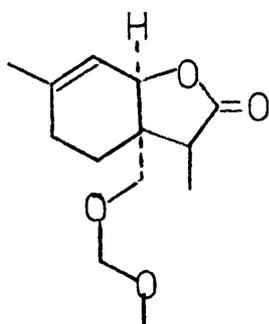


**132**

and the lactone (99) to 0.5 hr. and then proceeding in the previously described manner, yields of the methyl ester (120) were raised to 30%. This in itself, however, was far from satisfactory in a projected synthetic scheme necessitating a large number of complex transformations. Because of this and in view of the fact that work channelled along marginally different lines was showing the first signs of real success, the methyl ether (120) was discounted from being of further utility.

Chlorodimethyl ether has been employed in the protection of hydroxylic substituents; its use, however, has been largely confined to phenols<sup>77</sup> and has not been extended to aliphatic systems in any large degree. Its synthetic utility is twofold: it does not introduce any additional asymmetry into the molecular structure and its effect upon the n.m.r. spectrum is minimal, normally consisting of two singlets at  $\tau$  6.6 and  $\tau$  5.4.

At the outset attempts were made to effect conversion of the  $\delta$ -lactone alcohol (99) into its methoxymethyl derivative (132) by treatment of (99) with pyridine and chlorodimethyl ether in methylene chloride. These efforts proved singularly unsuccessful, invariably affording starting material. However, on dispensing with methylene chloride as cosolvent, and working with neat reagents, (132) could be isolated in 53% yield after chromatographic

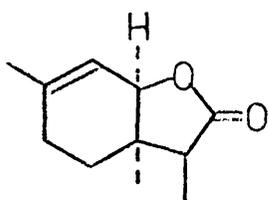


**133**

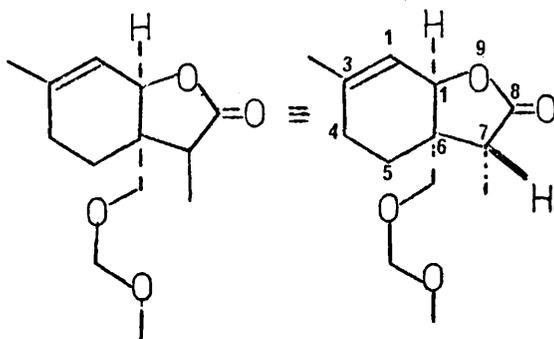
purification. The method involved addition of chlorodimethyl ether to a solution of the lactone (99) in dry pyridine, work-up and threefold recycling then furnishing the desired methoxymethyl-lactone (132). By reversing this procedure, viz. adding the pyridine to a solution of the lactone (99) in chlorodimethyl ether, the yields are markedly reduced, a by-product of the reaction being the spiro-lactones (125) and (126). This, in view of the results with methyl fluorosulphonate, hinted that formation of (132) involved heterolysis of chlorodimethyl ether and capture of the methoxymethyl carbonium ion by the lactone primary hydroxyl group.

The method was tedious and alternative experimental conditions were sought in an effort to improve yields and shorten the reaction times. When the  $\gamma$ -lactone (99) was treated with a twenty-fold excess of sodium hydride for a few minutes at 65° and the mixture then cooled and treated with chlorodimethyl ether, the lactone ether (132) was again obtained in 52% yield. In view of the simplicity of the procedure this became the method of choice in all subsequent runs.

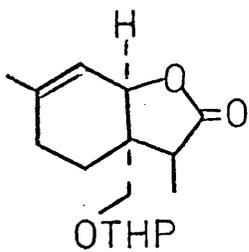
When the lactone (132) was treated with lithio diisopropylamide<sup>64</sup> and methyl iodide, the methylated lactone (133) was isolated in quantitative yield. Furthermore, the alkylation proved to be stereospecific, the compound



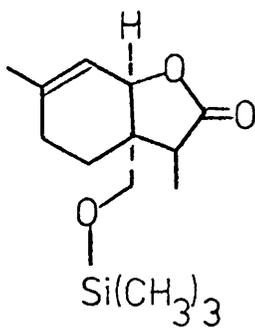
**8**



**133**



**103**

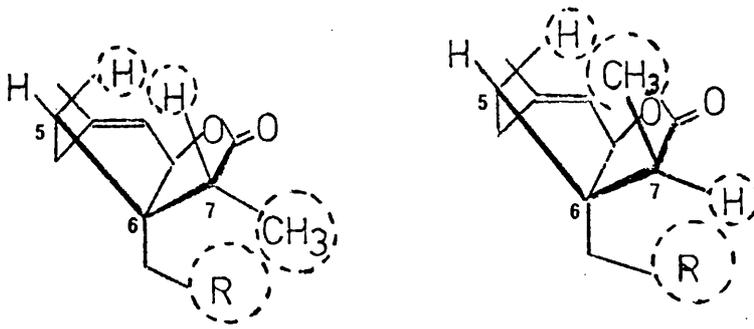


**117**

appearing as a single sharp peak on g.l.c. with its n.m.r. spectrum exhibiting a clean doublet for the C<sub>7</sub> methyl group.

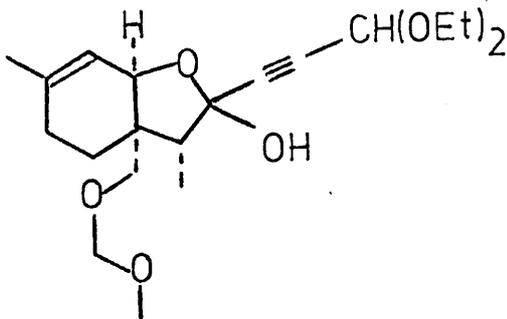
It may be useful to recap that of the five lactones alkylated in these investigations, under essentially identical conditions, only (9) and (132) showed total specificity in their incorporation of the methyl group. By analogy with cis-fused decalins<sup>78</sup> it may be argued that alkylation, under conditions of kinetic control, would be expected to proceed from the sterically more accessible convex side of the molecule. It seems likely, however, that the methylated lactones correspond to products arising as a result of thermodynamic control and the results for each methylation will have to be rationalised in terms of the energy inherent in the individual diastereomers.

The lactones (8) and (133) differ in one important aspect from (103) and (117). This difference lies in the steric bulk of the angular substituent in the latter group of compounds. The interaction between an  $\alpha$  disposed C<sub>7</sub> methyl and the angular grouping being sufficiently significant to give rise to some of the  $\beta$  isomer. With the lactones (8) and (133) the reduced C<sub>6</sub>-C<sub>7</sub> substituent interaction has to be tempered with a corresponding C<sub>5</sub>-C<sub>7</sub> nonbonded repulsion, the latter assuming sufficient importance for the reaction products to become exclusively



R = OTHP, OSi(CH<sub>3</sub>)<sub>3</sub>, H, OCH<sub>2</sub>OCH<sub>3</sub>

Diagram 1

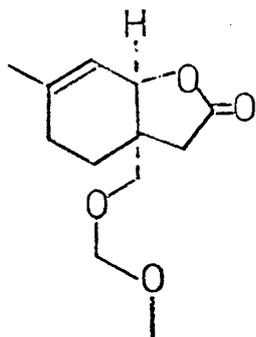


134

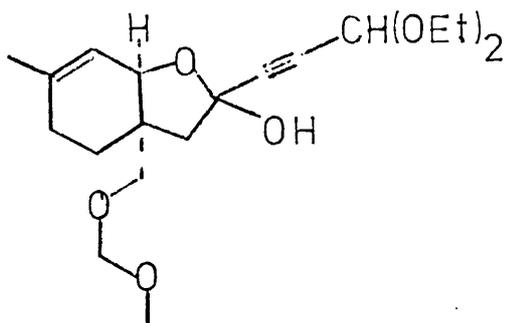
the  $\alpha$ -C<sub>7</sub> methyl isomers (Diagram 1).

Arguments of this nature are tenuous in the extreme and in the absence of further evidence the  $\alpha$  assignment of the C<sub>7</sub> substituent in (133) has to be treated with the caution which it warrants.

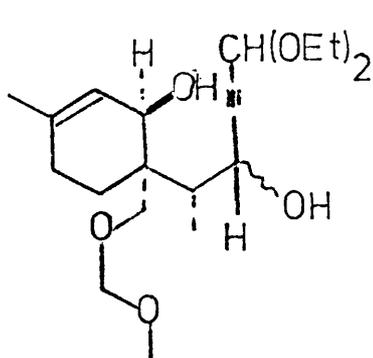
A large amount of time had been invested in arriving at a molecular structure (133) which now had to be subjected to the very conditions which had proven to be abortive in the case of the  $\gamma$ -lactone-tetrahydropyranyl ether (103). The stereochemical complexities of (103)- four diastereomers had been present -had been circumvented and the steric size of the tetrahydropyranyl grouping reduced to that of an unbranched array of carbon and oxygen atoms. The question of how the recalcitrant carbonyl moiety would behave towards nucleophilic attack was quickly resolved. Lithio 3,3-diethoxy propyne and (133) were allowed to react at -78° and the mixture warmed to room temperature over one hour. The i.r. spectrum of the crude material pointed to the presence of a weak lactone band at 1770 cm.<sup>-1</sup> also exhibiting an intense hydroxyl stretching frequency. The presence of a little starting material was also evidenced by t.l.c. Preparative t.l.c. furnished a reasonably pure sample of the hemi-acetal (134) exhibiting, nevertheless, a weak  $\gamma$ -lactone band in its i.r. spectrum. It was clear, however, that the reaction had been a success.



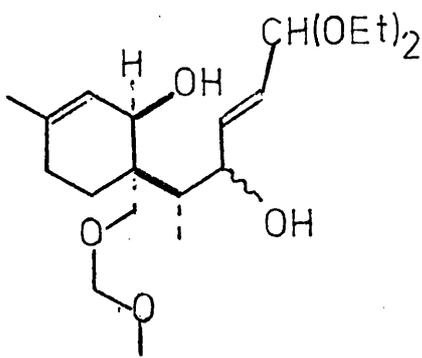
**132**



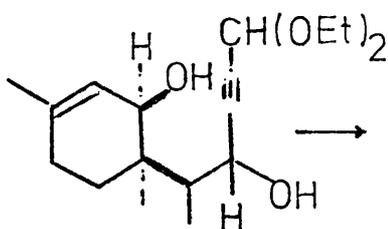
**135**



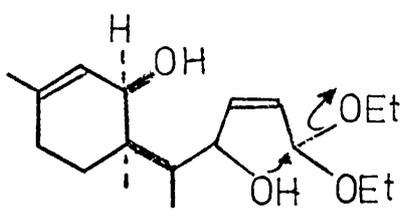
**136**



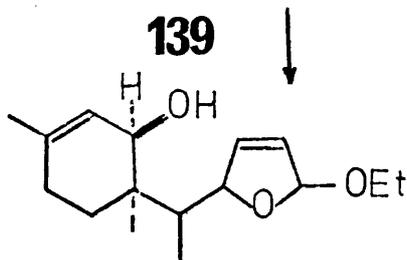
**137**



**138**



**139**



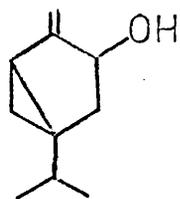
**139a**

**Scheme 18**

It may be mentioned that the nor methyl lactone (132), on treatment with the lithio acetylide (105) had afforded the hemi-acetal (135) in near quantitative yield, lending credence to the concept of steric interactions as a major cause for the retro-acetylene reaction.

Treatment of the hemi-acetal (134) with an excess of sodium borohydride in aqueous ethanol proceeded smoothly and the diol (136) was isolable as a tightly running band, after preparative t.l.c., in an overall yield of 50% from the lactone (132).

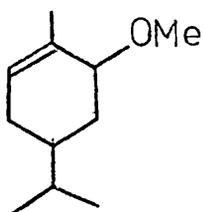
It was then required to effect a partial reduction of the acetylenic bond in (136) to give the olefinic-diol (137). In the trichodermin series a selective reduction had been achieved employing Lindlar catalyst<sup>79</sup>. Whereas the reduction of the diol (138) had proceeded without difficulty to afford the cis olefinic-diol (139), subsequent attempts to bring about hydrolysis of the acetal linkage, however, had resulted in the obtention of the furan (139a), see Scheme 18. In order to circumvent this problem it was decided to use sodium-liquid ammonia<sup>53, 67</sup> and prepare the trans olefinic-diol (137). Such an approach, however, was tempered with a considerable degree of caution, since it is a well established fact that benzylic and allylic ethers and alcohols are capable of undergoing hydrogenolysis with cleavage of the C-O bond<sup>80</sup>.



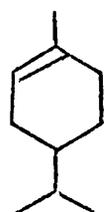
**140**



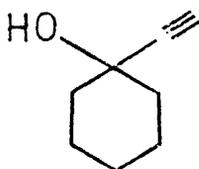
**141**



**142**



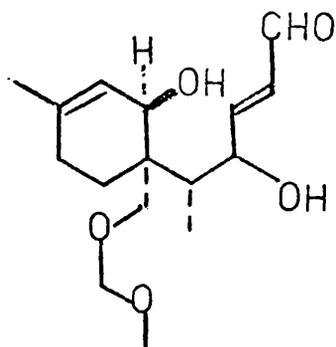
**143**



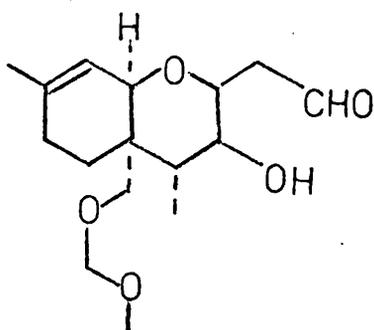
**144**



**145**



**146**

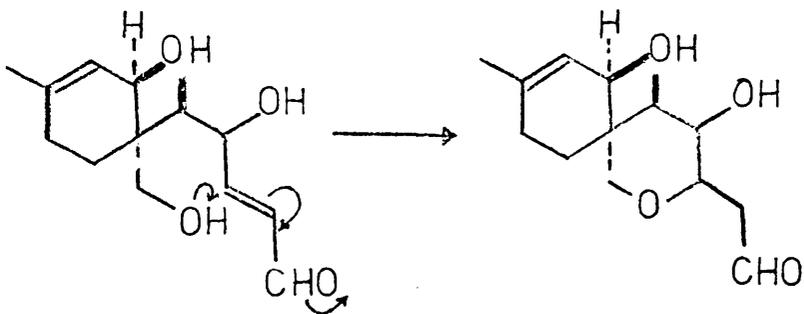


**147**

The fission of allylic alcohols in this manner is often encountered in terpene chemistry, viz. the conversion of sabinol (140) into  $\alpha$ -thujene (141)<sup>81</sup>; similarly (142) gives rise to (143)<sup>82</sup> and the acetylenic carbinol (144) is converted into the olefin (145)<sup>81</sup>.

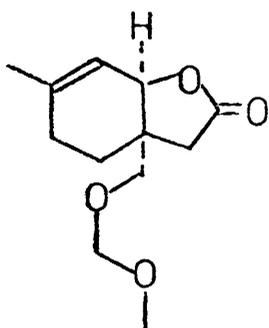
The diol (136) is richly endowed with reducible sites, no less than two allylic alcohols and a similar number of allylic ethers being in evidence. The frail nature of this array of functionality was immediately obvious, since only prolonged experimentation involving variations in reagent quantities and reaction times, afforded acceptable yields of the olefinic-diol (137). The course of the reduction was easily monitored by t.l.c., the olefinic-diol (137) staining with a characteristic cherry-red colour on development with Ceric (III) spray.

It was then intended to hydrolyse the diethyl-acetal linkage to the corresponding  $\alpha, \beta$  unsaturated aldehyde (146) and subsequently bring about an intramolecular Michael addition to the chromanol (147). Special mention, however, should be made of the simple fact that the molecule possessed two hydroxyl functions, the primary grouping protected as an acetal moiety. It was with trepidation that the hydrolysis was approached, since it was abundantly clear that only a selective cleavage of the diethyl-acetal could be tolerated at this juncture. Freeing the

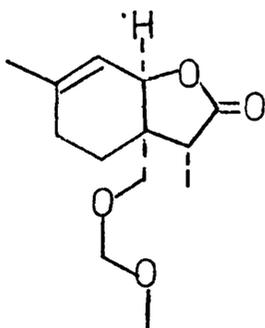


**148**

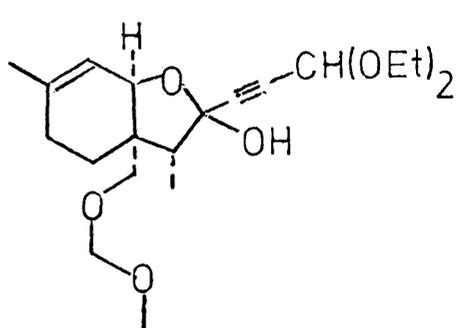
**Scheme 19**



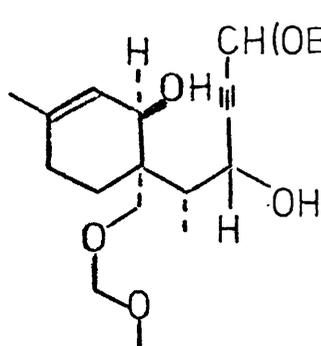
132



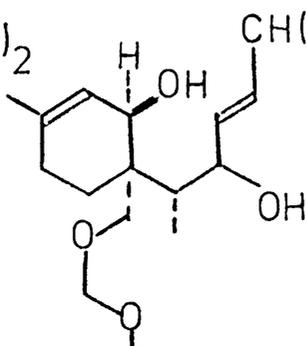
133



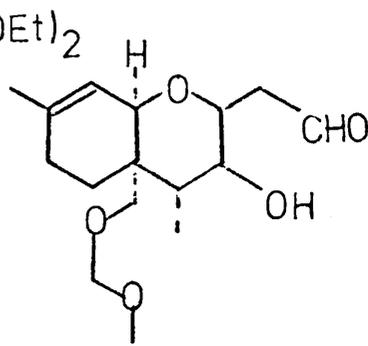
134



136



137



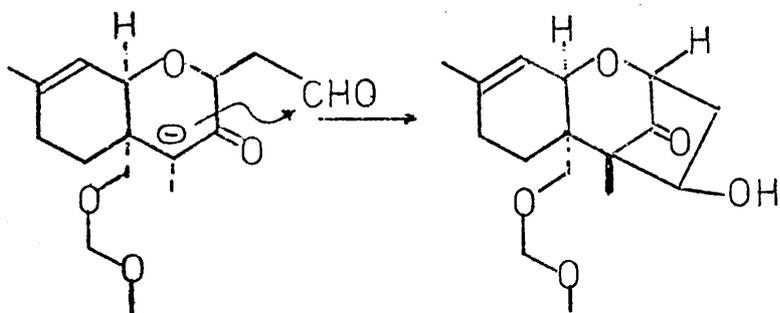
147

**Scheme 20**

primary hydroxyl of its protection could result in its competition for the  $\alpha, \beta$  unsaturated aldehyde linkage leading to the spiro compound (148), as shown in Scheme 19.

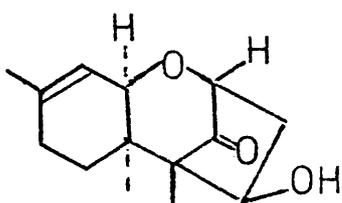
In the event, treatment of (137) with buffered acetic acid at room temperature for 18 hours allowed the chromanol (147) to be isolated in an overall yield of 24% from the  $\gamma$ -lactone (132). None of the alternate Michael product (148) was observed. The molecule (137) had behaved admirably; not only did acetal hydrolysis occur in a selective manner, but the desired Michael addition had proceeded concurrently. In view of all the aforementioned difficulties the obtention of (147) was viewed with immense satisfaction, since it vindicated all the earlier speculations pertaining to an overall synthetic approach towards verrucarol (80). From a practical point of view it should be mentioned that the transformations depicted in Scheme 20 were best carried out by deleting purification procedures at the individual stages. This resulted in an overall improved yield for the chromanol (147).

It was then required to bring about a ring closure between carbon atoms 4 and 5 resulting in the formation of a trichothecane skeleton. It was originally anticipated that this objective could be realised by an internal aldol condensation of the keto-aldehyde (149) utili-

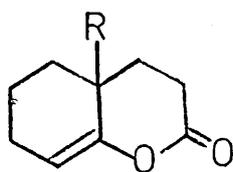


**149**

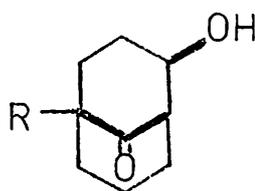
Scheme 21



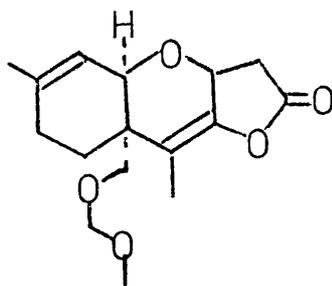
**150**



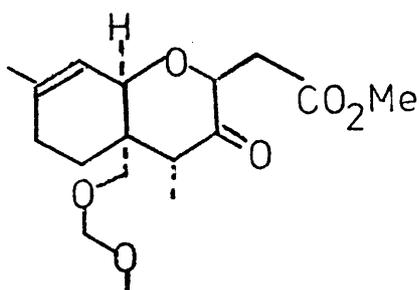
**151**



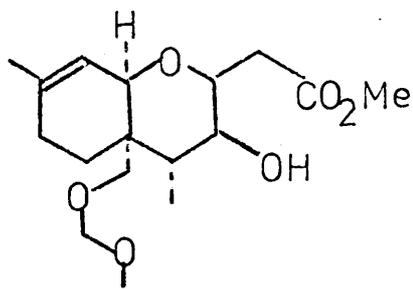
**152**



**153**



**154**

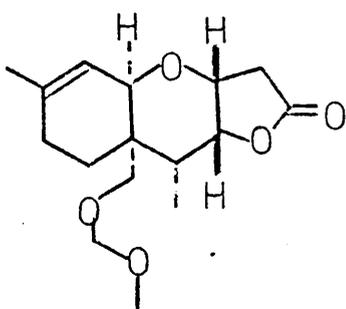


**155**

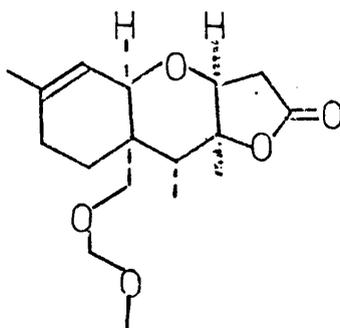
sing the suitably disposed carbanion at C<sub>5</sub> and the aldehyde group (Scheme 21). Normal aldol conditions, as work in the trichodermin synthesis had forcibly demonstrated<sup>53</sup>, were to no avail in as much as the aldol product (150) was never isolated. As a result an alternative route was employed.

It has been shown that enol lactones of type (151) are capable of undergoing reductive cyclisation to yield bicyclo[3,3,1]nonane derivatives (152)<sup>83</sup> with lithium hydridotri-*t*-butoxyaluminum<sup>84</sup>. The two most striking features of the rearrangement, the necessity for a double bond to be exocyclic to the lactone ring in the substrate, and the stereospecificity of the process leading to the bicyclic ketol, have been accommodated in a proposed mechanism for this transformation<sup>83</sup>. Efforts were thus channelled towards a synthesis of the enol lactone (153).

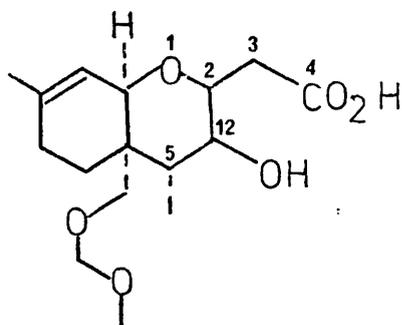
Oxidation of the hydroxy-aldehyde (147) with Cornforth's reagent<sup>85</sup> afforded, apart from considerable quantities of polymeric material, an acid fraction which, on treatment with ethereal diazomethane, and preparative t.l.c. furnished two crystalline compounds. The less polar one, isolable in 8% yield, was shown to be the keto-ester (154) by n.m.r., i.r. and analytical data. The more polar compound was the hydroxy-ester (155) obtained in 30% yield. The relative inaccessibility of the secondary hydroxyl



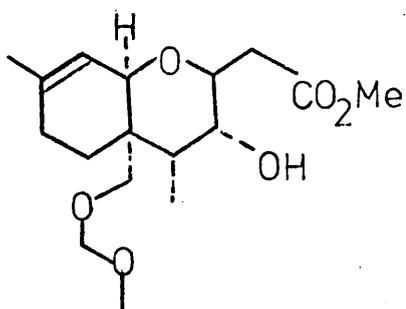
**156**



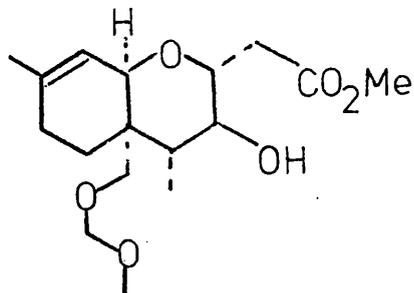
**157**



**158**



**155A**

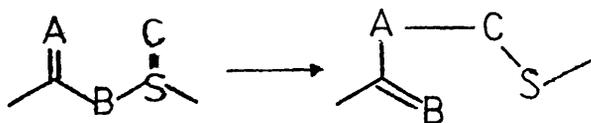


**155B**

group to the oxidising agent is reflected in the ratio of the isolated products, since it is a well-authenticated fact that oxidation of alcohols normally proceeds at a faster rate than that of aldehydes<sup>86</sup>. The neutral fraction afforded a small quantity of a product exhibiting a strong  $\gamma$ -lactone band in the i.r. G.l.c. showed it to be a mixture of two components to which structures (156) and (157) were tentatively assigned.

The small amount of lactonic material obtained in the oxidation raises an interesting point as to the stereochemical make-up of the hydroxy-ester (155). It may be anticipated that any cis orientated hydroxy-acid (158), as a consequence of the Cornforth work-up procedure, involving acidification of the reaction mixture, would have undergone cyclisation to afford the lactones (156) and (157). Isolation of the hydroxy-acid (158) implies that the C<sub>2</sub>-C<sub>12</sub> substituents are in a trans relation to one another and that the hydroxy-ester (155) corresponds to a mixture of diastereoisomers with the relative configurations (155a) and (155b).

The next stage in the drive towards the enol lactone (153) was the oxidation of the hydroxy-ester (155) to the corresponding keto-ester (154). This was readily achieved, in 85% yield, employing dicyclohexylcarbodiimide - dimethyl sulphoxide<sup>87</sup>. In an attempt to eliminate two

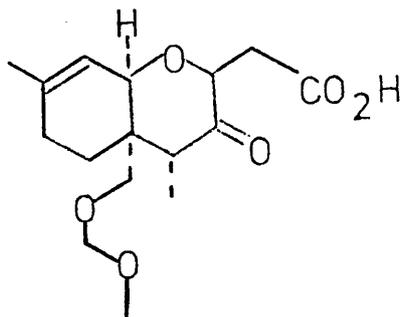


A=B=C=Carbon, vinyl sulphonium ylid rearrangement;

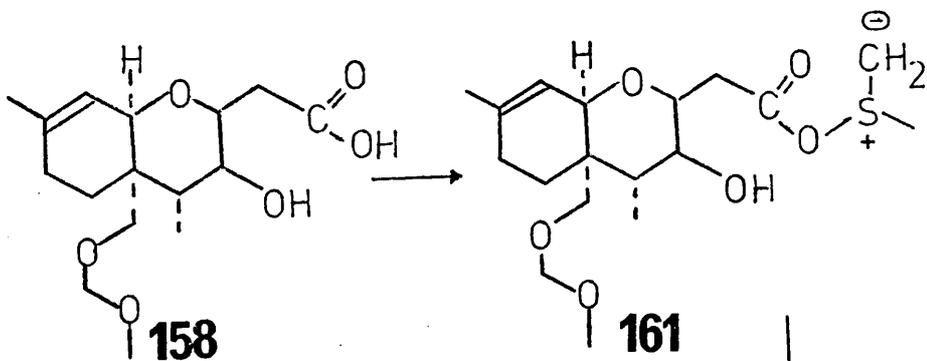
A=B=Oxygen, C=Carbon, Punmerer rearrangement;

A=Oxygen, B=C=Carbon, Stevens rearrangement<sup>90</sup>.

### Scheme 23

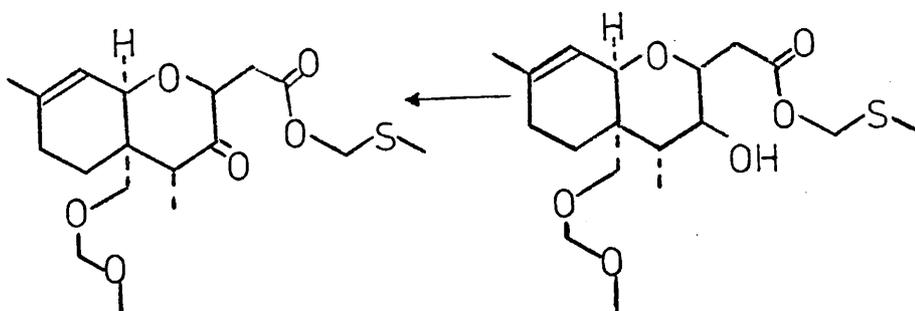


**159**



**158**

**161**



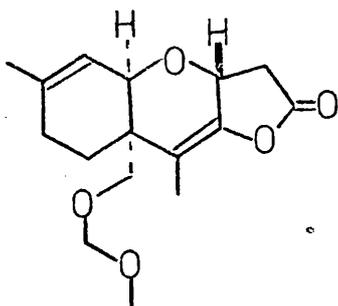
**160**

Scheme 22

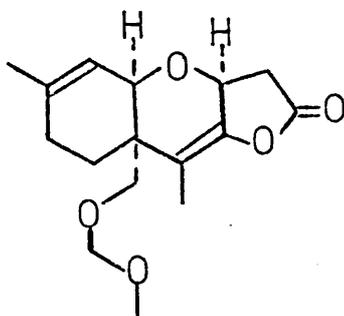
reaction steps from the overall conversion of the hydroxy-aldehyde (147) into the keto-acid (159), it was at one stage decided to attempt oxidation of the hydroxy-acid (158) under the above-mentioned conditions. Indeed, a small quantity of (159) was obtained, the primary product of the reaction, however, being the thioester (160). To account for its formation one has to invoke a dicyclohexylcarbodiimide induced condensation between dimethyl sulphoxide and the hydroxy-acid (158), a [2,3]-sigmatropic rearrangement of the ylid (161) and subsequent oxidation as shown in Scheme (22). Obtention of the thioester (160) may be likened mechanistically to the transformations observed in the Pummerer rearrangement<sup>88</sup> and the conversion of vinyl sulphonium ylids to thioethers<sup>89</sup> (Scheme 23)

Subsequently it was discovered that Jones oxidation<sup>55</sup> of the hydroxy-aldehyde (147), followed by esterification and preparative t.l.c. also afforded the keto-ester (154) in 30% yield. This simplification of the reaction procedure had been initially discounted in view of the suspected acid lability of the acetal linkage in (147). That these fears were inconsequential was forcibly illustrated by the great difficulty with which the acetal moiety lends itself to hydrolytic cleavage.

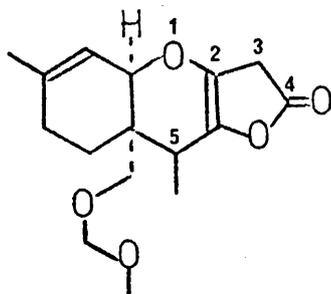
With the obtention of the keto-ester (154) the



**153 A**



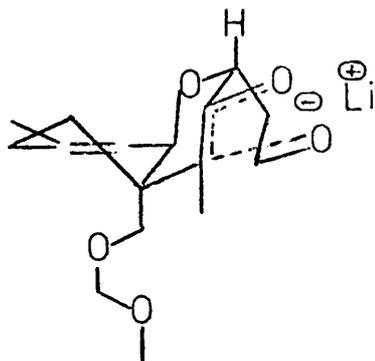
**153 B**



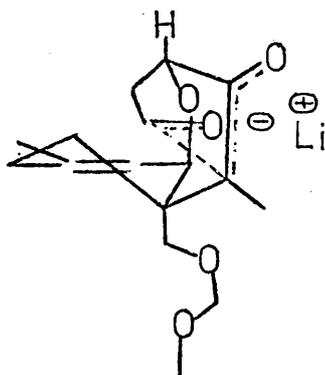
**162**

approach towards verrucarol (80) entered its final phase. In order to convert (154) into the enol lactone (153), the keto-ester was hydrolysed with dilute sodium hydroxide in methanol to the keto-acid (159) and the latter compound refluxed with three equivalents of sodium acetate in acetic anhydride<sup>91</sup> over a period of 3 hours. This gave rise to two compounds as indicated by both t.l.c. and g.l.c. Careful and not always reproducible preparative t.l.c. allowed a separation of the mixture into two viscous oils. I.r. and high resolution mass spectral data were indicative of enol lactones with a molecular formula of  $C_{16}H_{22}O_5$  and structures (153a) and (153b) were assigned on the basis of n.m.r. evidence without being able to differentiate between the two compounds.

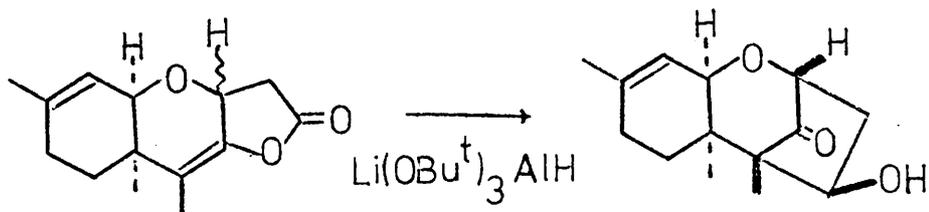
The possibility of the presence of the enol lactone (162) was discounted, the structure being incompatible with the n.m.r. data at hand. Thus both enol lactones exhibited an eight line AB part of an ABX system, the coupling constants  $J_{AX}$  and  $J_{BX}$  being 11.81 Hz., 9.5 Hz. and 7.19 Hz. and 11.5 Hz. respectively. The presence of (162) would necessitate one to postulate an ABX system comprising the protons at  $C_3$  and  $C_5$ . Theoretical predictions of homoallylic coupling constants, based on valence-bond formalisms, predict a maximum coupling of 4.99 Hz.<sup>92</sup> and experimental evidence tends to support this<sup>93</sup>.



Scheme 24



Scheme 25



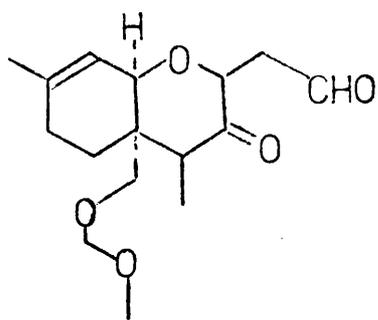
**163**

**150**

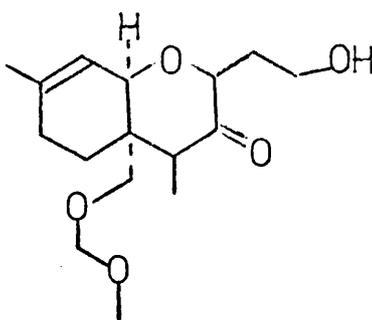
It would be unreasonable to ascribe a twofold increase in the magnitude of the homoallylic couplings in order to accommodate structure (162). On the basis of this evidence, as well as the chemical shift which one would have to ascribe to the allylic C<sub>5</sub> methine proton,  $\delta$  5.4 in the case in point, the enol lactone (162) was discounted from being a reaction product.

Of the two epimeric enol lactones (153a) and (153b) only the  $\beta$  epimer was capable of giving rise to a trichothecane-like skeleton on reductive cyclisation. It was argued a priori that the transition state leading to the trichothecane carbocyclic ring system would, in any event, be the energetically more favourable one (Scheme 24). The unfavourable disposition of rings A and C in the alternate pathway (Scheme 25), involving (153b), was clearly seen from molecular models. Work in the trichodermin series had vindicated this belief in the sense that only the ketol (150) was the only tricyclic material isolated from a mixture of the epimeric lactones (163)<sup>53</sup>.

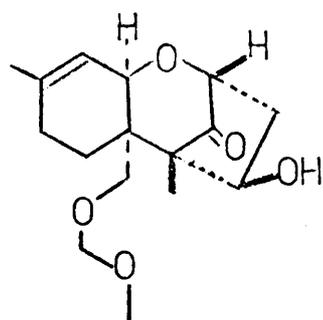
However, the enol lactones (153a) and (153b) failed to undergo cyclisation on treatment with lithium hydrido-tri-*t*-butoxyaluminate in ether. The reaction products were investigated for any high carbonyl stretching frequencies, associated with bicyclo[3,2,1]octan-8-ones<sup>94</sup>, but to no avail. Starting material was usually recovered



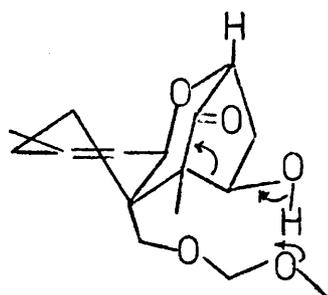
**164**



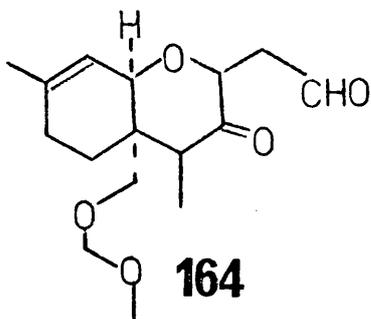
**165**



**166**

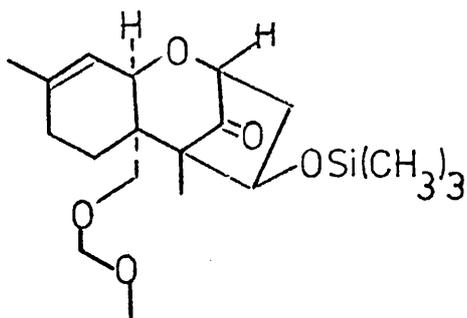


**166**

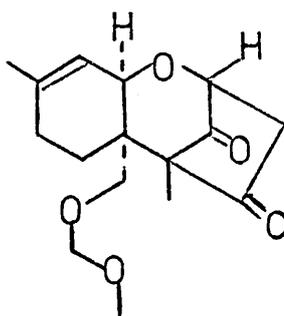


**164**

Scheme 26



**167**



**168**

together with two compounds to which structures (164) and (165) were tentatively assigned, without being extensively investigated.

It is premature to draw any definite conclusions from the limited experimentation devoted to this particular reaction. It may well transpire, and the long road to the enol lactone (153a) bears ample witness to this, that minor alterations in substrate or reaction conditions will bring about the desired transformation. One could, however, speculate and ascribe absence of any ketol (166) to its readiness to undergo a retro-aldol reaction, initiated intramolecularly by the oxygen of the methoxymethyl protecting group (Scheme 26). Consequently it may be beneficial to trap any ketol as its trimethylsilyl derivative (167) by quenching the reaction mixture with trimethylsilyl chloride.

Another possibility is the utilisation of a photochemically induced [1,3]-sigmatropic rearrangement of the enol lactone (153a) which could afford the diketone (168). This reaction has been employed in the synthesis of bicyclo[3,3,1]nonadiones<sup>95</sup>.

Irrespective of the approach adopted, it is felt that the synthesis of verrucarol (80) has only been temporarily halted and that the near future will see the remaining difficulties successfully circumvented.

## Experimental

## General Experimental and Abbreviations

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. Microanalysis were obtained by Mr. J.M.L. Cameron, Miss F. Cowan and their staff. Mass spectra were recorded by Mr. A. Ritchie on A.E.I.-G.E.C./MS 12 and A.E.I.-G.E.C./MS 902S mass spectrometers. Infra-red spectra were recorded by Mrs. F. Lawrie and her staff on a Unicam SP 100 Mark II spectrometer. Routine infra-red spectra were recorded on a Unicam SP 1000 instrument and were liquid-film unless otherwise stated. Ultra-violet spectra were recorded for ethanol solutions on a Unicam SP 800 spectrophotometer.

Nuclear magnetic resonance spectra were recorded by Mr. A. Haetzman or Mr. J. Gall on a Varian T-60 or a Varian HA 100 spectrometer using tetramethylsilane as an internal standard.

Kieselgel G (Merck) was used for preparative thin layer chromatography. Light petroleum refers to the fraction of b.p. 40°-60°. Analytical t.l.c. plates were stained with iodine vapour and/or ceric ammonium sulphate followed by heating to approximately 150°.

All dilute mineral acids were 6N unless otherwise stated. Methyl magnesium chloride was a 3M solution in ether.

All organic solutions, unless otherwise indicated,

were dried over anhydrous magnesium sulphate.

Dihydropyran was dried by refluxing with metallic sodium and subsequent distillation. Tetrahydrofuran was heated under reflux with lithium aluminium hydride and distilled prior to use. Dioxan and t-butanol were heated under reflux with calcium hydride and distilled. Methylene chloride was dried by passing it through a column of basic alumina (grade 1).

The following abbreviations and symbols have been employed primarily in the experimental section:-

- t.l.c. thin layer chromatography
- i.r. infra-red
- u.v. ultra-violet
- n.m.r. nuclear magnetic resonance
- s. singlet:
- d. doublet:
- t. triplet::
- q. quartet: (in n.m.r. spectra)
- m. multiplet:
- b. broad:
- d.d. doublet of doublets:
- g.l.c. gas liquid chromatography
- r.t. retention time
- [M<sup>+</sup>] molecular ion

1-Methoxy-4-methyl-6-carbomethoxy-bicyclo[2,2,2]oct-2-ene

(29)

Freshly distilled methyl acrylate (20 ml.), 1-methoxy-4-methyl-cyclohexa-1,4-diene (10 g., 80 m.moles) and hydroquinone (250 mg.) were heated in a sealed tube, under nitrogen, for 24 hrs. The temperature of the reaction vessel was maintained at 160-170°. The pale-yellow reaction mixture was taken up in ether and washed with aqueous sodium hydroxide (2%, 5 ml.), water and brine. After drying the solvent was removed in vacuo and the residual pale-yellow oil fractionally distilled. The ester (29) was obtained as a fragrant oil (9.85 g., 60%), b.p. 76-80°/0.25 mm. Preparative t.l.c. (20% ethyl acetate-light petroleum) allowed a separation of the epimeric mixture into:

i) the endo ester (29), as a pale-yellow oil ( $r_f$  0.27, 70%);

$\nu_{\max}$ . 1735, 1670, 1383, 1188 and 705  $\text{cm}^{-1}$ ;

$\tau(\text{CCl}_4)$  8.87 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.43 (6H; m.), 7.37 (1H;  $\text{CH-CO}_2\text{CH}_3$ , m.), 6.67 (3H;  $\text{CH}_3\text{-O-C}$ , s.), 6.37 (3H;  $\text{-CO}_2\text{CH}_3$ , s.), 3.91 (2H;  $\text{CH=CH}$ , AB q.,  $J=9$  Hz.),

ii) the exo epimer (29), a pale-yellow oil ( $r_f$  0.33, 30%);

$\nu_{\max}$ . 1725, 1670, 1382, 1190 and 705  $\text{cm}^{-1}$ ;

$\tau(\text{CCl}_4)$  8.85 (3H; s.), 8.57 (6H; m.), 7.2 (1H;  $\text{CH-CO}_2\text{CH}_3$ , m.), 6.72 (3H; s.), 4.05 (2H; AB q.,

J=9 Hz.);

mass spectral ion at m/e 210 [ $M^+$ ],  $C_{12}H_{18}O_3$  requires m/e 210. (Found: C, 68.32; H, 8.51;  $C_{12}H_{18}O_3$  requires C, 68.54; H, 8.63%).

1-Methoxy-4-methyl-6-diphenylhydroxymethyl-bicyclo[2,2,2]-oct-2-ene (30).

An ethereal solution of phenyl magnesium bromide (7.8 g., 50 m.moles) was prepared from rigorously purified bromobenzene (1.2 g., 50 m.moles) and magnesium turnings (1.32 g., 55 m.moles) in dry ether (50 ml.). The ester (29) (3.07 g., 14.51 m.moles) was added, via a pressure equilibrated funnel, to a stirred solution of the Grignard reagent in an atmosphere of nitrogen. When addition was complete the mixture was heated under reflux for a period of 4 hrs., by which time the heterogeneous mass had assumed a pink colouration. After cooling, saturated ammonium chloride solution was added, the granular precipitate formed was filtered off, washed with ether and the washings combined with the filtrate. Evaporation of solvent, under reduced pressure, gave the alcohol (30) as a pale-yellow solid (4.8 g.) in nearly quantitative yield. A small portion was recrystallised from ethyl acetate-light petroleum (1:1) to furnish colourless plates, m.p. 105-107°;

✓ Nujol max. 3430, 1600, 1150, 795 and 720  $cm^{-1}$ ;

$\tau$ (CDCl<sub>3</sub>) 8.97 (3H; CH<sub>3</sub>-C, s.), 8.53 (6H; m.), 6.93 and 6.82 (3H; CH<sub>3</sub>O-C, s.), 6.7 (1H; CH-C(Ph)<sub>2</sub>OH, m.), 4.38 and 3.88 (2H; CH=CH, AB q., J<sub>AB</sub> 10 Hz. and 9 Hz. respectively); mass spectral ion at m/e 334 [M<sup>+</sup>], C<sub>23</sub>H<sub>26</sub>O<sub>2</sub> requires m/e 334. (Found: C, 82.59; H, 7.77; C<sub>23</sub>H<sub>26</sub>O<sub>2</sub> requires C, 82.59; H, 7.84%).

4-Methyl-4-[3,3-diphenyl-prop-2-enyl]-cyclohex-2-enone (28).

The alcohol (30) (36.5 mg., 0.11 m.moles) was added to a mixture of glacial acetic acid (2 ml.) and aqueous perchloric acid (60%, 0.05 ml.). Almost immediately a deep blue colouration was observed which persisted for about 1 minute. The mixture was stirred for a further 5 min. and then neutralised with dilute potassium carbonate solution and extracted with ether. The ethereal layer was washed with water and brine and dried. Removal of solvent under reduced pressure gave the enone (28) as a pale-yellow, sweet smelling oil (21.3 mg.);

$\lambda_{\max.}$  (EtOH) 224 ( $\epsilon$ , 21450) and 248 ( $\epsilon$ , 14660) m $\mu$ ;

$\nu_{\max.}$  3040, 1674, 1594, 774 and 714 cm.<sup>-1</sup>;

$\tau$ (CCl<sub>4</sub>) 8.85 (3H; CH<sub>3</sub>-C, s.), 8.13 (2H; CH<sub>2</sub>-CH<sub>2</sub>, m.), 7.77 (2H; CH<sub>2</sub>-CO-, m.), 7.73 (2H; CH<sub>2</sub>-CH=C, d., J 7 Hz.), 3.96 (1H; CH=C, t., J 7 Hz.), 4.25 (1H; CO-CH=C, d.,

J 10 Hz.), 2.85 (10H; m.).

(Found: C, 87.37; H, 7.33;  $C_{22}H_{22}O$  requires C, 87.42; H, 7.44%).

Repetition of this reaction on a larger scale invariably resulted in the obtention of impure enone (28). Thus the crude alcohol (30) (4.1 g.) furnished the enone (28) (3.67 g.), the t.l.c. of which (20% ethyl acetate-light petroleum) showed it to be contaminated with two minor components. Purification was effected by column chromatography on silica gel (120 g.). Elution with ethyl acetate-light petroleum (2%-20%) furnished the enone (28) (2.4 g., 65%).

Attempted osmium tetroxide oxidation of the enone (28).

Osmium tetroxide (100 mg., 0.394 m.moles) in ether (1 ml.) was added dropwise to a stirred solution of the enone (28) (119 mg., 0.394 m.moles) in ether (4 ml.) and dry pyridine (0.06 ml.). The solution assumed a yellow coloration after a short period of time and a brown precipitate deposited on the sides of the flask. The mixture was stirred overnight. Aqueous sodium sulphite (180 mg. in 3 ml. of water) and pyridine were added, and stirring continued for a further 3 hours. The mixture was extracted with ether, and the ethereal extract washed with dilute hydrochloric acid, saturated sodium carbonate,

water, brine and dried. Evaporation of the ether in vacuo gave a viscous oil (80 mg.). Preparative t.l.c. (50% ethyl acetate-light petroleum) allowed the isolation of a nearly colourless oil (39 mg.),  $r_f$  0.4;

$\nu_{\max}$ . 3538, 3138, 1715, 1675, 1115, 777, and 715  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  8.82 (3H;  $\text{CH}_3\text{-C}$ , b.s.), 7.23 (1H;  $\text{OH}$ , s.), 6.0 (1H;  $\text{CH-O-}$ , m.), 5.08 (1H;  $\text{O-CH-C-OH}$ , b.m.), 2.8 (10H, b.m.).

The same product was obtained by acid treatment of the enone epoxide (33), and structure (32) was tentatively assigned to it.

4-Methyl-4-(3,3-diphenyl-2,3-epoxypropyl)cyclohex-2-enone (33).

m-Chloroperbenzoic acid (46 mg., 0.24 m.moles) was added to a solution of the enone (28) (60 mg., 0.2 m.moles) in dry methylene chloride (5 ml.). The mixture was stirred for 6 hours, when t.l.c. showed absence of starting material and the presence of a new compound ( $r_f$  0.65, 50% ethyl acetate-light petroleum). Aqueous sodium sulphite (30%, 5 ml.) was added to the reaction mixture, and stirring continued for a further 2 hours. The mixture was extracted with ether and the organic layer washed thoroughly with saturated sodium bicarbonate, water, brine and

dried. Removal of solvent under reduced pressure afforded the enone-epoxide (33) as a viscous, pale yellow oil (68.1 mg.), contaminated with a trace of peracid reagent. An analytical sample was obtained by preparative t.l.c. (50% ethyl acetate-light petroleum) and short-path distillation.

$\nu_{\text{max}}$ . 3090, 1680, 1603, 1128, 770 and 720  $\text{cm}^{-1}$ ;  
 $\tau(\text{CCl}_4)$  8.83 (3H; b.s.), 8.30 (4H; m.), 7.81 (2H; m.), 6.67 (1H;  $\text{CH}_2\text{-C}$ , X part of ABX system,  $J_{\text{AX}}$  8 Hz.,  $J_{\text{BX}}$  4 Hz.), 4.27 (1H;  $\text{COCH}=\text{CH}$ , d.d., A part of AB quartet,  $J_{\text{AB}}$  10 Hz. and small splitting of J 2 Hz.), 3.42 (1H;  $\text{COCH}=\text{CH}$ , d., B part of AB quartet,  $J_{\text{BA}}$  10 Hz.), 2.65 (10H; m.);

mass spectral ion at  $m/e$  318 [ $\text{M}^+$ ],  $\text{C}_{22}\text{H}_{22}\text{O}_2$  requires  $m/e$  318.

(Found: C, 82.76; H, 6.78;  $\text{C}_{22}\text{H}_{22}\text{O}_2$  requires C, 82.98; H, 6.96%).

1-Methyl-1-hydroxy-4-methyl-4-(3,3-diphenyl-2,3-epoxypropyl)-cyclohex-2-ene (40).

An ethereal solution of methyl magnesium chloride (0.34 ml., 3M, 1.02 m.moles) was added dropwise, via a syringe, to a vigorously stirred solution of the epoxy-enone (33) (315 mg., 0.99 m.moles) in dry ether (25 ml.) in an atmosphere of nitrogen. The temperature of the

reaction vessel was maintained at approximately 5°C throughout the addition. After completion of the addition of the Grignard reagent the creamy, heterogeneous mass was allowed to stir for a further 10 min., then decomposed by addition of aqueous, saturated sodium sulphate. The granular precipitate formed was filtered and washed with ether. The organic extracts were combined and concentrated in vacuo. The epoxy-alcohol (40) was obtained as a viscous, sharp-smelling oil (287 mg., 87%).

$\nu_{\text{max}}$ . 3445, 1603, 1124, 792 and 720  $\text{cm}^{-1}$   
 $\tau(\text{CCl}_4)$  8.93 (6H; m.), 7.66 (1H; OH, b.m.), 6.65  
(1H; CH-C, b.m.), 4.57 (2H; b.s.), 2.75  
(10H; m.);

mass spectral ion at  $m/e$  316 (corresponding to  $[\text{M}^+]-18$ ),  
 $\text{C}_{23}\text{H}_{26}\text{O}_2$  requires  $m/e$  334.

No purification of the epoxy-alcohol (40) was attempted at this juncture, and the crude material was employed in the subsequent reactions.

Acid-catalysed rearrangement of the epoxy-alcohol (40).

Aqueous perchloric acid (60%, 8 drops) was added to a stirred solution of the epoxy-alcohol (40) (160 mg., 0.48 m.moles) in ether (10 ml.). Aliquots of the reaction mixture were withdrawn at regular intervals, and the progress of the reaction monitored by t.l.c. (5% ether-

light petroleum). After 0.5 hr., an invariant reaction mixture and the absence of starting material indicated the completion of the reaction. The mixture was poured into saturated sodium bicarbonate solution and extracted with ether. The organic layer was washed with water, brine and dried. Evaporation of solvent under reduced pressure yielded a viscous, yellow oil (110 mg.). Preparative t.l.c. (5% ether-light petroleum) allowed a separation of the mixture into:

i) the enol ether (46) as a colourless viscous oil (17.6 mg., 11.6%,  $r_f$  0.75), b.p. 200-205°/0.7 mm.;

$\nu_{\max}$ . 3113, 1643, 1595, 1498, 1008, 790 and 713  $\text{cm}^{-1}$ ;

$\nu(\text{CCl}_4)$  8.98 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.12 (3H;  $\text{CH}_3\text{-C=C}$ , b.s.), 8.04 (2H;  $\text{CH}_2\text{-C}(\text{CH}_3)=\text{C}$ , m.), 7.55 (2H;  $\text{CH}_2\text{-C=CPh}_2$ , s.), 5.73 (1H;  $\text{CH-O}$ , b.d.) 4.40 (1H;  $\text{CH=C}$ , m.), 2.78 (10H; m.);

$\lambda_{\max}$ . (EtOH) 274  $\mu\text{m}(\epsilon, 10920)$ .

(Found: C, 87.33; H, 7.87;  $\text{C}_{23}\text{H}_{24}\text{O}$  requires C, 87.30; H, 7.65%);

ii) the less polar epimeric alcohol (39), as colourless plates (27.5 mg., 17.2%,  $r_f$  0.68), m.p. 39-43°;

$\nu_{\max}$ . 3593, 3100, 1673, 1498, 1023, 765 and 713  $\text{cm}^{-1}$

$\nu(\text{CCl}_4)$  8.93 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.29 (3H;  $\text{CH}_3\text{-C=C}$ ,

b.s.), 6.97 (1H;  $\underline{\text{OH}}$ , s.), 6.02 (1H;  $\text{CH}=\text{C}-\underline{\text{CH}}-\text{O}$ , m.), 4.94 (1H;  $\text{O}-\underline{\text{CH}}-\text{CH}_2$ , X part of ABX system,  $J_{\text{AX}}$  9 Hz.,  $J_{\text{BX}}$  7.5 Hz.), 4.76 (1H;  $\underline{\text{CH}}=\text{C}$ , m.), 2.65 (10H; b.m.);

mass spectral ion at 316 (corresponding to  $[\text{M}^+]-18$ ),

$\text{C}_{23}\text{H}_{26}\text{O}_2$  requires m/e 334;

iii) the more polar epimeric alcohol (39) as a colourless gum which crystallised on standing. Recrystallisation from light petroleum furnished colourless plates (32.8 mg., 20.5%,  $r_f$  0.62), m.p. 104-105.5°;

$\nu_{\text{max.}}$  3590, 1673, 1020, 767 and 710  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CCl}_4$ ) 9.03 (3H;  $\underline{\text{CH}}_3-\text{C}$ , s.), 8.26 (3H;  $\underline{\text{CH}}_3-\text{C}=\text{C}$ , b.s.), 6.96 (1H;  $\underline{\text{OH}}$ , s.), 6.10 (1H;  $\text{C}=\text{C}-\underline{\text{CH}}-\text{O}$ , b.d.), 4.90 (1H;  $\text{O}-\underline{\text{CH}}-\text{CH}_2$ , X part of ABX system,  $J_{\text{AX}}$  9 Hz. and  $J_{\text{BX}}$  7.5 Hz.), 4.48 (1H;  $\underline{\text{CH}}=\text{C}$ , m.), 2.70 (10H; b.m.).

(Found: C, 82.44; H, 8.01;  $\text{C}_{23}\text{H}_{26}\text{O}_2$  requires C, 82.59; H, 7.84%).

Conversion of the alcohol (39) into the enol ether (46).

a) The alcohol (39) (5 mg.) was added to a cooled mixture of phosphorus oxychloride/pyridine (0.5 ml., 2:5, v./v.) and then, with stirring, the reaction vessel was allowed to warm up to room temperature. Prolonged stirring and monitoring of the reaction mixture by t.l.c.

indicated only the presence of starting material.

b) Repetition of the above reaction with thionyl chloride/pyridine gave the same result.

c) The alcohol (39) (16 mg., 0.05 m.moles) was dissolved in acetic acid/acetic anhydride (1.5 ml., 1:2, v./v.) and the mixture refluxed. T.l.c. monitoring, over a period of several hours again indicated only the presence of starting material.

d) Anhydrous magnesium sulphate (20 mg.) was mixed with the alcohol (39) (10 mg., 0.03 m.moles). The mixture was introduced into a sublimation tube and heated at 150° and 0.01 mm. for 2 hrs. The black mass was extracted with ether, washed with brine and dried. Removal of solvent in vacuo gave a yellow oil (7 mg.) which on preparative t.l.c. (5% ether-light petroleum) furnished a colourless gum (4 mg.) identical by i.r. and t.l.c. with the enol ether (46).

### 2-Carbomethoxy-tetrahydrofuran

2-Carbomethoxy-tetrahydrofuran was prepared by a modification of the procedure employed by Adams et. al.<sup>21</sup> Furoic acid (45) (1 g., 8.92 m.moles) was dissolved in ethyl acetate (25 ml.) and the solution hydrogenated in the presence of palladium/charcoal (10%, 25 mg.). After 4 hrs. the theoretical amount of hydrogen (800 ml.) had

been taken up. Standard isolation procedures gave tetrahydrofuroic acid (960 mg., 95%), shown to be pure by t.l.c. Treatment of the acid with ethereal diazomethane furnished 2-carbomethoxy-tetrahydrofuran (905 mg.).

2-[Diphenyl-hydroxymethyl]-tetrahydrofuran (44).

This was prepared by the method of Dounce et. al.<sup>22</sup>, m.p. 73-75° (lit. m.p., 79-80°);

$\nu_{\text{max}}$  3590, 1498, 765 and 711  $\text{cm}^{-1}$ ;  
 $\tau(\text{CCl}_4)$  8.23 (4H; C- $\underline{\text{CH}}_2$ - $\underline{\text{CH}}_2$ -C, b.m.), 7.0 (1H; OH, s.), 6.09 (2H;  $\underline{\text{CH}}_2$ -O, m.), 5.11 (1H;  $\underline{\text{CH}}_2$ -O, m.), 3.0-2.15 (1OH; b.m.).

Peracid oxidation of the enol ether (46).

m-Chloroperbenzoic acid (24 mg., 0.14 m.moles) was added to a solution of the enol ether (46) (40 mg., 0.127 m.moles) in methylene chloride (5 ml.). The mixture was allowed to stand for 1 hr. at room temperature and then diluted with ether. The organic layer was washed with saturated sodium bicarbonate solution, water, brine and dried. The solvent was evaporated in vacuo and the viscous, residual oil subjected to t.l.c. (5% ether-light petroleum). This separated the reaction mixture into three components:

i) a colourless oil (7.5 mg.,  $r_f$  0.54);

$\nu_{\text{max}}$ . 3600, 1725, 1660, 1500, 770 and 718  $\text{cm}^{-1}$ ;  
the n.m.r. spectrum exhibited aromatic signals and a highly complex pattern of signals between 4-9. The compound was not further investigated.

ii) A colourless oil (5.5 mg.,  $r_f$  0.4) whose i.r. and n.m.r. spectra were similar to those of (ii).

iii). A crystalline solid (6.5 mg.) whose spectral and t.l.c. properties were similar to those of benzophenone. Repetition of this oxidation procedure with varying quantities of oxidising agent, reaction time and temperature did not lead to the isolation of the desired  $\gamma$ -lactone (9).

3,6-Dimethyl-8-oxo-9-oxabicyclo[4,3,0]non-2-ene (9).

Jones' reagent (1 ml., 8N) was added dropwise to an ice-cold solution of the carbinol (39) (60 mg., 0.18 m.-moles) in acetone (2 ml., AnalaR). The reaction flask was stoppered and allowed to stand at room temperature. A green precipitate had formed at the end of this time. Addition of the reaction mixture to water, extraction with ether and successive washing of the organic layer with dilute sodium bicarbonate solution, water and brine, followed by drying and removal of solvent in vacuo, afforded a viscous oil (52 mg.). T.l.c. examination showed a highly complex mixture of products. Preparative t.l.c. (40% ethyl acetate-light petroleum) allowed the isolation

of the  $\delta$ -lactone (9) (4.5 mg., 15%) as fine needles, m.p. 47-48.5°;

$\nu_{\text{max.}}$  1775, 1675, 1240, 1170 and 965  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.86 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.6-7.8 (4H; b.m.),  
8.23 (3H;  $\text{CH}_3\text{-C=C}$ , b,s.), 7.73 (2H;  $\text{CH}_2\text{-CO}$ ,  
s.), 5.73 (1H;  $\text{CH-O}$ , b.m.), 4.47 (1H;  
 $\text{CH}_3\text{-C=CH}$ , m.);

mass spectral ion at  $m/e$  166 [ $\text{M}^+$ ],  $\text{C}_{10}\text{H}_{14}\text{O}_2$  requires  $m/e$  166; an analytical sample was prepared by recrystallisation from benzene.

(Found: C, 72.07; H, 8.76;  $\text{C}_{10}\text{H}_{14}\text{O}_2$  requires C, 72.26; H, 8.49%).

Attempted preparation of 1-methoxy-4-methyl-6-acetoxy-bicyclo[2,2,2]oct-2-ene (51).

A mixture of 1-methoxy-4-methyl-cyclohexa-1,4-diene (2.48 g., 0.02 moles), vinyl acetate (8.6 g., 0.1 moles) and hydroquinone (100 mg.) was heated in a sealed tube at 180°, under nitrogen, for 18 hrs. The volatile materials were removed in vacuo and the resulting viscous, dark-brown oil was distilled. Three fractions were collected. Fractions 1 and 2 (418 mg.), b.p. 45-60° and 60-70°/0.3 mm. respectively were combined in view of their similar i.r. and t.l.c. properties and shown to be 4-methyl anisole. Fraction 3 (102 mg.), b.p. 70-100°/0.3 mm. was a complex

mixture of products showing no saturated carbonyl stretching frequency in the i.r. and was discarded.

Varying reaction conditions did not result in the obtention of the desired product and this approach was abandoned.

Attempted preparation of 1-methoxy-4,5-dimethyl-6-nitro-bicyclo[2,2,2]oct-2-ene (52).

A mixture of the diene (24, R=Me) (1.24 g., 0.01 moles), nitropropene (1.54 g., 0.02 moles) and hydroquinone (50 mg.) were heated in a sealed tube, in an atmosphere of nitrogen, for 15 hrs. A viscous, black oil was obtained which, on t.l.c. examination, appeared to be polymeric material and starting diene (24, R=Me). This reaction was not further investigated.

2-Acetoxy-1-butenonitrile.

The compound was prepared according to the method of Finch Jr. et. al.<sup>56</sup> Propionyl bromide was obtained as a colourless oil, b.p. 99-108° (lit. b.p. 99-110°). Ethyl cyanoketone was a colourless, viscous oil, b.p. 106-110° (lit. b.p. 108-110°). 2-Acetoxy-1-butenonitrile was a colourless, mobile oil, b.p. 101-104°/25 mm. (lit. b.p. 95-101°/33 mm.).

Attempted preparation of 1-methoxy-4,5-dimethyl-6-cyano-6-acetoxy-bicyclo[2,2,2]oct-2-ene (53).

2-Acetoxy-1-butenonitrile (700 mg., 4.96 m.moles), 1-methoxy-4-methyl-cyclohexa-1,4-diene (1.4 g., 9.92 m.moles) and hydroquinone (25 mg.) were heated in a sealed tube, under nitrogen, for 44 hrs. at 170°. Volatile materials were removed in vacuo at 100° and the viscous, dark-brown residue was thoroughly extracted with light petroleum. Evaporation of solvent under reduced pressure gave a brown, mobile oil. T.l.c. examination of this did not indicate the presence of any major product and only one discrete spot was discernable which was isolated by preparative t.l.c. (25% ethyl acetate-light petroleum). N.m.r. and i.r. data showed it to be incompatible with the anticipated product and the reaction was not further investigated.

1-Methoxy-4-methyl-6-cyano-6-chloro-bicyclo[2,2,2]oct-2-ene  
(54).

1-Methoxy-4-methyl-cyclohexa-1,4-diene (3.72 g., 0.03 moles) and 2-chloroacrylonitrile (1.75 g., 0.02 moles) were heated under reflux, with hydroquinone (50 mg.), for 24 hrs. under nitrogen. The dark-brown reaction mixture was allowed to cool and the resulting viscous oil diluted with ether. A brown, curdy precipitate formed which was

filtered off and washed with ether. The ethereal extracts were combined and the solvent removed in vacuo. The residual material was distilled to afford a pleasant smelling oil (1.52 g.), b.p. 152-162°/18 mm., which was absorbed on silica gel (45 g.) from light petroleum. The fractions eluted with 2% ethyl acetate-light petroleum were combined on the basis of t.l.c. behaviour to give the chloro-nitrile (54) as a gum (622 mg., 14%) which crystallised on standing. Recrystallisation from light petroleum furnished (54) as fine needles, m.p. 63-64°;

$\nu_{\max}$ . 2370, 1118, 760 and 705  $\text{cm.}^{-1}$ ;

$\tau(\text{CDCl}_3)$  8.78 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.6-7.8 (6H; methylene envelope), 8.23 (1H;  $\text{CH-CClCN}$ , d., A part of AB q.,  $J_{AB}$  14 Hz.), 7.45 (1H;  $\text{CH-CClCN}$ , d., B part of AB q.,  $J_{BA}$  14 Hz.), 6.67 (3H;  $\text{CH}_3\text{-O}$ , s.), 3.9 (1H;  $\text{CH=CH}$ , d., A part of AB q.,  $J_{AB}$  9 Hz.), 3.71 (1H;  $\text{CH=CH}$ , d., B part of AB q.,  $J_{BA}$  9 Hz.).

(Found: C, 62.49; H, 6.55; N, 6.49;  $\text{C}_{11}\text{H}_{14}\text{N O Cl}$  requires C, 62.52; H, 6.67; N, 6.64%).

Combination of the fractions eluted with ethyl acetate-light petroleum (20-50%) furnished a crystalline compound (350 mg.) which on recrystallisation from light petroleum gave fine needles, m.p. 95-98°. Structure (55) was assigned to it on the basis of spectroscopic and analytical data.

$\nu_{\text{max}}$ . 2340 and 1720  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.68 (3H;  $\text{CH}_3\text{-C}$ , s.), 4.05 (1H;  $\text{CH}=\text{CH}$ ,

A part of AB q., d.,  $J_{\text{AB}}$  5 Hz.), 3.86

(1H;  $\text{CH}=\text{CH}$ , B part of AB q., d.,  $J_{\text{BA}}$  5 Hz.);

mass spectral ion at  $m/e$  161 [ $\text{M}^+$ ],  $\text{C}_{10}\text{H}_{11}\text{N O}$  requires  $m/e$  161.

(Found: C, 74.72; H, 6.62; N, 8.88;  $\text{C}_{10}\text{H}_{11}\text{N O}$  requires C, 74.5; H, 6.88; N, 8.69%).

A superior method<sup>37</sup> of preparing the chloro-nitrile (54) involved refluxing equimolar quantities of 2-chloroacrylonitrile and the diene (24, R=Me) for 9 hrs. in benzene. Yield 60%.

Attempted preparation of 1-methoxy-4-methyl-bicyclo[2,2,2]-oct-5-ene-2-one (49).

a) The chloro-nitrile (54) (503 mg., 2.38 m.moles) was added to a mixture of aqueous potassium hydroxide (2 ml., 28%), tetrahydrofuran (7.5 ml.) and methanol (2 ml.). The mixture, initially inhomogeneous, was stirred at 40° for 19 hrs. Water was added and the mixture thoroughly extracted with ether. The organic layer was washed with water until neutral, then a little brine and dried. Evaporation of solvent in vacuo gave a crystalline material (456 mg.) which by t.l.c. (20% ethyl acetate-light petroleum) and i.r. was identical with starting material.

b) Aqueous potassium hydroxide (0.09 ml., 85%, w./v.) was injected into a mixture of the chloro-nitrile (54) (250 mg., 1.18 m.moles) in dimethyl sulphoxide (2 ml.). The mixture was stirred for 17 hrs. at 25° and then poured on to crushed ice (5 g.). The slurry was extracted with ether, washed with water, brine and dried. Removal of solvent under reduced pressure afforded starting material (210 mg.), as evidenced by t.l.c. and i.r.

1-Methoxy-4-methyl-bicyclo[2,2,2]oct-2-ene-5-one (49).

The compound was prepared according to the method of Evans et. al.<sup>37</sup> The chloro-nitrile (54) (20 g., 95 m.moles) was refluxed with sodium sulphide (30 g., 125 m.moles) in ethanol (150 ml.). A yellow precipitate formed during the course of the reaction. The mixture was poured on to ice and water (300 g.) and thoroughly extracted with ether. The organic phase was washed with brine and dried. Removal of solvent in vacuo afforded a mobile, yellow oil (10.5 g.). Fractional distillation furnished the ketone (49) as a colourless oil (8.5 g.), b.p. 130-135°/14 mm.

$\nu_{\max}$ . 3050, 1730, 705 and 670  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.71 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.52-7.7 (6H; methylene envelope), 6.45 (3H;  $\text{CH}_3\text{-O}$ , s.), 4.78 (2H; t., J 8 Hz.).

Peracid oxidation of the ketone (49).

With m-chloroperbenzoic acid

The ketone (49) (130 mg., 0.794 m.moles) was dissolved in dry methylene chloride (5 ml.) and m-chloroperbenzoic acid (161 mg., 0.794 m.moles) added with external cooling. The reaction flask was stoppered and set aside for 24 hrs. Then 30% aqueous sodium sulphite solution was added and the mixture stirred for 1.5 hrs. The mixture was extracted with ether and the organic phase washed with saturated sodium bicarbonate solution, brine and dried. Evaporation of solvent in vacuo afforded a viscous oil (122 mg.). T.l.c. (20% ethyl acetate-light petroleum) showed the presence of two compounds. The less polar one by virtue of its  $r_f$  value and staining properties was starting material. The more polar component was isolated by preparative t.l.c. (20% ethyl acetate-light petroleum) as a viscous, pale-yellow oil (90 mg.) whose spectral and analytical data are consistent with the epoxide (65).

$\nu_{\text{max}}$  1740, 1097, 905, 880, 830 and 693  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.73 (3H;  $\text{CH}_3\text{-C}$ , s.), 8.45-7.8 (6H; methylene envelope), 6.69 and 6.46 (2H; AB q.,  $J_{\text{AB}}$  5 Hz.), 6.63 (3H;  $\text{CH}_3\text{-O}$ , s.).

An analytical sample was prepared by short-path distillation, b.p. 90-95°/0.25 mm.

(Found: C, 65.84; H, 7.66;  $C_{10}H_{14}O_3$  requires C, 65.91; H, 7.74%).

With trifluoroacetic acid

Trifluoroacetic anhydride (0.74 ml., 5.24 m.moles) was added to an ice cold solution of hydrogen peroxide (90%, 0.12 ml., 4.36 m.moles) in dry methylene chloride via a syringe, in an atmosphere of nitrogen. The mixture was stirred at 5° for 0.5 hr. and then transferred, via a syringe, into a 2-necked flask containing a suspension of anhydrous sodium hydrogen phosphate (1.16 g.) in dry methylene chloride (5 ml.) containing the ketone (49) (419 mg., 2.9 m.moles). After 4.5 hrs. the mixture was worked up, in a manner similar to that described for the previous experiment, to yield a viscous oil (405 mg.). T.l.c. indicated a reaction composition quite analogous to that described for the m-chloroperbenzoic acid oxidation.

Oxime of 1-methoxy-4-methyl-bicyclo[2,2,2]oct-2-ene-5-one

(72).

Hydroxylamine hydrochloride (8.4 g., 0.12 moles) and sodium acetate (9.7 g., 0.12 moles) were added to a solution of the ketone (49) (10.5 g., 63.3 m.moles) in ethanol/water (100 ml., 1:2, v./v.) and the mixture was refluxed for 4 hrs. The hot reaction mixture was then poured on to crushed ice (150 g.) and thoroughly extracted with

ether. The ethereal layer was washed with water, brine and dried. Evaporation of solvent in vacuo furnished the crude, crystalline hydroxylamine (72) (10.67 g.).

Recrystallisation from chloroform-light petroleum furnished colourless plates (7.31 g.), m.p. 127-128.5°.

$\nu$   $\text{CCl}_4$  max. 3600, 3280 (absent on high dilution), 1160 and 690  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.75 (3H; s.), 8.7-8.0 (4H; methylene envelope), 7.76 (2H;  $\text{CH}_2\text{-C=N-OH}$ , b.s.), 6.48 (3H;  $\text{CH}_3\text{-O}$ , s.), 3.97 and 3.67 (2H;  $\text{CH=CH}$ , AB q.,  $J_{\text{AB}}$  8.5 Hz.);

mass spectral ion at  $m/e$  181 [ $\text{M}^+$ ],  $\text{C}_{10}\text{H}_{15}\text{N O}_2$  requires  $m/e$  181.

(Found: C, 66.27; H, 8.34; N, 7.73;  $\text{C}_{10}\text{H}_{15}\text{NO}_2$  requires C, 66.39; H, 8.24; N, 7.66%).

#### 4-Methyl-4-cyanomethyl-cyclohex-2-enone (74).

A 60% dispersion of sodium hydride in mineral oil (1.425 g., 35.7 m.moles) was washed three times with light petroleum in an atmosphere of nitrogen. A 2-necked flask (500 ml.) was then charged with dry ether (200 ml.) and the oxime (72) (4.31 g., 23.8 m.moles) was added in small portions over a period of 10 min. Effervescence ceased after approximately 0.5 hr. After further stirring for 3.5 hrs. a grey slurry was obtained. The reaction

mixture was cooled to  $-78^{\circ}$  and freshly crystallised toluene-p-sulphonyl chloride (6.5 g., 33.4 m.moles) added in small portions. The reaction vessel was allowed to warm slowly to room temperature and then left for 24 hrs. Saturated potassium carbonate solution (30 ml.) and ethanol (30 ml.) were then added and the inhomogeneous mixture stirred for 6 hrs., when a clear solution was obtained. The mixture was extracted with ether, the organic phase washed with water, brine and dried. Evaporation of solvent under reduced pressure furnished the enone (74)

(2.78 g., 79%) as a pale-yellow oil;

$\nu_{\text{max.}}$  2240, 1670 and 800  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.62 (3H;  $\text{CH}_3$ -C, s.), 8.2-7.3 (4H; methylene envelope), 7.48 (2H;  $\text{CH}_2$ -CN, s.), 4.03 and 3.31 (2H; AB q.,  $J_{\text{AB}}$  11 Hz.);

$\lambda_{\text{max.}}$  (EtOH) 223  $\text{m}\mu$  ( $\epsilon$ , 9900);

mass spectral ion at  $m/e$  149 [ $\text{M}^+$ ],  $\text{C}_9\text{H}_{11}\text{NO}$  requires  $m/e$  149. The enone (74) was characterised as its 2,4-dinitrophenylhydrazone, fine orange needles, m.p.  $142-143^{\circ}$ . (Found: C, 54.87; H, 4.54; N, 21.08;  $\text{C}_9\text{H}_{11}\text{NO}$  requires C, 54.71; H, 4.59; N, 21.27%).

1-Hydroxy-1,4-dimethyl-4-cyanomethyl-cyclohex-2-ene (77).

Methyl magnesium chloride (0.18 ml., 3M, 0.53 m.moles) was added rapidly to a vigorously stirred solution of

the enone-nitrile (74) (69 mg., 0.46 m.moles) in dry ether in an atmosphere of nitrogen. The temperature of the reaction vessel was maintained at approximately 5° throughout the addition. The mixture was then stirred for a further 20 min. and decomposed by a dropwise addition of aqueous, saturated sodium sulphate solution. The granular precipitate formed was filtered and washed with ether. The organic extracts were combined and concentrated in vacuo. The alcohol (77) was obtained as a viscous, colourless oil (68 mg., 89%).

$\nu_{\text{max.}}$  3450, 2235 and 1100  $\text{cm}^{-1}$

The alcohol was employed immediately in the next reaction step.

Acid-catalysed rearrangement of the alcohol (77) to the  $\gamma$ -lactone (9).

a) Dilute hydrochloric acid (1 ml.) and perchloric acid (1 ml., 60%) was added to the alcohol (77) (68 mg., 0.425 m.moles) in methanol (2 ml.) and the mixture heated at 85° for 12 hrs. The mixture was extracted with ether and the organic layer washed with aqueous, saturated sodium bicarbonate solution, water, brine and dried. Removal of solvent in vacuo gave a yellow oil. Preparative t.l.c. (40% ethyl acetate-light petroleum) allowed the isolation of the  $\gamma$ -lactone (9) (7 mg., 10%).

b) The alcohol (77) (350 mg., 2.13 m.moles) in methanol (5 ml.) containing concentrated hydrochloric acid (0.5 ml.) was refluxed for 12 hrs. The  $\gamma$ -lactone (9) (212 mg., 61%) was isolated in the manner described in (a).

3-Hydroxy-3-methyl-butyr-aldehyde-dimethylacetal (86).

$\beta$ -Ketobutyraldehyde-dimethylacetal (85) (11g., 0.1 moles) was added dropwise to a stirred, ethereal solution of methyl magnesium iodide (0.15 moles) in an atmosphere of nitrogen. Stirring was continued for a further 2 hrs. at room temperature. Saturated sodium sulphate solution was added and the ethereal solution was decanted. The residual, granular precipitate was washed several times with ether, the organic extracts were combined and concentrated in vacuo. A pale-yellow oil was obtained which, on distillation, furnished two fractions, b.p. 60-88°/19-20 mm. (3.5 g.) and 90-93°/19-20 mm. (5.2 g.), which were combined in view of their similar spectroscopic properties;

$\nu_{\text{max.}}$  3600 and 1200-1100  $\text{cm}^{-1}$ ;  
 $\nu(\text{CCl}_4)$  8.83 (6H;  $(\text{CH}_3)_2\text{-C}$ , s.), 8.30 (2H;  $\text{CH}_2\text{-CH}$ , d., J 6 Hz.), 7.37 (1H;  $\text{OH}$ , m.), 6.7 (6H;  $(\text{CH}_3\text{O})_2\text{C}$ , s.), 5.42 (1H;  $\text{CH}(\text{OMe})_2$ , t., J 6 Hz.).

3,3-Dimethyl-crotonaldehyde (87).

The hydroxy-acetal (86) (8.0 g., 63 m.moles) was shaken vigorously with ice-cold, dilute sulphuric acid (50 ml., 10% v./v.) for 20 min.; the mixture was steam-distilled, the distillate extracted with ether, washed

with aqueous sodium bicarbonate solution, water, brine and dried. Removal of solvent in vacuo furnished a yellow oil (3.0 g.) which was fractionally distilled. The aldehyde (87) was obtained as a pale-yellow, pungent oil (1.5 g.), b.p. 132-138°.

$\nu_{\text{max.}}$  1682, 1634 and 850  $\text{cm.}^{-1}$ ;

$\tau(\text{CCl}_4)$  8.0 (3H; d., J 2 Hz.), 7.77 (3H; d., J 1.5 Hz.), 4.18 (1H; b.d.), 0.07 (1H;  $\underline{\text{CHO}}$ , d., J 8 Hz.).

1-Acetoxy-3-methyl-but-1,3-diene (84) and (84a).

A mixture of the aldehyde (87) (1.5 g., 14.4 m.moles), acetic anhydride (4.2 ml., 41.1 m.moles) and fused potassium acetate (120 mg., 1.23 m.moles) was heated, with stirring, at 140° for 6 hrs. The black reaction product was cooled and saturated potassium carbonate solution added. Solid potassium carbonate was introduced into the reaction vessel at 5 min. intervals until all effervescence ceased (0.5 hr.) and the solution was alkaline to litmus. The mixture was extracted with ether, the ethereal extract washed with water, brine and dried. The solvent was carefully removed under reduced pressure and the residual, yellow oil fractionally distilled. A stereoisomeric mixture of dienes (84) and (84a) was obtained (1.10 g., 47%), b.p. 132-138°;

$\nu_{\text{max}}$ . 1755, 1655, 1220 and 1110  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  8.16 (3H; m.), 7.98 and 7.88 (3H;  $\text{CH}_3\text{-CO}_2$ , s.), 5.17-4.66 (2H;  $\text{CH}_2=\text{C}$ , b.m.), 4.20 and 3.96 (1H;  $\text{CH}=\text{CH-OAc}$ , b.d. and d., A part of AB q.,  $J_{\text{AB}} \sim 8$  Hz. and 12 Hz. resp.), 2.80 and 2.70 (1H;  $\text{CH}=\text{CH-OAc}$ , d. and d., B part of AB q.,  $J_{\text{BA}} 8$  Hz. and 12 Hz. resp.);

mass spectral ion at  $m/e$  126 [ $\text{M}^+$ ],  $\text{C}_7\text{H}_{10}\text{O}_2$  requires 126.

Attempted Diels-Alder reaction between the dienes (84) and (84a) and itaconic acid (83).

Itaconic acid (83) (1.0 g., 6.67 m.moles), the dienes (84), (84a) and hydroquinone (25 mg.) were heated at 160-165°, for 11.5 hrs., under nitrogen. On cooling the dark-brown melt was diluted with ether, washed with cold, saturated sodium bicarbonate solution, water, brine and dried. The solvent was removed in vacuo to yield a viscous, brown oil (800 mg.). T.l.c. (20% ethyl acetate-light petroleum) showed a streak of products, the i.r. and n.m.r. data of the crude material being totally uninformative as to the nature of the reaction mixture, but nonetheless suggesting extensive decomposition. Repetition, employing shorter reaction times, sealed tubes and acetonitrile as cosolvent did not result in the isolation of the desired adduct (88) and this approach was abandoned.

4-Carbethoxy-4-carbethoxymethyl-cyclohex-2-enone (91).

The compound was prepared by the method of Flieninger et. al.<sup>59</sup>, b.p. 130-137°/0.02 mm. (lit. b.p. 126-130°/0.01mm.). Purification of the enone (91) was effected via its semi-carbazone derivative which was washed with ice-cold ether prior to regeneration.

1-Methyl-1-hydroxy-4-carbethoxy-4-carbethoxymethyl-cyclohex-2-ene (92).

The enone (91) (20 g., 79 m.moles) in dry ether (20 ml.) was added over one minute to a vigorously stirred, ice-cold solution of methyl magnesium iodide (87 m.moles) in dry ether (200 ml.) in an atmosphere of nitrogen. The creamy, heterogeneous reaction mixture was stirred for a further 10 min., then quenched with saturated sodium sulphate solution. The supernatant ethereal layer was decanted and the residual precipitate thoroughly extracted with ether. The organic extracts were combined and concentrated in vacuo. A pale-yellow, viscous oil (92) (21 g.) was obtained,  $r_f$  0.5 (60% ethyl acetate-light petroleum);

$\nu_{\max.}$  3509, 1730, 1205 and 1040  $\text{cm}^{-1}$

No purification was attempted at this stage; the alcohol (92) was immediately employed in the subsequent reaction.

3-Methyl-6-carboxy-8-oxo-9-oxabicyclo[4,3,0]non-2-ene (82).

Aqueous sodium hydroxide (100 ml., 4N) and the crude alcohol (92) (20.5 g.) were stirred vigorously, at 80° for 13 hrs., when the reaction mixture had become homogeneous and had acquired a brown colouration. The mixture was cooled in an ice-salt bath and carefully acidified with dilute sulphuric acid. Stirring was continued for a further 1.5 hrs., during which time a yellow precipitate was deposited. The solution was saturated with salt and extracted with ethyl acetate (3 150 ml.). The combined organic extracts were washed with saturated brine (50 ml.) and dried. Evaporation of solvent in vacuo gave a brown gum which, on trituration with cold ether, furnished a solid (12 g.); recrystallisation from ethyl acetate gave the  $\gamma$ -lactone acid (82) as a white, amorphous powder, m.p. 146-148°. Overall yield from the enone (91) 44%;

$\nu$  Nujol max. 3420-2400, 1740, 1705, 1230 and 970  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.2 (3H;  $\text{CH}_3\text{-C}=\text{C}$ , b.s.), 7.38 and 6.87 (2H;  $\text{CH}_2\text{-CO}$ , AB q.,  $J_{\text{AB}}$  18 Hz.), 4.9 (1H;  $\text{CH-C}$ , m.), 4.4 (1H;  $\text{CH}=\text{C}$ , m.), 2.1 (1H;  $\text{CO}_2\text{H}$ , m.).

The acid was characterised as its methyl ester, m.p. 85-87°, from benzene;

mass spectral ion at  $m/e$  210 [ $H^+$ ],  $C_{11}H_{14}O_4$  requires  $m/e$  210.

(Found: C, 62.71; H, 6.63;  $C_{11}H_{14}O_4$  requires C, 62.84; H, 6.71%).

Acid chloride (98) from the  $\gamma$ -lactone acid (82).

a) With thionyl chloride

The  $\gamma$ -lactone acid (18.5 mg., 0.95 m.moles) was heated under reflux with freshly distilled thionyl chloride (150 mg., 1.38 m.moles) in dry methylene chloride (2.5 ml.) for 13 hrs. The solvent was removed in vacuo and excess thionyl chloride azeotropically distilled with benzene. The acid chloride (98) was obtained as a viscous, dark-brown oil (20 mg.), which solidified on standing. I.r. showed residual contamination by starting material.

b) With oxalyl chloride

The  $\gamma$ -lactone acid (82) (1 g., 5.12 m.moles) was partially dissolved in dry methylene chloride (50 ml.) in a 100 ml. flask fitted with a calcium chloride drying tube. Oxalyl chloride (0.7 ml., 8.33 m.moles), and a drop of dimethylformamide was then added to the stirred mixture. Vigorous effervescence occurred and the reaction became homogeneous (1 hr.). Stirring was continued for a further 12 hrs. Methylene chloride was then removed

under reduced pressure and excess oxalyl chloride azeotropically distilled with benzene. The acid chloride (98) was obtained as a pale-brown solid (1.12 g.);

$\nu_{\text{max.}}$  1777, 1673, 1190, 1000 and 808  $\text{cm}^{-1}$

The acid chloride (98) was employed immediately in the subsequent reaction step.

Sodium borohydride reduction of the acid chloride (98).

a) The acid chloride (98) (30 mg., 0.14 m.moles) was taken up in dry dioxan (2 ml.), sodium borohydride (100 mg., 2.63 m.moles) was added and the reaction mixture was stirred for 50 hrs. It was then poured on to water, extracted with ethyl acetate and the organic extract washed with brine and dried. Removal of solvent in vacuo gave a viscous oil (20 mg.), t.l.c. of which (50% ethyl acetate-light petroleum) showed the presence of one major component with  $r_f$  0.1;

$\nu_{\text{max.}}$  3450, 1670 and 1145  $\text{cm}^{-1}$

The intensity of the hydroxyl stretching frequency and the absence of the  $\gamma$ -lactone carbonyl band suggested that over-reduction had occurred.

b) A mixture of the acid chloride (98) (42 mg., 0.242 m.moles), sodium borohydride (42 mg., 1.11 m.moles) and dry dioxan (10 ml.) was stirred at room temperature for 1 hr. and then for 3.5 hrs. at 85°. Work-up, as

described in (a), and preparative t.l.c. (50% ethyl acetate-light petroleum) furnished the  $\gamma$ -lactone alcohol (99) (14 mg., 30%).

c) An analogous procedure to (b), employing equimolar amounts of the acid chloride (98) and sodium borohydride allowed the isolation of the desired alcohol (99) in 28% yield.

d) The following experimental procedure was rigorously adhered to in all subsequent conversions of the acid chloride (98) to the corresponding alcohol (99).

The acid chloride (98) obtained from the lactone acid (82) (1 g., 5.12 m.moles) by the procedure described, was taken up in dry dioxan (25 ml.) and sodium borohydride (1 g., 26.3 m.moles) added to the solution. The heterogeneous mixture was stirred for 3 hrs. at 20° and for 0.5 hr. at 85°. The pale-yellow mixture was poured on to crushed ice (100 g.) and extracted with ethyl acetate (2x150 ml.). The combined organic extracts were washed with water, brine and dried. Removal of solvent under reduced pressure furnished a colourless gum (675 mg.), which solidified on trituration with cold ether. One recrystallisation from benzene afforded an analytical sample of the  $\gamma$ -lactone alcohol (99) as colourless cubes, m.p. 71.5-78°; g.l.c., 1% OV-17, 175°, flow-rate 48 ml./min., r.t. 3.75 min.;

$\nu_{\text{max.}}$  3500, 1745, 1665, 1205 and 905  $\text{cm}^{-1}$ ;  
 $\nu$  ( $\text{CDCl}_3$ ) 8.2 (3H;  $\text{CH}_3\text{-C=C}$ , b.d.), 8.0 (4H; m.),  
7.58 (1H;  $\text{OH}$ , b.m.), 7.70 and 7.35 (2H;  
 $\text{CH}_2\text{-CO}$ , AB q.,  $J_{\text{AB}}$  17 Hz.), 6.44 (2H;  $\text{CH}_2\text{-O}$ ,  
s.), 5.33 (1H;  $\text{CH-O}$ , m.), 4.46 (1H;  $\text{CH=C}$ ,  
m.);

mass spectral ion at  $m/e$  182 [ $\text{M}^+$ ],  $\text{C}_{10}\text{H}_{14}\text{O}_3$  requires  
 $m/e$  182.

(Found: C, 65.79; H, 7.68;  $\text{C}_{10}\text{H}_{14}\text{O}_3$  requires C, 65.91;  
H, 7.74%).

$\gamma$ -Lactone tetrahydropyranyl ether (102).

The  $\gamma$ -lactone alcohol (99) (76.2 mg., 0.42 m.moles) was dissolved in dry benzene (5 ml.) and purified dihydropyran (67.2 mg., 0.8 m.moles) together with a drop of phosphorus oxychloride added. The mixture was stirred at room temperature and the progress of the reaction monitored by t.l.c. (20% ethyl acetate-light petroleum). After 1.5 hrs. absence of all starting material and the presence of a less polar compound with  $r_f$  0.5 indicated the completion of the reaction. The mixture was poured on to saturated sodium bicarbonate solution and thoroughly extracted with ether. The ethereal layer was washed successively with water, brine and dried over anhydrous sodium sulphate. Evaporation of solvent in vacuo furnished

the tetrahydropyranyl ether (102) as a colourless, viscous oil (94 mg., 85%); g.l.c., 1% OV-17, 175°, flow-rate 48 ml./min., r.t.. 15 min. An analytical sample was prepared by short-path distillation, b.p. 148-152°/0.2 mm.;

$\nu_{\max.}$  1780, 1675, 1150, 1080, 980 and 760  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  7.5 (2H;  $\text{CH}_2\text{-C=C}$ , m.), 6.77 and 6.3 (2H;  $\text{CH}_2\text{-CO}$ , AB q.,  $J_{\text{AB}}$  9.5 Hz.), 6.57-6.0 (2H;  $\text{CH}_2\text{-CH-O}$ , b.m.), 5.38 (2H;  $\text{C=C-CH-O}$ , and  $\text{O-CH-O}$ , m.), 4.46 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at  $m/e$  266 [ $\text{M}^+$ ],  $\text{C}_{15}\text{H}_{22}\text{O}_4$  requires  $m/e$  266.

(Found: C, 67.55; H, 8.51;  $\text{C}_{15}\text{H}_{22}\text{O}_4$  requires C, 67.64; H, 8.33%).

#### Methylation of the lactone tetrahydropyranyl ether (102).

Di-isopropylamine (296 mg., 2.95 m.moles) in dry ether (5 ml.) was stirred in an atmosphere of nitrogen. To this was added butyl lithium (1.6 ml., 2.1M in hexane, 2.96 m.moles) via a syringe. Addition was complete in 30 seconds and the solution acquired a faint milkyness. A further 15 min. were allowed before the  $\gamma$ -lactone tetrahydropyranyl ether (102) (718 mg., 2.69 m.moles) was added in dry ether (5 ml.). After 0.5 hr. methyl iodide (1 ml.) was added to the reaction mixture and stirring continued for 25 min. at a gentle reflux temperature.

The mixture was cooled and acidified with dilute sulphuric acid. The solution was poured on to saturated sodium bicarbonate solution and extracted with ether. The organic layer, after successive washings with water and brine, drying over anhydrous sodium sulphate and concentration in vacuo, furnished a viscous, yellow oil (650 mg.). The oil was absorbed on basic alumina (grade 1, 15 g.) from light petroleum; elution with ethyl acetate-light petroleum (5% and 10%) furnished the methylated  $\gamma$ -lactone (103) [422 mg., 50% overall from (99)] as a colourless, sweet smelling oil; g.l.c., 1% OV-17, 175°, flow-rate 48 ml./min., r.t. 16.7, 17.6 and 18.4 min.;

$\nu_{\text{max}}$ . 1775, 1675 1134, 1030, 990, 920 and 885  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.87 and 8.83 (3H;  $\text{CH}_3\text{-C}$ , overlapping d.,  
8.6-7.7 (10H; methylene envelope), 7.43  
(1H;  $\text{CH-CH}_3$ , b.q., J 7.5 Hz.), 6.94-6.17  
(4H;  $\text{CH}_2\text{-O}$ , b.m.), 5.4 (1H;  $\text{C=C-CH-O}$ , m.),  
5.2 (1H;  $\text{O-CH-O}$ , m.), 4.6-4.23 (1H;  $\text{CH=C}$ ,  
b.m.);

mass spectral ion at  $m/e$  280 [ $\text{M}^+$ ],  $\text{C}_{16}\text{H}_{24}\text{O}_4$  requires  
 $m/e$  280.

(Found: C, 68.36; H, 8.47;  $\text{C}_{16}\text{H}_{24}\text{O}_4$  requires C, 68.54;  
H, 8.63%).

Attempted addition of lithio 3,3-diethoxy-propyne (105)  
to the lactone (103).

a) Butyl lithium (0.86 ml., 2.1M in hexane, 1.8 m.moles) was injected into a stirred solution of 3,3-diethoxy-propyne in dry ether (5 ml.) in an atmosphere of nitrogen. The reaction vessel was maintained at  $-78^{\circ}$  for 0.5 hr. The  $\gamma$ -lactone (103) (250 mg., 0.89 m.moles) in dry ether (5 ml.) was then added and stirring continued for a further 3 hrs. The mixture was then allowed to warm to room temperature (2 hrs.).

Saturated sodium sulphate solution was added and the resulting dark-brown solution extracted with ether. The ethereal layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of solvent at reduced pressure gave a yellow oil (400 mg.). T.l.c. (20% ethyl acetate-light petroleum) showed two closely running, major components, the more polar one corresponding to the  $\gamma$ -lactone (103). Preparative t.l.c. (20% ethyl acetate-light petroleum) allowed the isolation of the less polar band as a viscous oil (250 mg.);

$\nu_{\text{max.}}$  3445, 1765, 1675 and 1100  $\text{cm.}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.75 (6H;  $\text{CH}_3\text{CH}_2\text{-O}$ , t., J 7 Hz.), 8.67-7.84 (10H; b.m.), 5.43 (2H;  $\text{O-CH-O}$  and  $\text{C=C-CH-O}$ , b.m.), 4.7 (1H;  $\text{CH-C}\equiv\text{C}$ , s.), 4.45 (1H; m.).

Spectral and t.l.c. data pointed to the presence of both starting material (103) and hemi-acetal (106). Repeated t.l.c. did not effect purification of the desired hemi-acetal (106), decomposition invariably occurring. It was decided to proceed to the next stage with the crude material.

The experimental details for the following reaction sequence are fully incorporated in the analogous and subsequently successful series of reactions with the  $\gamma$ -lactone (133).

Attempted sodium borohydride reduction of the hemi-acetal  
(106).

b) The crude mixture from (a) (220 mg.) was treated with sodium borohydride (1 g.) in ethanol/water (10 ml., 1:1, v./v.). After 3 hrs. an oil was isolated (200 mg.), t.l.c. of which showed two major components with  $r_f$  0.54 and 0.61 (40% ethyl acetate-light petroleum).

Preparative t.l.c. (50% ethyl acetate-light petroleum) afforded a yellow oil (108 mg.);

$\nu_{\text{max}}$  3500, 1743, 1675 and 1100  $\text{cm}^{-1}$

The n.m.r. spectrum of the isolated material was totally uninformative. The intense hydroxyl stretching frequency in the i.r. prompted an extrapolation of the reaction sequence to the next stage.

Attempted sodium-liquid ammonia reduction of the product from (b).

c) The crude product from (b) (100 mg.) was treated with sodium (19 mg.) in liquid ammonia (30 ml.) for 4 min. and the mixture quenched with ethanol. A yellow, viscous oil (100 mg.) was obtained on work-up. T.l.c. (40% ethyl acetate-light petroleum) showed extensive decomposition of the reaction mixture, but also indicated the presence of two components at  $r_f$  0.5 and 0.42. Since spectral data in no way allowed a clarification of the product composition, an attempt was made to induce any olefinic diol (114) present to undergo cyclisation to the desired chromanol (115).

Attempted cyclisation of the products from (c) to the chromanol (115).

d) The reaction mixture from (c) (100 mg.) after being stirred with buffered acetic acid (sodium acetate/acetic acid/water, 2.1 g., 1.5 g. and 10 ml. respectively) for 12 hrs., showed a plethora of products on t.l.c. One compound predominated with  $r_f$  0.3 (40% ethyl acetate-light petroleum). Preparative t.l.c. (40% ethyl acetate-light petroleum) furnished the compound as a colourless oil (7 mg.);

$\nu_{\max}$  3400, 1030, 903, 867 and 810  $\text{cm}^{-1}$

The absence of any saturated carbonyl stretching frequency from the i.r. of the isolated compound prompted an abandonment of the reaction sequence.

$\gamma$ -Lactone trimethylsilyl ether (116).

The  $\gamma$ -lactone alcohol (99) (172 mg., 0.95 m.moles) was dissolved in acetone (5 ml., AnalaR) and trimethylsilyl diethylamide (0.4 ml., 3.92 m.moles) added. The reaction flask was stoppered and allowed to stand for 4 hrs., when t.l.c. (20% ethyl acetate-light petroleum) indicated absence of all starting material. The solvent and excess reagent were removed in vacuo to furnish the trimethylsilyl ether (116) as a yellow oil (240 mg.) which crystallised on standing. Recrystallisation from chloroform gave cubes, m.p. 80-81°;

$\nu_{\max}$ . 1780, 1675, 1255, 980, 860, 755 and 697  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  8.23 (3H;  $\text{CH}_3\text{-C=C}$ , b.s.), 8.0 (2H;  $\text{CH}_2\text{-C=C}$ , m.), 7.7 and 7.35 (2H;  $\text{CH}_2\text{CO}$ , AB q.,  $J_{\text{AB}}$  18 Hz.), 6.43 (2H;  $\text{CH}_2\text{-O}$ , s.), 5.3 (1H;  $\text{CH-O}$ , m.), 4.47 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at  $m/e$  182 [ $\text{M}^+$ ] (loss of  $\text{C}_3\text{H}_8\text{Si}$ ),

$\text{C}_{11}\text{H}_{22}\text{O}_3\text{Si}$  requires  $m/e$  254.

(Found: C, 61.60; H, 8.84;  $\text{C}_{11}\text{H}_{22}\text{O}_3\text{Si}$  requires C, 61.39; H, 8.72%).

Methylation of the trimethylsilyl ether (116).

The procedure for this methylation was analogous to that described for the  $\gamma$ -lactone tetrahydropyranyl ether (102). The trimethylsilyl ether (116) (231 mg., 0.96 m.moles) was treated with lithio di-isopropylamide (1.05 m.moles) in ether and then methyl iodide (1 ml.). Standard isolation procedures furnished the methylated lactone (117) as a yellow oil (186 mg.); g.l.c., 1% OV-17, 175°, flow-rate 48 ml./min., r.t. 3.3 min. (80%) and 4.85 min. (20%);

$\nu_{\text{max}}$ . 1775, 1675, 1255, 1200-1100, 980 and 865  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  9.01 and 8.98 (3H;  $\text{CH}_3\text{-CH}$ , overlapping d., J 7.5 Hz.), 7.55 (1H;  $\text{CH-CH}_3$ , b.q., J 7.5 Hz.), 6.75 and 6.55 (2H;  $\text{CH}_2\text{-O}$ , AB q.,  $J_{\text{AB}}$  10 Hz.), 5.63-5.16 (1H;  $\text{C=C-CH-O}$ , b.m.), 4.73-4.37 (1H;  $\text{CH=C}$ , b.m.).

Addition of lithio 3,3-diethoxy propyne (105) to the trimethylsilyl ether (117).

The lithio salt (105) (0.6 m.moles) was prepared in the manner previously described. The methylated lactone (117) (100 mg., 0.37 m.moles) was added to a stirred,

ethereal solution of the lithio salt (105) at  $-78^{\circ}$ , in an atmosphere of nitrogen, and the reaction vessel maintained at this temperature for 3 hrs. The acetone/Drikold bath was then removed and stirring continued for a further 12 hrs. Work-up procedure, in the manner previously described, furnished a yellow oil (137 mg.) which on preparative t.l.c. (20% ethyl acetate-light petroleum) yielded the lactone alcohol (118) (50 mg.) and four minor components (16 mg.) which were not investigated any further. The approach based on the lactone trimethylsilyl ether (117) was discontinued.

Methylation of the  $\delta$ -lactone acid (82).

The lactone acid (82) (107 mg., 0.546 m.moles) in dry tetrahydrofuran (2 ml.) was added to a stirred solution of lithio di-isopropylamide (1.2 m.moles) in dry tetrahydrofuran, in an atmosphere of nitrogen. A gelatinous precipitate formed almost immediately. The mixture was stirred for a further 10 min. and methyl iodide (0.5 ml.) added. On gentle warming the solution became homogeneous. After 0.5 hr. the mixture was cooled, acidified with dilute hydrochloric acid and extracted with ether. The organic layer was washed with dilute sodium bicarbonate solution, water, brine and dried. Removal of solvent in vacuo furnished a pale-yellow oil

(16 mg.) which rapidly darkened on exposure to air and corresponded to an intractable mixture of products. The aqueous washings were acidified with dilute hydrochloric acid, saturated with sodium chloride and extracted with ether. The ethereal layer was washed with brine and dried. Removal of solvent in vacuo afforded a viscous oil which was esterified with ethereal diazomethane.

Preparative t.l.c. of this colourless gum (96 mg.) (20% ethyl acetate-light petroleum) and isolation of the band with  $r_f$  0.55-0.45 furnished the methylated  $\gamma$ -lactone ester (119) as a viscous oil (80 mg.);

$\nu_{\max}$ . 1775, 1735, 1190 and 975  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.80 and 8.76 (3H;  $\text{CH}_3\text{-CH}$ , overlapping d., J 7 Hz.), 8.23 (3H;  $\text{CH}_3\text{-C=C}$ , b.s.), 8.07-7.63 (4H; methylene envelope), 7.3 and 7.05 (1H;  $\text{CH-CH}_3$ , overlapping q., J 7 Hz.), 6.23 (3H;  $\text{-CO}_2\text{CH}_3$ , s.), 5.1-4.8 (1H;  $\text{CH-O}$ , b.m.), 4.37 (1H;  $\text{CH=C}$ , m.).

(Found: C, 64.09; H, 7.38;  $\text{C}_{12}\text{H}_{16}\text{O}_4$  requires C, 64.27; H; 7.19%).

Addition of lithio 3,3-diethoxy propyne (105) to the  $\gamma$ -lactone ester (119).

The experimental technique was identical to that described for the lactone tetrahydropyranyl ether (103).

This approach resulted in the isolation of starting material and a gamut of products too complex to warrant further investigation.

Approaches to the synthesis of the  $\gamma$ -lactone methyl ether  
(120).

a) Potassium t.-butoxide/t.-butanol/methyl iodide

The lactone alcohol (99) (98 mg., 0.54 m.moles) was treated with potassium t.-butoxide (70 mg., 0.61 m.moles) in t.-butanol (10 ml.) for 1.15 hrs. under nitrogen. Methyl iodide (0.5 ml.) was added and the solution stirred for a further 8 hrs. The mixture was acidified with dilute sulphuric acid, extracted with ether, washed with saturated sodium bicarbonate solution, water, brine and dried. Evaporation of solvent in vacuo furnished an oil (65 mg.) whose t.l.c. and i.r. data was compatible with starting material.

b) Diazomethane/boron trifluoride etherate

Diazomethane was bubbled into an ice-cold solution of the lactone alcohol (99) (138 mg., 0.76 m.moles) and boron trifluoride etherate (11 mg., 0.08 m.moles) in ether (50 ml.) until the solution had acquired a permanent yellow coloration. The solution was stirred for 12 hrs., washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent at reduced pressure furnished a crys-

talline compound (120 mg.) identical by t.l.c. and i.r. with starting material.

Treatment of the  $\gamma$ -lactone alcohol (99) with the reagents (c)-(f) did not allow isolation of the desired lactone ether (120). The lactone alcohol was generally exposed to 1.1-1.2 equivalents of base and treated with an excess of methyl iodide. The work-up procedure was analogous to that described in (a).

c) Sodium/ether.

d) Sodium hydride/ tetrahydrofuran.

e) Lithio di-isopropylamide/tetrahydrofuran.

f) Sodium methoxide/methanol.

h) Sodium hydride/dimethyl formamide/methyl iodide

Sodium hydride (96 mg., 2.2 m.moles) was added to a stirred solution of the lactone alcohol (99) (368 mg., 2.02 m.moles) in dimethyl formamide (10 ml.), at 80°, in an atmosphere of nitrogen. The mixture was stirred for 2 hrs., methyl iodide (1 ml.) was added, and stirring continued for a further 15 hrs. The mixture was cooled and extracted with ether. The organic extract was washed with water, brine and dried. Removal of solvent in vacuo afforded a mobile oil (413 mg.). T.l.c. (30% ethyl acetate-light petroleum) showed three components with  $r_f$  0.5, 0.35 and 0.1. Preparative t.l.c. allowed a separation of the

reaction mixture into:

i) the spiro-lactones (125) and (126), as a colourless oil (171 mg.);

$\nu_{\max.}$  1780, 1180, 1025, 850 and 750  $\text{cm}^{-1}$ ;  
 $\lambda_{\max.}$  (EtOH) 232 and 264  $\mu$ ;  
 $\tau$  ( $\text{CDCl}_3$ ) 8.23 (3H;  $\text{CH}_3\text{-C=C}$ , m.), 7.8-7.4 (obscured) (4H;  $\text{CH}_2\text{-C=C}$ , m.), 7.53 (4H;  $\text{CH}_2\text{-CO}_2^-$ , t., J 18 Hz.), 5.9, 5.8 and 6.01 (4H;  $\text{CH}_2\text{-O-CO}$ , s. and AB q. resp.,  $J_{AB}$  9 Hz.), 5.07 (2H;  $\text{CH}_2=\text{C}$ , b.s.), 4.53 (1H;  $\text{CH}=\text{CCH}_3$ , m.), 4.37 and 4.05 (2H;  $\text{CH}=\text{CH}$ , AB q.,  $J_{AB}$  11 Hz.), 4.07 and 3.75 (2H;  $\text{CH}=\text{CH}$ , AB q.,  $J_{AB}$  10 Hz.);

mass spectral ion at  $m/e$  164 [ $M^+$ ],  $\text{C}_{10}\text{H}_{12}\text{O}_2$  requires  $m/e$  164;

ii) the  $\gamma$ -lactone methyl ether (120) (30 mg., 8%) as a colourless oil;

$\nu_{\max.}$  1775, 1675, 1200 and 980  $\text{cm}^{-1}$ ;  
 $\tau$  ( $\text{CDCl}_3$ ) 8.2 (3H;  $\text{CH}_3\text{-C=C}$ , b,s.), 8.0 (2H;  $\text{CH}_2\text{-C=C}$ , m.), 7.67 and 7.3 (2H;  $\text{CH}_2\text{-CO}_2$ , AB q., J 18 Hz.), 6.7 (2H;  $\text{CH}_2\text{-O}$ , s.), 6.6 (3H;  $\text{CH}_3\text{-O}$ , s.), 5.3 (1H;  $\text{CH-O}$ , m.), 4.41 (1H;  $\text{CH}=\text{C}$ , m.);

mass spectral ion at  $m/e$  196 [ $M^+$ ],  $\text{C}_{11}\text{H}_{16}\text{O}_3$  requires  $m/e$  196;

iii) the  $\gamma$ -lactone alcohol (99).

$\gamma$ -Lactone methoxymethyl ether (132).

a) Chlorodimethyl ether/pyridine

The lactone alcohol (99) (2.59 g., 1.42 m.moles) was taken up in dry pyridine (3.3 ml., 42 m.moles) and chlorodimethyl ether (2.3 ml., 24.4 m.moles) carefully added to the solution. A vigorous, exothermic reaction occurred immediately and a viscous, yellow oil was formed which solidified on cooling. The mass was broken up by addition of ice/water and the mixture extracted with ethyl acetate. The organic layer was washed with aqueous copper sulphate solution, to remove pyridine, water, brine and dried. Removal of solvent in vacuo furnished a pale-yellow oil whose t.l.c. indicated both starting material and a less polar component. The crude mixture was recycled three times, in the manner indicated above, until t.l.c. showed the presence of only a small quantity of the  $\gamma$ -lactone alcohol (99). Final isolation gave an oil (2.87 g.) which was adsorbed on to basic alumina (grade 1, 90 g.) from light petroleum. Successive elution with ethyl acetate-light petroleum (1%-50%) furnished the lactone ether (132) as a faint-yellow, mobile oil (1.52 g., 53%); further elution with acetone gave the lactone alcohol (99) (678 mg.). G.l.c., 1% OV-17, 175°, flow-

rate 30 ml./min., r.t. 6.2 min;

$\nu_{\text{max.}}$  1780, 1680, 1160, 1055 and 990  $\text{cm}^{-1}$ ;  
 $\tau$  ( $\text{CDCl}_3$ ) 8.22 (5H; m.), 8.0 (2H;  $\text{CH}=\text{C}-\underline{\text{CH}}_2$ , m.),  
7.69 and 7.31 (2H;  $\underline{\text{CH}}_2-\text{CO}_2$ , AB q.,  $J_{\text{AB}}$   
17.5 Hz.), 6.61 (3H;  $\underline{\text{CH}}_3-\text{O}$ , s.), 6.53  
(2H;  $\text{C}-\underline{\text{CH}}_2-\text{O}$ , s.), 5.37 (2H;  $\text{O}-\underline{\text{CH}}_2-\text{O}$ , s.),  
5.3 (1H;  $\underline{\text{CH}}-\text{O}$ , m.), 4.43 (1H;  $\underline{\text{CH}}=\text{C}$ , m.);

mass spectral ion at  $m/e$  226 [ $\text{M}^+$ ],  $\text{C}_{12}\text{H}_{18}\text{O}_4$  requires  
 $m/e$  226.

(Found: C, 63.64; H, 8.08;  $\text{C}_{12}\text{H}_{18}\text{O}_4$  requires C, 63.70;  
H, 8.02%).

b) Chlorodimethyl ether/sodium hydride

Sodium hydride (750 mg., 18.8 m.moles) was added rapidly,  
with stirring, to the lactone alcohol (99) (1.5 g., 0.83  
m.moles) in dimethyl formamide (20 ml.) at 65°. Stirring  
of the cream-coloured, vigorously effervescing mixture  
was continued for a further 3 min. The reaction vessel  
was then cooled in an ice/salt bath (5 min.) and chloro-  
dimethyl ether (0.9 ml., 9.5 m.moles) added over a period  
of 1 min. After 10 min. a further addition of chlorodi-  
methyl ether (0.9 ml.) was made; the reaction mixture was  
allowed to reach ambient temperature (20 min.), then  
quenched by careful addition of crushed ice and dilute  
hydrochloric acid (1N). Extraction with ethyl acetate,

successive washings of the organic phase with dilute sodium bicarbonate solution, water, brine and drying over anhydrous sodium sulphate, followed by removal of solvent in vacuo, furnished a yellow oil (1.5 g.). The oil was adsorbed on basic alumina (grade 1, 45 g.) from light petroleum; the fractions eluted with ethyl acetate-light petroleum (10-50%) were combined to afford the lactone ether (132) as a pale-yellow oil (655 mg.). Further elution furnished slightly contaminated lactone ether (132) (500 mg.) from which (132) could be isolated by preparative t.l.c. (30% ethyl acetate-light petroleum) (300 mg.). Overall yield 52%.

This procedure was employed in all subsequent reaction sequences.

#### Methylation of the $\gamma$ -lactone ether (132).

To a stirred solution of di-isopropylamine (645 mg., 6.36 m.moles) in dry ether (25 ml.), under an atmosphere of nitrogen, was added n-butyl lithium (3.16 ml., 2.1M solution in hexane, 6.65 m.moles) at such a rate as to cause gentle refluxing; stirring was continued for a further 10 min. A solution of the lactone (132) (1.3 g., 5.75 m.moles) in dry ether (10 ml.) was added and stirring continued for 15 min. Methyl iodide (4 ml.) was added and the mixture stirred, with heating, for 30 min.

It was then cooled, water added, and the mixture acidified with dilute, aqueous sulphuric acid. The aqueous layer was extracted with ether, the ethereal extracts washed with saturated sodium bicarbonate solution, water, brine and dried. Removal of solvent under reduced pressure afforded the methylated lactone (133) as a yellow oil (1.40 g.) in quantitative yield; g.l.c., 1% OV-17, 175°C, flow-rate 30 ml./min., r.t. 7.3 min.;

$\nu_{\text{max}}$  1778, 1675, 1050 and 990  $\text{cm}^{-1}$ ;

$\tau(\text{CDCl}_3)$  8.83 (3H;  $\text{CH}_3\text{-CH}$ , d., J 8 Hz.), 8.27 (5H; m.), 8.0 (2H;  $\text{CH}_2\text{-C=C}$ , m.), 7.41 (1H;  $\text{CH-CH}_3$ , q., J 8 Hz.), 6.63 (3H;  $\text{CH}_3\text{-O}$ , s.), 6.58 (2H;  $\text{C-CH}_2\text{-O}$ , m. obscured), 5.4 (2H;  $\text{O-CH}_2\text{-O}$ , s.), 5.23 (1H;  $\text{CH-O}$ , m.), 4.55 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at  $m/e$  240 [ $\text{M}^+$ ],  $\text{C}_{13}\text{H}_{20}\text{O}_4$  requires  $m/e$  240.

(Found: C, 64.93; H, 8.38;  $\text{C}_{13}\text{H}_{20}\text{O}_4$  requires C, 64.98; H, 8.39%).

Addition of lithio 3,3-diethoxy propyne (105) to the  $\gamma$ -lactone (133).

n-Butyl lithium (4.25 ml., 2.1M solution in hexane, 8.9 m.moles) was added to a stirred solution of 3,3-diethoxy propyne (1.14 g., 8.9 m.moles) in dry ether

( 25 ml.), in an atmosphere of nitrogen, at  $-78^{\circ}$ . The pale-yellow solution was then stirred for a further 0.5 hr. A solution of the lactone (133) (1.29 g., 5.94 m.moles) in dry ether (10 ml.) was added and stirring continued for 1.5 hrs. The reaction mixture was allowed to warm to room temperature (1 hr.), then quenched by addition of saturated sodium sulphate solution until a fine, granular precipitate was obtained. The ethereal layer was decanted and the precipitate thoroughly washed with ether. The ethereal extracts were combined and solvent removed in vacuo. A yellow oil was obtained which was evaporated several times with carbon tetrachloride to furnish a gum (2.25 g.). The i.r. spectrum exhibited a strong hydroxyl stretching frequency at  $3440\text{ cm}^{-1}$  and a weak carbonyl band at  $1770\text{ cm}^{-1}$ , suggesting the presence of both starting material and product (134). T.l.c. showed two components with  $r_f$  0.55 and 0.46. Preparative t.l.c. (20% ethyl acetate-light petroleum) did not allow isolation of an analytically pure sample of the less polar hemiacetal (134), the lactone (133) invariably being a minor contaminant. The material, however, was sufficiently pure to allow a spectral characterisation of (134);

$\nu_{\text{max}}$ . 3440, 1770 (weak), 1670 and 1100-1000  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.92 (3H;  $\text{CH}_3\text{-CH}$ , d., J 7 Hz.), 8.8 (6H;  $\text{CH}_3\text{-CH}_2\text{-O}$ , t., J 6 Hz.), 8.28 (3H;

$\underline{\text{CH}}_3\text{-C}=\text{C}$ , b.s.), 6.6 (3H;  $\underline{\text{CH}}_3\text{-O}$ , s.), 6.7-6.0 (6H;  $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$  and  $\text{C-CH}_2\text{-O-CH}_2$ , b.m.), 5.57 (1H;  $\underline{\text{CH}}\text{-O}$ , m.), 5.43-5.07 (3H; b.m.), 4.7 (1H;  $\underline{\text{CH}}\text{-C}=\text{C}$ , b.s.), 4.47 (1H;  $\underline{\text{CH}}=\text{C}$ , m.);

high resolution mass spectroscopy showed an ion at  $m/e$  350.2106 (loss of  $\text{H}_2\text{O}$ ),  $\text{C}_{20}\text{H}_{30}\text{O}_5$  requires 350.2093.

Sodium borohydride reduction of the hemi-acetal (134).

Sodium borohydride (2 g., 52.6 m.moles) was added to a stirred, ice-cold solution of the acetal (134) (2.1 g.) in ethanol/water (10 ml., 1:1, v./v.) and stirring continued at room temperature for 2 hrs. The solution was extracted with ethyl acetate and the organic phase washed with water, brine and dried over magnesium sulphate-potassium carbonate. Removal of solvent in vacuo afforded the diol (136) as a colourless oil (2.07 g.). T.l.c. (60% ethyl acetate-light petroleum) showed one major product,  $r_f$  0.47, staining black with Ceric (III) spray. Preparative t.l.c. of a sample allowed isolation of the diol (136); the overall yield from the lactone (132) was 50%;

$\nu_{\text{max}}$ . 3360, 1674 and 1200-1050  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  8.81 (3H;  $\underline{\text{CH}}_3\text{-CH}$ , d.,  $J$  7.5 Hz.), 8.78  
(6H;  $\underline{\text{CH}}_3\text{-CH}_2\text{-O}$ , t.,  $J$  6.5 Hz.), 8.3 (3H;  
 $\underline{\text{CH}}_3\text{-C}=\text{C}$ , b.s.), 8.5-7.54 (5H; b.m.), 6.63

(3H;  $\text{CH}_3\text{-O}$ , s.), 6.8-5.9 (7H; b.m.), 5.41  
(2H;  $\text{O-CH}_2\text{-O}$ , s.), 5.08 (1H;  $\text{CH-O}$ , b.s.),  
4.68 (1H;  $\text{CH-C C}$ , b.s.), 4.41 (1H;  $\text{CH=C}$ , m.);

high resolution mass spectroscopy showed an ion at  
m/e 307.19622 (loss of  $\text{C}_2\text{H}_7\text{O}_2$ ),  $\text{C}_{18}\text{H}_{27}\text{O}_4$  requires m/e  
307.19092.

Sodium/liquid ammonia reduction of the acetylenic diol (136).

A 500 ml. flask, fitted with an acetone-Drikold  
condenser and a mechanical stirrer was charged with liquid  
ammonia (250 ml., distilled from sodium). Sodium metal  
(644 mg., 28 m.moles) was then added in portions and the  
resulting dark-blue solution stirred for 5 min. The  
crude acetylenic diol (136) (2.58 g.) in dry ether (10 ml.)  
was added rapidly and the mixture stirred for 10 min.  
The reaction was quenched by dropwise addition of absolute  
ethanol. Ammonia was allowed to evaporate and ice-water  
was added to the residual, yellow slurry. The aqueous  
mixture was saturated with salt, then thoroughly extrac-  
ted with ethyl acetate. The organic extracts were com-  
bined, washed with brine/water (1:1) and dried over anhyd-  
rous magnesium sulphate-potassium carbonate. Evaporation  
of solvent in vacuo afforded a yellow gum (1.9 g.). T.l.c.  
(60% ethyl acetate-light petroleum) showed the olefinic  
diol (137) as a characteristic cherry-red spot with  $r_f$  0.35  
[developed with Ceric (III) spray]. A purified sample of

(137) was obtained after preparative t.l.c.;

$\nu_{\text{max.}}$  3400, 1675 and 1200-1100  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  9.15 (3H;  $\text{CH}_3\text{-CH}$ , d., J 7.5 Hz.), 8.89  
(3H;  $\text{CH}_3\text{-CH}_2$ , t., J 7 Hz.), 8.39 (3H;  
 $\text{CH}_3\text{-C=C}$ , b.s.), 6.73 (3H;  $\text{OCH}_3$ , s.), 5.5  
(2H;  $\text{O-CH}_2\text{-O}$ , s.), 5.13 (1H;  $\text{CH(OEt)}_2$ , d.,  
J 3 Hz.), 4.1 (1H;  $\text{C=CH-CH(OEt)}_2$ , d.d.,  
J 16 Hz. and 3Hz.).

High resolution mass spectroscopy did not allow a characterisation of (137).

Acid catalysed rearrangement of the olefinic diol (137).

The crude olefinic diol (137) (1.9 g.) was added to a solution of buffered acetic acid (sodium acetate/acetic acid/water-4.1 g./4 g./20 ml.) and the mixture stirred vigorously for 18 hrs. The solution was extracted with ether and the organic layer washed with saturated sodium bicarbonate solution, water, brine and dried. Removal of solvent in vacuo afforded a viscous, yellow oil (1.4 g.) which was purified by preparative t.l.c. (60% ethyl acetate-light petroleum). Extraction of the band with  $r_f$  0.35-0.5 furnished the hydroxy-aldehyde (147) as a pale-yellow oil (467 mg.);

$\nu_{\text{max.}}$  3440, 2740, 1720, 1674 and 1150-1100  $\text{cm}^{-1}$ ;  
 $\tau(\text{CDCl}_3)$  9.0 (3H;  $\text{CH}_3\text{-CH}$ , d., J 7.5 Hz.), 7.27

(2H;  $\underline{\text{CH}}_2\text{-CHO}$ , m.), 6.63 (3H;  $\underline{\text{CH}}_3\text{O}$ , s.),  
5.5 (1H;  $\text{C}=\text{C}-\underline{\text{CH}}-\text{O}$ , m.), 5.38 (2H;  $\text{O}-\underline{\text{CH}}_2-\text{O}$ ,  
s.), 4.67 (1H;  $\underline{\text{CH}}=\text{C}$ , m.), -0.7 (1H;  $\underline{\text{CHO}}$ ,  
t., J 2.5 Hz.);

high resolution mass spectroscopy showed an ion at  
m/e 266.15143 (loss of  $\text{CH}_3\text{CHO}$ ),  $\text{C}_{15}\text{H}_{22}\text{O}_4$  requires m/e  
266.15180.

Cornforth oxidation<sup>85</sup> of the hydroxy-aldehyde (147).

A solution of chromium trioxide (2.57 g., 25.7  
m.moles) in water (2.9 ml.) was added, with external  
cooling and stirring, to pyridine (29 ml.). The hydroxy-  
aldehyde (147) (530 mg., 1.71 m.moles) in pyridine (5.4  
ml.) was then added to the mixture and the dark-brown  
solution stirred vigorously for 18 hrs. The reaction  
vessel was cooled in an ice-bath for a few minutes, the  
viscous mixture acidified with aqueous, dilute hydrochloric  
acid (1N) and filtered through a pad of celite.  
The aqueous solution was saturated with sodium chloride  
and extracted with ethyl acetate. The organic phase was  
washed with brine and dried. Removal of solvent in vacuo  
afforded an intense-yellow gum (510 mg.). The gum was  
taken up in ether and extracted with aqueous, saturated  
sodium carbonate solution. The aqueous layer was reaci-  
dified with dilute hydrochloric acid (1N), saturated with

sodium chloride and extracted with ethyl acetate. The organic phase was washed with brine, dried and solvent removed under reduced pressure. The pale-yellow gum (275 mg.) thus obtained was immediately esterified with ethereal diazomethane and subjected to preparative t.l.c. (75% ether-light petroleum) to furnish two components: i) the keto-ester (154) (48 mg., 8.3%) as a crystalline compound, m.p. 52-55°; g.l.c., 5% QF1, 175°, flow-rate 69 ml./min., r.t. 12.94 min.;

ν Nujol max. 1735, 1720, 1670, 1150 and 925 cm.<sup>-1</sup>;

τ (CDCl<sub>3</sub>) 9.0 (3H; CH<sub>3</sub>-CH, d., J 7 Hz.), 8.27 (3H; CH<sub>3</sub>-C=C, b.s.), 8.12-7.9 (2H; CH<sub>2</sub>-C=C, b.m.), 7.51 (1H; CH-CO<sub>2</sub>Me, A part of ABX system, J<sub>AB</sub> 17 Hz., J<sub>AX</sub> 7 Hz.), 7.11 (1H; CH-CO<sub>2</sub>Me, B part of ABX system, J<sub>AB</sub> 17 Hz., J<sub>BX</sub> 7 Hz.), 7.29 (1H; COCH-CH<sub>3</sub>, q., J 7 Hz.), 6.73 and 6.66 (2H; C-CH<sub>2</sub>-O, AB q., J<sub>AB</sub> 9 Hz.), 6.72 (3H; CH<sub>3</sub>-O-CH<sub>2</sub>, s.), 5.53 (2H; COCH-CH<sub>2</sub>, b.t., C=C-CH-O, obscured), 5.5 (2H; O-CH<sub>2</sub>-O, s.), 4.52 (1H; m.);

high resolution mass spectral ion at m/e 326.172124 [M<sup>+</sup>], C<sub>17</sub>H<sub>26</sub>O<sub>6</sub> requires m/e 326.172934;

ii) the hydroxy-ester (155) (173 mg., 30%) as a crystalline compound. Recrystallisation from chloroform-benzene gave fine needles, m.p. 89.5-95°; g.l.c., 5% QF1, 160°,

flow-rate 40 ml./min., r.t. 6.8 min. (broad peak);

$\nu$  <sub>max.</sub> Nujol 3490, 1740, 1672, 1160 and 1050  $\text{cm}^{-1}$ ;

$\nu$  ( $\text{CDCl}_3$ ) 9.02 (3H;  $\text{CH}_3\text{-CH}$ , d., J 7 Hz.), 7.68 (1H;  $\text{CH-OH}$ , m.), 7.45 (1H;  $\text{CH-CO}_2\text{Me}$ , A part of ABX system,  $J_{\text{AB}}$  16 Hz.,  $J_{\text{AX}}$  5.5 Hz.), 7.23 (1H;  $\text{CH-CO}_2\text{Me}$ , B part of ABX system,  $J_{\text{BA}}$  16 Hz.,  $J_{\text{BX}}$  6 Hz.), 6.69 (3H;  $\text{COCH}_3$ , s.), 6.4-6.08 (2H; m.), 6.32 (3H;  $\text{CO}_2\text{Me}$ , s.), 5.54 (1H;  $\text{C=C-CH-O}$ , m.), 5.42 (2H;  $\text{O-CH}_2\text{-O}$ , s.), 4.67 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at m/e 328,  $\text{C}_{17}\text{H}_{28}\text{O}_6$  requires m/e 328.

(Found: C, 62.34; H, 8.55;  $\text{C}_{17}\text{H}_{28}\text{O}_6$  requires C, 62.18; H, 8.59%).

The neutral fraction (105 mg.) derived from the oxidation showed a gamut of products on t.l.c. and a  $\gamma$ -lactone stretching frequency in the i.r. spectrum. The major component (13 mg.) was isolated by preparative t.l.c. (20% ethyl acetate-light petroleum);

$\nu$  <sub>max.</sub> 1765, 1665, 1150, 1110, 1050 and 970  $\text{cm}^{-1}$ ;

g.l.c., 5% QF1, 175°, flow-rate 58 ml./min., r.t. 8.55 and 9.34 min.

No definite structural assignment was made; it is possible that the material corresponds to the tricyclic lactones (156) and (157).

Dicyclohexylcarbodiimide-dimethyl sulphoxide<sup>87</sup> oxidation  
of the hydroxy-ester (155).

Pyridinium trifluoroacetate (44.6 mg., 0.23 m.moles) and dicyclohexylcarbodiimide (268 mg., 1.3 m.moles) were dissolved in dimethyl sulphoxide-benzene (3.6 ml., 1:1, v./v.). The hydroxy-ester (155) (159 mg., 0.49 m.moles) was added to the stirred solution. Almost immediately a fine, silvery precipitate of dicyclohexyl-urea was deposited. After 4 hrs. the mixture was taken up in ethyl acetate (5 ml.) and filtered. The filtrate was concentrated in vacuo and subjected to preparative t.l.c. (75% ether-light petroleum). The keto-ester (154) (110 mg., 85%) was isolated together with a little starting material (155) (29.6 mg.).

Dicyclohexylcarbodiimide-dimethyl sulphoxide<sup>87</sup> oxidation  
of the hydroxy-acid (158).

The crude acidic fraction obtained from the Cornforth oxidation procedure (470 mg.) was oxidised in the manner described above. After removal of dicyclohexyl-urea by filtration, the filtrate was taken up in ether and extracted with aqueous, dilute sodium carbonate. The aqueous layer was acidified with dilute hydrochloric acid (1N), saturated with sodium chloride and extracted with ethyl acetate. The organic phase was washed with brine

and dried. Removal of solvent at reduced pressure furnished the keto-acid (159) (12 mg.). The neutral extract, after drying and removal of solvent at reduced pressure, afforded a viscous oil with a sharp, sulphurous odour. Preparative t.l.c. allowed the isolation of the thioester (160) as a pale-yellow oil (97 mg.);

$\nu_{\text{max}}$  1742, 1720, 1160, 1120 and 1050  $\text{cm}^{-1}$ ;  
 $\tau$  ( $\text{CDCl}_3$ ) 8.95 (3H;  $\text{CH}_3\text{CH}$ , d., J 7 Hz.), 7.75 (3H;  $\text{CH}_3\text{-S}$ , s.), 7.57-6.93 (3H;  $\text{CH}_2\text{-CO}_2^-$ , and  $\text{CH-CH}_3$ , m.), 6.66 (3H;  $\text{CH}_3\text{-O}$ , s.), 5.47 (2H;  $\text{O-CH}_2\text{-O}$ , s.), 4.82 (2H;  $\text{O-CH}_2\text{-S}$ , s.), 4.47 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at  $m/e$  372.160075 [ $\text{M}^+$ ],  $\text{C}_{18}\text{H}_{28}\text{O}_6\text{S}$  requires 372.160657.

Jones oxidation<sup>55</sup> of the hydroxy-aldehyde (147).

Jones' reagent (8N) was added to a solution of the hydroxy-aldehyde (147) (75 mg., 0.24 m.moles) in acetone (10 ml., AnalaR) at  $0^\circ$  until the solution became permanently orange coloured. The mixture was allowed to stand for 1 hr. and then poured on to saturated sodium bicarbonate solution. The solution was extracted with ether and the aqueous layer acidified with dilute hydrochloric acid (1N) and saturated with sodium chloride. The aqueous solution was extracted with ethyl acetate, the organic

phase washed with brine and dried. Removal of solvent in vacuo afforded a gum which was esterified with diazomethane. Preparative t.l.c. (75% ether-light petroleum) furnished the keto-ester (154) (25 mg., 30%).

Hydrolysis of the keto-ester (154).

The keto-ester (154) (150 mg., 0.46 m.moles) was heated with aqueous sodium hydroxide (5 ml., 4N) and methanol (5 ml.) for 1.5 hrs. at 40°. The aqueous solution was cooled and extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid (1N), saturated with sodium chloride and thoroughly extracted with ethyl acetate. The organic layer was washed with brine and dried. Removal of solvent in vacuo afforded the keto-acid (159) (138 mg., 96%) as a viscous oil;

$\nu_{\text{max.}}$  3600-2450, 1720, 1155, 1115 and 1050  $\text{cm.}^{-1}$

Treatment of the keto-acid (159) with sodium acetate-acetic anhydride.

A mixture of the keto-acid (159) (138 mg., 0.45 m.moles), fused sodium acetate (110 mg., 1.34 m.moles) and acetic anhydride (3.3 ml.) was refluxed for 1.5 hrs. The black reaction product was cooled and saturated potassium carbonate solution added. Solid potassium carbonate was introduced into the reaction flask at

5 min. intervals until all effervescence had ceased and the solution was alkaline to litmus. The mixture was extracted with ether, the organic layer was washed with water, brine and dried. Removal of solvent furnished a dark-brown oil (120 mg.). T.l.c. (50% ethyl acetate-light petroleum) showed two products with  $r_f$  0.58 and 0.53. Preparative t.l.c. (25% ethyl acetate-light petroleum) allowed the mixture to be separated into:

i) the less polar enol lactone (153), as a colourless oil (23.4 mg.); g.l.c., 5% QF1, 175°, flow-rate 58 ml./min., r.t. 12.47 min.;

$\nu_{\max}$  1810, 1725, 1670, 1250-1000, 970 and 860  $\text{cm}^{-1}$ ;

$\tau$  ( $\text{CDCl}_3$ ) 8.30 (3H;  $\text{CH}_3\text{-C=C-O}$ , d.,  $J$  2 Hz.), 8.23 (3H;  $\text{CH}_3\text{-C=C}$ , b.s.), 7.39 (1H;  $\text{O-CH-CH}_2$ , A part of ABX system,  $J_{AB}$  16 Hz.,  $J_{AX}$  11.81 Hz.), 7.27 (1H;  $\text{O-CH-CH}_2$ , B part of ABX system,  $J_{BA}$  16 Hz.,  $J_{BX}$  7.19 Hz.), 6.68 (3H;  $\text{CH}_3\text{-O}$ , s.), 6.58 and 6.50 (2H;  $\text{C-CH}_2\text{-O}$ , AB q.,  $J_{AB}$  9 Hz.), 5.44 (2H;  $\text{O-CH}_2\text{-O}$ , s.), 4.75 (1H;  $\text{CH=C}$ , m.);

mass spectral ion at  $m/e$  294.146476 [ $\text{M}^+$ ],  $\text{C}_{16}\text{H}_{22}\text{O}_5$  requires  $m/e$  294.146472;

ii) the more polar enol lactone (153), as a colourless oil (43 mg.); g.l.c., 5% QF1, 175°, flow-rate 58 ml./

min., r.t. 14.5 min;

$\nu$  max. 1810, 1730, 1675, 1130, 1050, 960 and  
870  $\text{cm}^{-1}$ ;

$\delta$  ( $\text{CDCl}_3$ ) 7.43 (1H; O-CH-CH<sub>2</sub>, A part of ABX system,  
 $J_{AB}$  17.5 Hz.,  $J_{AX}$  9.5 Hz.),  
7.33 (1H; B part of ABX system,  $J_{BA}$  17.5  
Hz.,  $J_{BX}$  11.5 Hz.), 6.74 (3H; CH<sub>3</sub>-O, s.),  
6.62 and 6.48 (2H; C-CH<sub>2</sub>-O, AB q.,  $J_{AB}$   
10 Hz., 5.94 (1H; C=C-CH-O, b.d.), 5.48  
(2H; O-CH<sub>2</sub>-O, s.), 5.54-5.16 (1H; O-CH-CH<sub>2</sub>,  
m.), 4.50 (1H; CH=C, b.d.);

mass spectral ion at  $m/e$  294.146568 [ $M^+$ ],  $\text{C}_{16}\text{H}_{22}\text{O}_5$   
requires  $m/e$  294.146472.

Attempted reductive cyclisation of the enol lactone (153).

Dry *t*-butanol (17.7 mg., 0.24 m.moles) in dry ether (1 ml.) was added to a stirred dispersion of lithium aluminium hydride (3.3 mg., 0.086 m.moles) in dry ether (2 ml.) in an atmosphere of nitrogen. The mixture was then cooled to  $-78^\circ$  and a solution of the less polar enol lactone (153) (18 mg., 0.061 m.moles) in dry ether (1 ml.) added. The mixture was allowed to warm to room temperature and then stirred for 45 min. Saturated sodium sulphate solution was added until a fine, grey precipitate was obtained. The mixture was filtered and

the filtrate concentrated in vacuo. A viscous oil was obtained, whose i.r. spectrum did not show the high carbonyl stretching frequency normally associated with bicyclo[3,2,1]octan-8-ones, and whose t.l.c. (90% ethyl acetate-light petroleum) showed the presence of two major products with  $r_f$  0.55 and 0.47 together with starting material. The more polar compound was isolated by preparative t.l.c. as a gum (4 mg.);

$\nu_{\max}$ . 3470, 1720, 1200-1000 and 920  $\text{cm}^{-1}$

This compound was not further investigated but was probably the hydroxy-ketone (165).

The less polar component was also obtained as a gum (4 mg.);

$\nu_{\max}$ . 1720, 1150, 1050 and 930  $\text{cm}^{-1}$

It is conceivable that the compound in question is the keto-aldehyde (164).

Subsequent attempts to induce the enol lactone mixture (153a) and (153b) to undergo cyclisation to the ketol (166), under similar conditions, were unsuccessful.

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