DIELS-ALDER APPROACHES TOWARDS T-2 TOXIN AND RELATED TRICHOTHECENES

by

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I wish to dedicate this thesis to my parents.

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SUMMARY

The trichothecenes are a group of some 80 structurally complex sesquiterpenoids of considerable environmental importance. It is difficult to obtain many of these compounds in significant amounts from natural sources, and much effort has been directed towards devising efficient, practicable syntheses of these molecules and their analogues.

In the course of this research, a study of intermolecular Diels-Alder routes towards potential trichothecene precursors was carried out. Particular attention was paid to devising a general route towards T2 toxin (185), a highly oxygenated trichothecene which has yet to yield to total synthesis. To this end the cycloaddition reaction between a suitably functionalised 1,3-butadiene and an alkyl coumalate was investigated. Two major areas of study were undertaken: the Diels-Alder reaction between isoprene and a coumalic acid derivative and the cycloaddition reaction between a 2-silyloxy-substituted buta-1,3-diene and methyl coumalate.

The Diels-Alder reaction between isoprene and methyl coumalate suffered from poor regioselectivity and afforded low yields of the desired adduct (157a). Significant improvements in both the regioselectivity and yield of desired adduct were obtained when coumalyl chloride (191) was employed as dienophile. Seleno- and iodolactonisation of carboxylic acid (186a) derived from adduct (157a) afforded the unexpected bicyclo [2.2.2] octane systems (192) and (195) respectively, neither of which could be converted into useful trichothecene precursors.

Alternatively, bromination of the conjugate addition product (158), followed by a sequence of acetolysis and hydrolysis, furnished a 1:1 mixture of α-allylic alcohol (200a) and β-allylic alcohol (200b). α-Allylic

alcohol (200a) possesses ideal functionality for further elaboration to T2 toxin, and was accordingly converted into the corresponding γ-lactone (203), thereby establishing the desired α-configuration of the 8-hydroxyl group.

Catalytic osmylation of the conjugate addition product (158) afforded cis diol (205a) as the major product, which after a sequence of silylation, dehydration and finally fluoride-induced desilylation was transformed into the same α-allylic alcohol (200a)'.

Cycloaddition between 2-silyloxy-substituted buta-1,3-dienes and methyl coumalate was observed to be a highly regiospecific process, affording the expected silyl enol ethers in respectable yields.

In an attempt to prepare α-bromoketone (228) it was observed that the product obtained from bromination of the t-butyldimethylsilyl enol ether (218a) depended upon the reaction conditions employed. In the absence of pyridine the expected α-bromoketone was obtained. Interestingly, however, in the presence of pyridine the α-bromo silyl enol ether (231) was formed regioselectively.

ABBREVIATIONS

Ac	Acetate
Bz	Benzyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	3-(N,N-Dimethylamino)pyridine
DMF	N,N-Dimethylformamide
Im	Imidazole
LDA	Lithium diisopropylamide
mCPBA	Meta-Chloroperbenzoic acid
Ms	Methane Sulphonyl
NMMO	N-Methylmorpholine-N-oxide
PDC	Pyridinium dichromate
p-TSA	p-Toluene sulphonic acid
Py	Pyridine
THF	Tetrahydrofuran
TBDMS	t-Butyldimethylsilyl
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
Ts	p-Toluenesulphonyl

BIOLOGICAL ACTIVITY

The trichothecene mycotoxins constitute a class of highly oxygenated, complex sesquiterpenoids, which share many structural features, in particular a tricyclic skeleton, a 12,13-spiro epoxide and a 9,10-double bond.

The trivial name, trichothecene, was coined by Godtfredsen[1] in 1967, after trichothecin, the first member of this family of compounds to be isolated, by Freeman and Morrison, in 1949 from a culture of *Trichoderma roseum*, while screening for new antibiotic compounds.[2]

Since then, more than 80 trichothecene mycotoxins have been identified. Usually each trichothecene was isolated because of some interesting biological properties; for example, trichothecin and crotocin were isolated as a result of their antibiotic activity, whereas the verrucarins and roridins were observed to have pronounced cytostatic and antifungal behaviour.

These mould metabolites, with the exception of the baccharins, are produced by nine species of taxonomically-unrelated, imperfect fungi[3]: *Fusarium*, *Myrothecium*, *Trichoderma*, *Trichothecium*, *Cephalosporium*, *Cyclindrocarpen*, *Stachybotrys*, *Verticimonosporium* and *Calonectria*. Alternatively, the macrocyclic baccharins, isolated from the shrub *Baccharis megapotamica*, are fungal metabolites, absorbed from the soil and subsequently biotransformed by the plant[4].

The synthetic challenge, combined with the pronounced biological activity of the trichothecenes has generated much interest in this class of compounds. These complex target molecules have captured the attention of synthetic chemists to the extent that, since 1980, intense research effort has resulted in more than ten syntheses of naturally occurring trichothecenes; a discussion of these will be detailed later.

Additionally, the staggering array of biological activity which has been attributed to these mould metabolites has attracted the keen interest of biologists. Coupled with this is the interest of pharmaceutical companies interested in developing novel antibiotics and active antitumour agents from this family of compounds.

From an economic standpoint, the trichothecenes are of worldwide importance because they contaminate economically important crop plants, which if consumed result in human and animal toxicoses. This problem would not be of such great importance if the occurrence of these fungi was restricted to rare ecological niches. However, they do enjoy widespread occurrence and have been known to contaminate a wide variety of host plants including barley, maize, rice, rye and wheat.

Because these mycotoxins induce their adverse effects on both man and domestic animals at concentrations in the low level, contaminated crops should not be used as feedstocks. Indeed the number of human poisonings[5] resulting from ingestion of the trichothecene mycotoxins far outnumbers those of any other, apart from the aflatoxins. More recently with the development of improved detection techniques, these compounds have been implicated as the causative agents in a number of ailments[6] including mouldy-corn toxicoses[7], food-refusal phenomena[8] and also human alimentary toxic aleukia[9].

Furthermore, a moral issue concerning these compounds arose recently, when they were implicated as substances which may have been used in biological warfare in South East Asia and Afghanistan.

It is a well established fact that the trichothecene mycotoxins have a wide array of biological activity. Their most notable biological properties include antifungal, insecticidal, phytotoxic and cytostatic behaviour, with a few compounds also exhibiting antiviral action.

In addition, the adverse mammalian symptoms for which these compounds are responsible range from severe skin irritations[10], haematological disorders[6], vomiting[5] and diarrhoea, to eventual death. They are believed to be potent inhibitors of protein synthesis in eukaryotes[11].

T-2-toxin, isolated from Fusarium tricinctum, is one of the most toxic members of this family of compounds. Their toxicity has been shown to be associated with the presence of the 12,13-epoxide group; removal of this function resulted in loss of toxicity[12]. Additionally, the 9,10-double bond is believed to be a contributing factor, although to a lesser extent than the aforementioned epoxide group, and esterification of some of the hydroxyl groups has been shown to be important in the manifestation of high toxicity.

Although no attempt should be made to underestimate the adverse mammalian effects that these substances induce, it is believed that some properties of the trichothecenes, for example antileukemic activity, could be beneficial to man, particularly in cancer treatment. This belief arose initially as a result of studies carried out by Harri and coworkers[13], which showed that the majority of trichothecenes exhibited in vitro cytotoxic activity. Verrucarin A was observed to be particularly active, causing inhibition of mouse tumour cell growth at a concentration of only 0.6ng/ml. Furthermore, one of the simpler trichothecenes, anguidine, isolated from Fusarium scirpi, exhibited cytopathogenic effects against tumour cells; because of its lower mammalian toxicity, it has recently completed Phase 1 Clinical cancer trials in the United states[14,15].

The major problem in clinical use of trichothecenes is their toxicity towards man. Research is currently being carried out in an attempt to

develop synthetic analogues which ideally would retain their beneficial cytostatic activity, but lose their adverse toxic effects. Forseeably, the discovery of such a compound would contribute significantly towards the successful treatment of cancer and would fill an obvious niche in today's drug arsenal.

In addition, many trichothecenes have been tested against a variety of both human and plant pathogenic fungi. Anguidine was observed to be completely inhibitory to Candida albicans[16], a pathogenic yeast infection, and it has been proposed that anguidine be used therapeutically for such infections in man.

In conclusion, it would appear that the trichothecenes pose a particularly serious problem to man and his domestic animals. However, it is hoped that synthetic and biosynthetic manipulation will result in man's fuller exploitation of the potentially beneficial properties of these compounds.

STRUCTURE

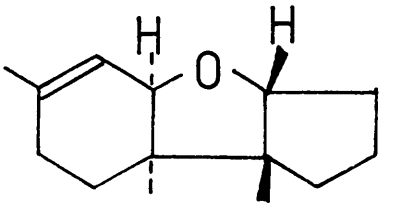
The naturally occurring trichothecenes are colourless, optically active crystalline solids. They are quite stable and can withstand prolonged laboratory storage, but under suitable conditions they undergo characteristic reactions. For example, the ester functions undergo facile hydrolysis, the hydroxyl groups can be oxidised to the corresponding aldehydes or ketones, and the epoxide ring can be opened under a variety of normally intramolecular conditions.

Although trichothecin was isolated as early as 1949, the structural determination of this group of compounds presented a problem which was not fully solved until fifteen years later.

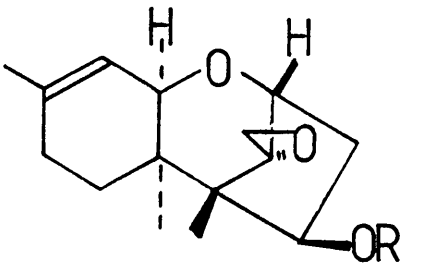
Chemical degradation and correlation have played a major role in structure determination, with extensive chemical studies, including oxidation, hydrolyses and treatment with acids and bases regularly being used[18].

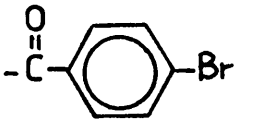
Initial structure determination studies on the trichothecenes were carried out at the laboratories of Freeman[18], Fishman[19] and Tamm[13]. Independently, all three groups of workers arrived at a similar, but incorrect structure, now known as the apotrichothecene framework (1).

A major structural breakthrough was made in 1964, as a result of single crystal x-ray diffraction studies, carried out by Godtfredsen, on the p-bromobenzoate derivative of trichodermol (2)[20,21]. These studies proved unequivocally that the structure was in fact the tricyclic epoxide (3), which is now recognised as being characteristic of the naturally occurring trichothecenes. Revision in structural assignments were made and all known trichothecenes were correlated with trichodermol(3).



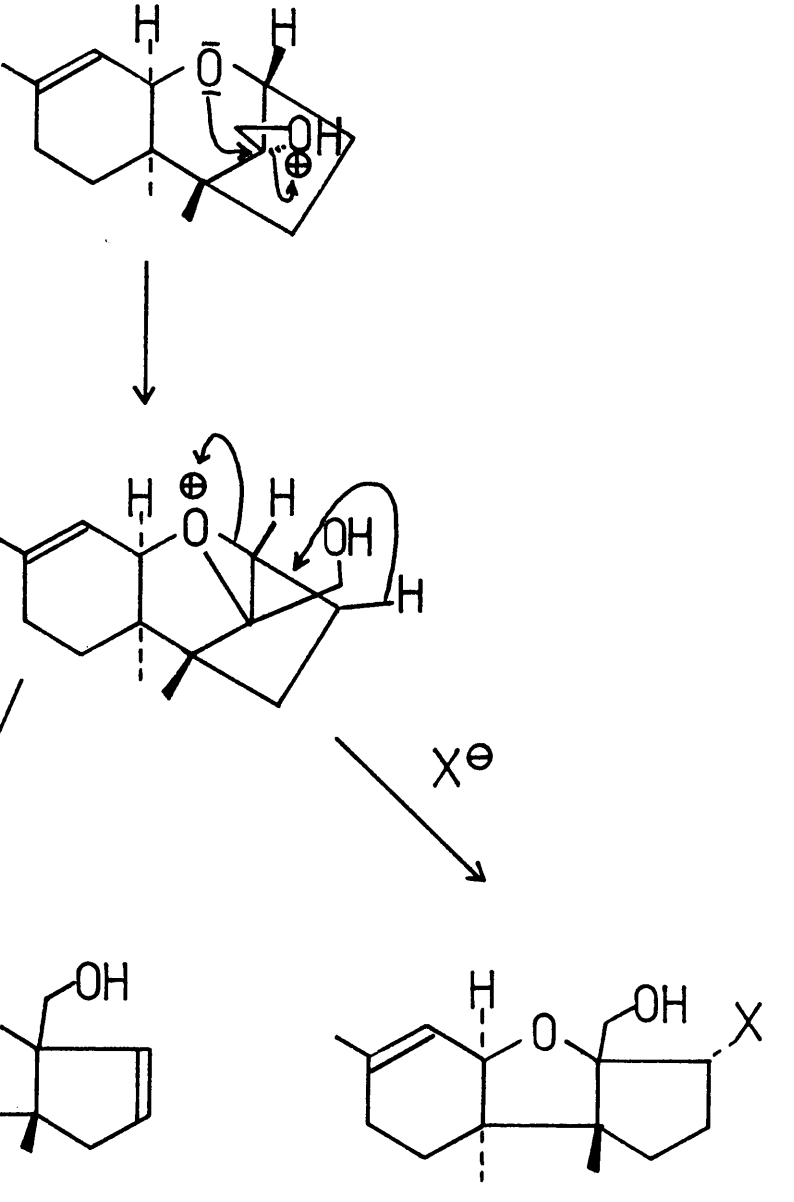
(1)



(2) 

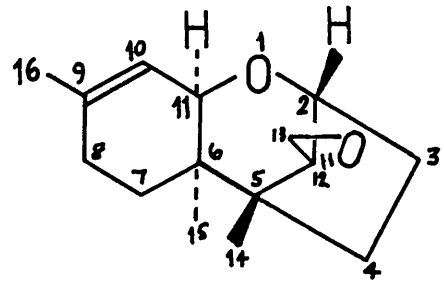
(3) R=H

Scheme 1



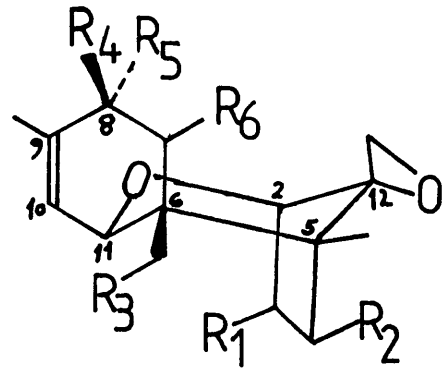
It is important to note at this point that rearrangement of the tricyclic 12,13-epoxytrichothec-9-ene to the corresponding apotrichothecene system is a facile process, which can be readily effected by mild acid treatment, when it is believed to follow the mechanism indicated in Scheme (1).

Accordingly, the trichothecene skeleton is commonly represented by structure (4) with the numbering system shown:-



(4)

In addition, conformational studies have indicated that structure (5) is likely to represent the most stable conformer of the trichothecene framework[22].



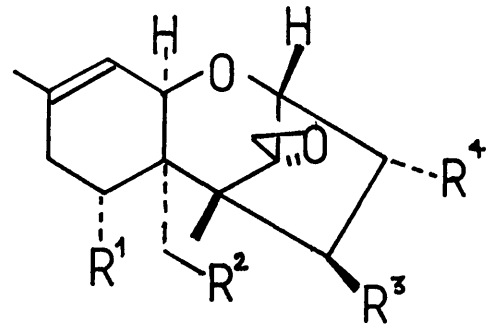
(5)

As a result of improved instrumentation and the development of sophisticated nuclear magnetic resonance techniques, both ^{1}H- and ^{13}C-nmr now play important roles in structural analyses of the trichothecenes. The rigid nature of the tetracyclic skeleton means that the trichothecenes lend themselves ideally to ^{1}H-nmr analyses, with the rigid nucleus providing a number of diagnostic long-range proton-proton couplings, along with characteristic chemical shift values.

Furthermore, ^{1}H-nmr has been extensively used to determine both the site and stereochemistry of hydroxylation in trichothecene molecules.[17] Unfortunately this technique has proven to be of limited utility in the assignment of stereochemistry and double bond geometry in the more flexible ester chains of the macrocyclic trichothecenes. Moreover, it has been shown that few useful correlations can be drawn from mass spectral fragmentation patterns of these compounds[12].

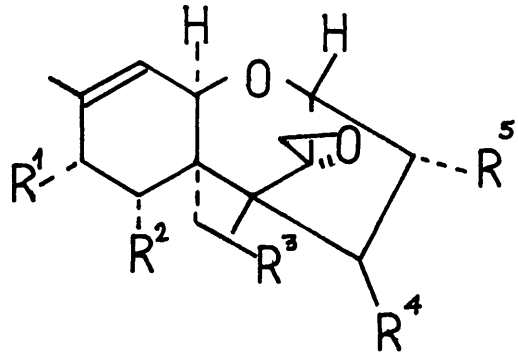
For the purpose of structural discussion, it is customary to subdivide the eighty or so known trichothecenes into three distinct structural sub-groups. The simple trichothecenes, of which there are currently 38 members, will form the main subject of this report. Tables 1, 2 and 3[23] contain a full list of this group of compounds. As indicated, this subset comprises the basic mono- or polyhydroxylated sesquiterpenoids, which can have none, one or more of the hydroxyl groups esterified with acetic, crotonic, isovaleric, lactic or β-hydroxy-isovaleric acid. Furthermore, the oxidation level at C-8 can vary from saturation to an α-hydroxyl to a carbonyl function. T-2-toxin, which served as a synthetic target for this research project, proved to be a formidable challenge; it is a 3α, 4β, 8α and 15-hydroxy trichothecene with the 8α-hydroxyl esterified with isovaleric acid.

TABLE 1



Name	R^1	R^2	R^3	R^4
12,13-epoxytrichothec-9-ene	H	H	H	H
Trichodermol	H	H	OH	H
Trichodermin	H	H	OAC	H
15-Deacetylcalonectrin	H	OH	H	OAC
Calonectrin	H	OAC	H	OAC
Di-O-acetylverrucarol	H	OAC	OAC	H
Scirpentriol	H	OH	OH	OH
15-Acetoxyscirpenol	H	OAC	OH	OH
Anguidine	H	OAC	OAC	OH
7-Hydroxyanguidine	OH	OAC	OAC	OH
4-Acetoxyscirpendiol	H	OH	OAC	OH
Triacetoxyscirpenol	H	OAC	OAC	OAC
7-Hydroxyscirpentriol	OH	OH	OH	OH
Verrucarol	H	OH	OH	H

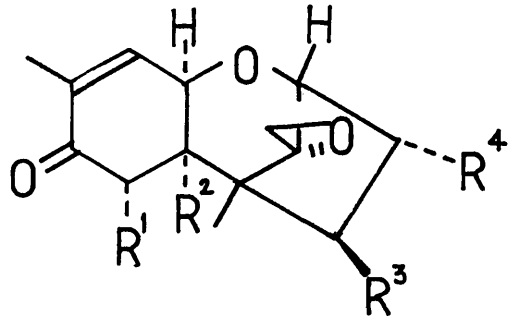
TABLE 2



Name	R^1	R^2	R^3	R^3	R^5
4β,8α-Dihydroxy-12,13-epoxytrichothec-9-ene	OH	H	H	OH	H
T-2-Tetraol	OH	H	OH	OH	OH
HT-2-Toxin	OX^a	H	OAC	OH	OH
T-2-Toxin	OX^a	H	OAC	OAC	OH
Acetyl-T-2-Toxin	OX^a	H	OAC	OAC	OAC
Solaniol	OH	H	OAC	OAC	OH
NT-1-Toxin	OAC	H	OH	OAC	OH
7,8-Dihydroxyanguidine	OH	OH	OAC	OAC	OH
8-Acetoxy-7-hydroxyanguidine	OAC	OH	OAC	OAC	OH
Neosolaniol monoacetate	OAC	H	OAC	OAC	OH
N-T-2-Toxin	OH	H	OH	OAC	OH

$X^a = COCH_2CH(CH_3)_2$

TABLE 3



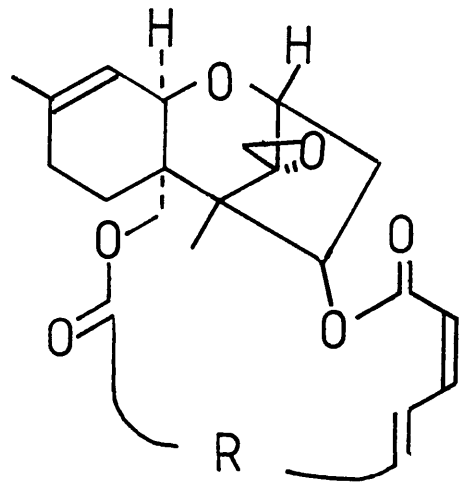
Name	R^1	R^2	R^3	R^4
Trichothecolone	H	H	OH	H
Trichothecin	H	H	OCr[a]	H
Vomitoxin	OH	OH	H	OH
Deoxynivalenol mono-acetate	OH	OH	H	OAC
Nivalenol	OH	OH	OH	OH
Fusarenone	OH	OH	OAC	OH
Nivalenol diacetate	OH	OAC	OAC	OH
4-O-Acetyltrichothecolone	H	H	OAC	H
CBD_2	H	H	OLac[b]	H
3,15-Dihydroxy-12,13-epoxytrichothec-9-en--8-one	H	OH	H	OH
3,15-Diacetyldeoxynivalenol	OH	OAC	H	OAC
4-O-Cinnamoyltricho--thecolone	H	H	OX[c]	H

a. Cr = $COCH = CHCH_3$ (Z-isomer)

b. Lac = $COCH(OH)CH_3$ (R-isomer)

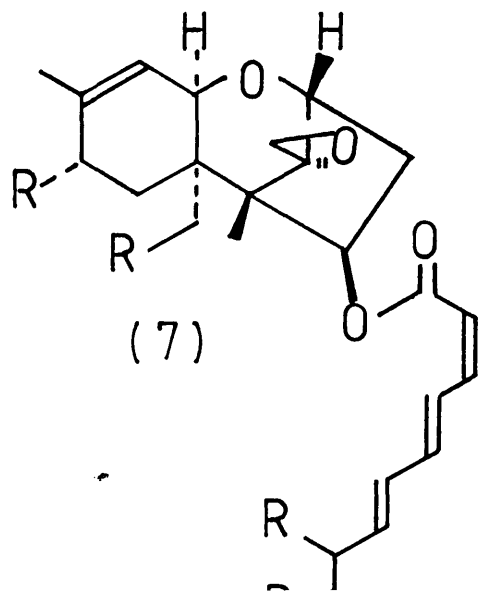
c. X = COCH = CHPh (E-isomer)

The second structural sub-group is made up of the macrocyclic trichothecenes which have the C-4β and C-15 hydroxyl groups of the simple trichothecene bridged by a di- or trilactide ribbon. This group includes the verrucarins (triesters), the roridins (diesters) and finally the baccharins (diesters). These compounds are structurally represented by (6)



(6)

The trichoverroids form the third distinct subset. These compounds have partial or complete chains at C-4 and C-15, but lack the requisite ring-forming bond of their macrocyclic counterparts. Structure (7) is a representative member of this group of compounds.



(7)

Neither the macrocyclic trichothecenes, nor the trichoverroids will be dealt with in detail since they are not the subject of this thesis; they are included here only for completeness.

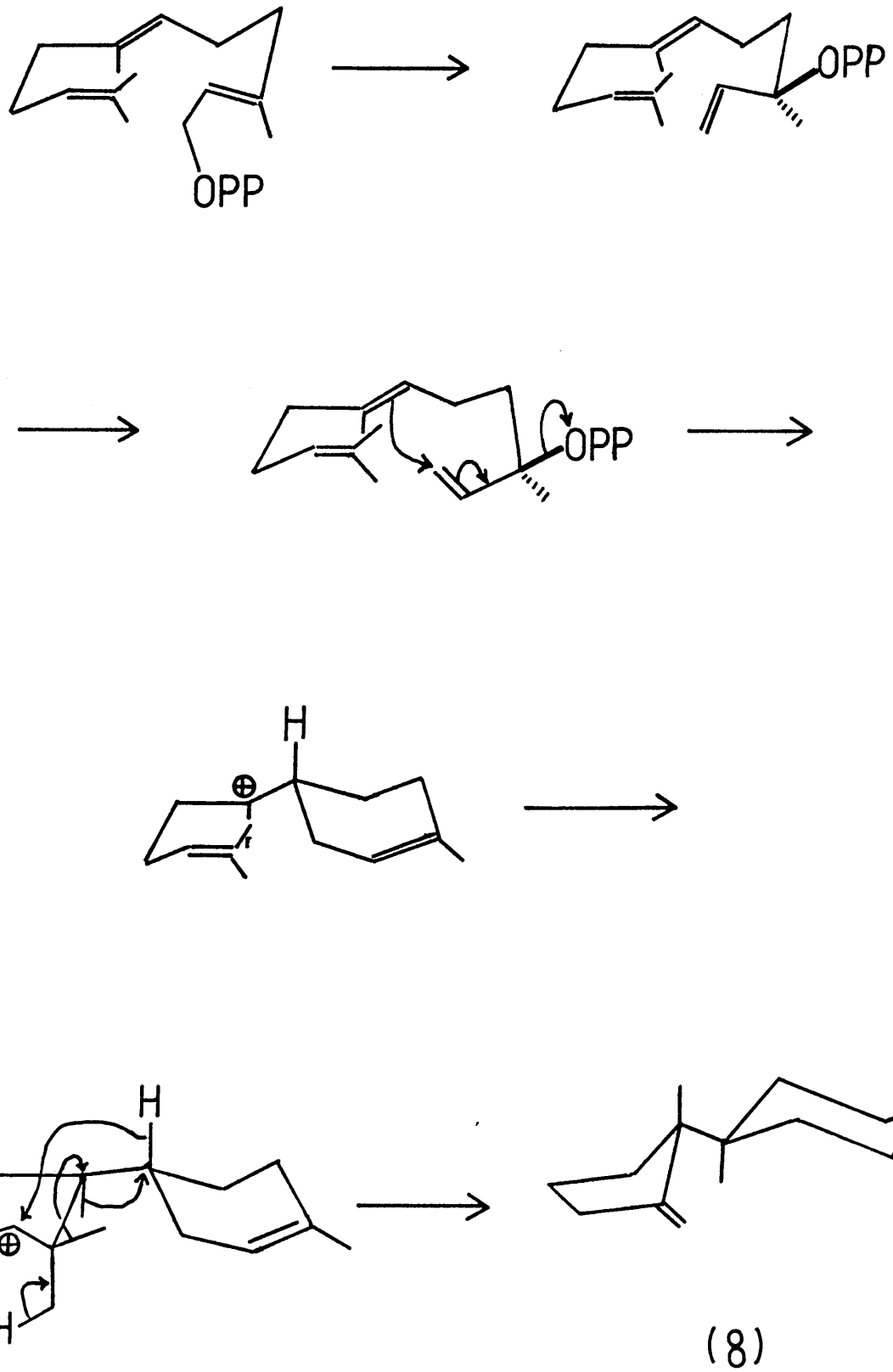
BIOSYNTHESIS

The biosynthesis of this intriguing class of compounds has aroused considerable interest. From the outset, the 15 carbon skeleton of the trichothecenes suggested that they were sesquiterpenoid in origin. However, the characteristic tetracyclic nucleus cannot be immediately derived from the usual head-to-tail linking of three isoprene units. The structure is consistent with the Ruzicka biogenetic isoprene rule, which allows for a double 1,2-methyl group migration.

Labelling studies have shown that farnesyl pyrophosphate is incorporated and results obtained suggest that these sesquiterpenoids are derived via a pathway involving the trichodiene (8), formed by two 1,2-methyl shifts as outlined in Scheme 2[24,25].

An extensive study including the main features of trichothecene biosynthesis has been carried out by Tamm[26] and Bamburg[27].

Scheme 2



(8)

CHEMICAL SYNTHESIS OF THE SIMPLE TRICHOTHENES

Chemical synthesis of the trichothecene mycotoxins is an area of research effort which has grown quickly over the past ten years or so. As a result, a number of quite efficient total syntheses of trichothecene systems now exist.

In 1971, Colvin, Raphael and Roberts reported the first synthesis of the trichothecenes with the monohydroxylated trichodermin[28]. This target molecule was a logical choice for the first synthesis of a trichothecene, because it is one of the least complicated members of this family of compounds. In the immediate years that followed no alternative syntheses of any naturally occurring trichothecenes were reported. However at this time, intense effort was being devoted to alternative strategies towards the trichothecene skeleton, notably by Fujimoto[29] and Masuoka[30] in Japan and in the U.S.A. by Still[31], who reported an alternative synthesis of trichodermol in 1980.

It was not until 1982, more than ten years after the first synthesis of trichodermin that chemists managed to synthesise any of the polyhydroxylated trichothecenes.

This second milestone was achieved simultaneously in 1982 by Kraus and coworkers[32] with a synthesis of the dioxygenated trichothecene calonectrin; and by Schlessinger and Nugent[33] with a verrucarol synthesis. Following soon thereafter, Roush and D'Ambra[34], along with Trost and McDougal[35] independently published alternative syntheses of verrucarol.

More recently, Brooks[36] and coworkers completed the impressive task of synthesising anguidine, the first trihydroxylated trichothecene to be prepared by total synthesis. Furthermore, this work represented the first chiral synthesis of a trichothecene toxin.

Synthetic approaches towards the simpler sesquiterpenoid trichothecenes can be categorised by the sequence used to form the tricyclic ring system. Generally, four kinds of bond-forming reactions have been used as depicted in Scheme 3.

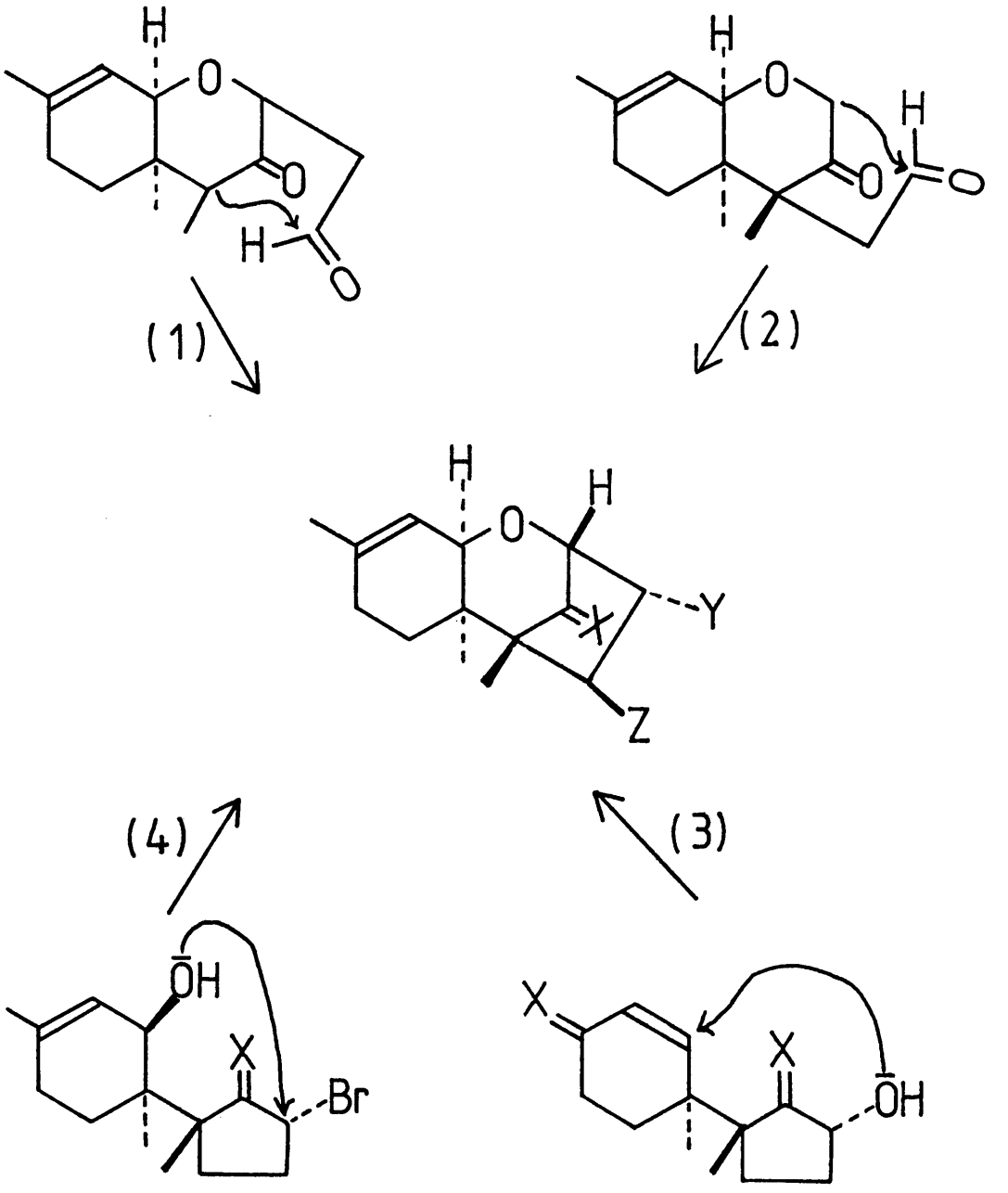
Strategies 1 and 2 (X = O, Y or Z = OH), are collectively referred to as the aldol approach, which depends upon assembly of the cis fused A-B-ring system at an earlier stage in the reaction sequence. The requisite C-ring of the tricycle is subsequently attached by either of the two possible aldol reactions shown; formation of C-4-C-5, or C-2-C-3 respectively.

Strategies 3 and 4 (any variation at X, Y and Z) rely upon formation of the B-ring by a biomimetic-like cyclisation of the pre-formed A- and C-rings; formation of O-1-C-11, or O-1-C-2 respectively.

In previous discussions it has been the usual practise to include only the group 3 cyclisation in the biomimetic category. However, for the purpose of this report, it is believed that inclusion of the group 3 and group 4 approaches in one subset is justified because it emphasises the similar synthetic features that both strategies share. Furthermore the exact sequence of events leading to trichothecene biosynthesis has not yet been fully elucidated.

A comparison of the synthetic utility of these four individual approaches has shown the group 1 aldol approach to be of very limited applicability. Although this strategy was successfully applied to the total synthesis of trichodermol, the all-important, aldol cyclisation was found to be very low yielding. Moreover, numerous attempts to extend this methodology to a synthesis of verrucarol were unsuccessful[37].

Scheme 3



On the other hand, the group 2 aldol approach has proven to be an excellent route into trichothecene systems. This strategy has been successfully used to prepare the 12,13-epoxytrichothec-9-ene system[29], along with calonectrin[32], and more recently in our own research group, it has been used in synthetic studies towards vomitoxin[38].

The group 3 biomimetic approach has proven to be the most versatile of the four stated approaches. As a result, it has enjoyed the most prominent role in trichothecene synthesis, and it has been used to synthesise efficiently a variety of trichothecene metabolites including a 12,13-epoxytrichothec-9-ene system, trichodermin[31], verrucarol[33,34], and more recently anguidine[36].

Although the alternative group 4 biomimetic methodology has not been used as extensively as its group 3 counterpart, it has been successfully applied to syntheses of model aromatic trichothecanoid systems[40,41], and more recently to an efficient synthesis of verrucarol[35].

A detailed discussion of these four different strategies, including representative synthesis for each, shall be dealt with sequentially.

At this stage there shall be no discussion of approaches which employ intermolecular Diels-Alder reactions between substituted butadienes and coumalic acid derivatives to assemble the AB-ring system. These shall be dealt with more appropriately, in the Discussion section, alongside Diels-Alder approaches towards T2 toxin, which were carried out in our laboratories during the course of this research.

As previously mentioned, Colvin and Raphael's stereoselective synthesis of (±)-trichodermin(30) provided the initial, historic entry into chemical syntheses of the trichothecenes[28]. The overall synthetic plan employed was that of the group 1 aldol approach, as outlined in

Scheme 4, where the successful application of this methodology was predicated on an intramolecular aldol cyclisation of the key intermediate, keto-aldehyde (20).

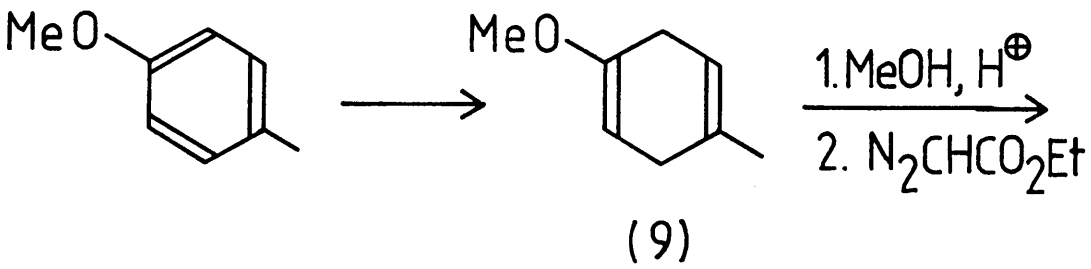
A consideration of the structure of trichodermin revealed the features which had to be incorporated into the overall synthetic plan. Any approach towards the eventual preparation of this target molecule had to take into account the cis-anti-cis relationship of the tricyclic ring system. Moreover, it had to allow for regioselective introduction of the 9,10-double bond; stereochemical considerations included stereoselective introduction of the 4β-hydroxyl group and also of the 12,13-epoxy function.

Bearing all of this structural complexity in mind, it was decided that it would be desirable to incorporate the requisite cis-fusion between the AB-ring system of trichodermin at an early stage in the synthesis. It is a well established fact that systems of type (13) will cyclise to afford the thermodynamically more favoured cis-stereoisomer. To this end, one of the early aims of the overall synthesis was to obtain the potentially useful cis-fused bicyclic γ-lactone (14).

Accordingly, p-methoxy toluene underwent Birch reduction to afford the expected 1,4-dihydro-compound (9). Subsequent treatment with acidic methanol gave the corresponding dimethyl acetal, which on reaction with ethyl diazoacetate furnished the cyclopropane ester (10). Transketalisation with acetone yielded the corresponding ketone (11), which underwent smooth fragmentation to the cyclohexenone (12).

Careful treatment of the α,β-unsaturated keto-ester (12) with methyl magnesium chloride gave the tertiary alcohol (13), which under base

Scheme 4



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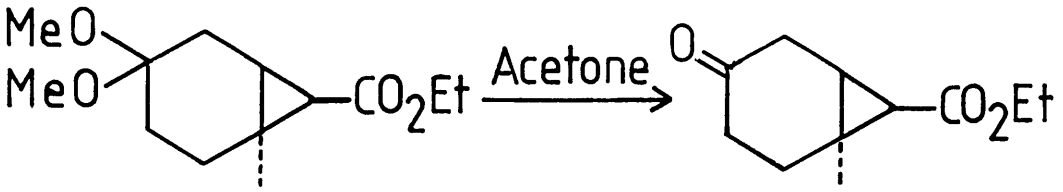

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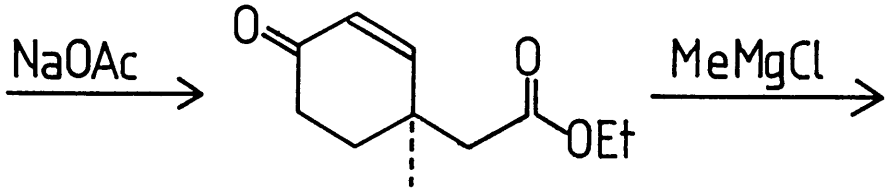
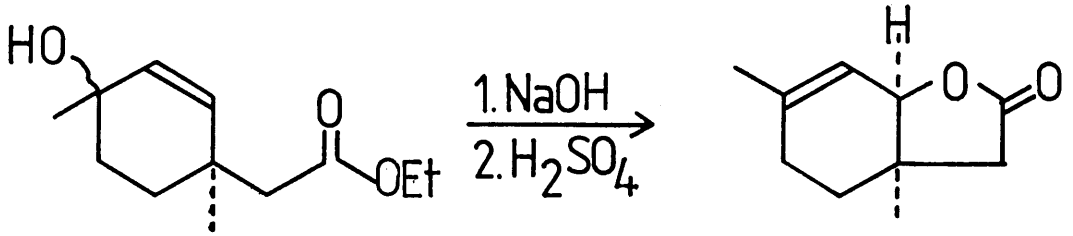
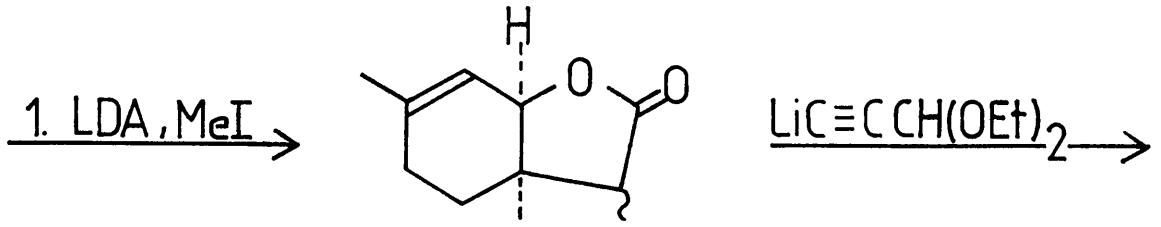


(12)



(13) (14)



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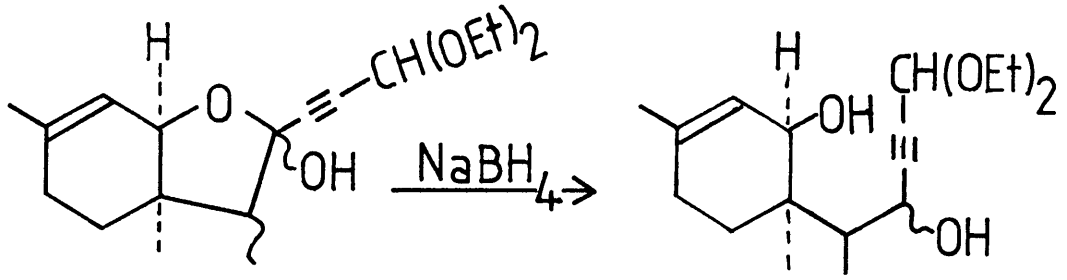
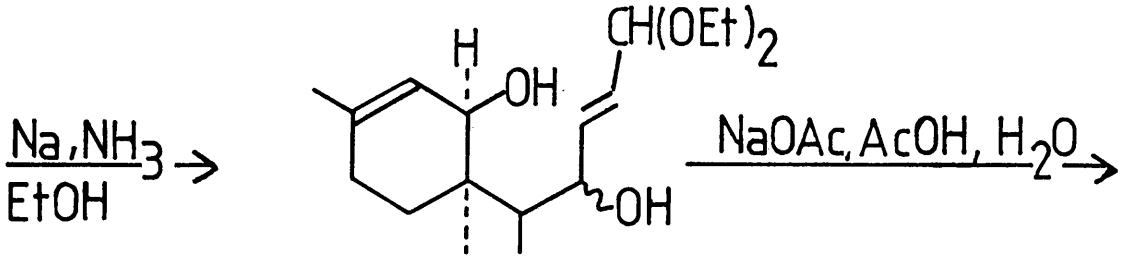


(16) (17)



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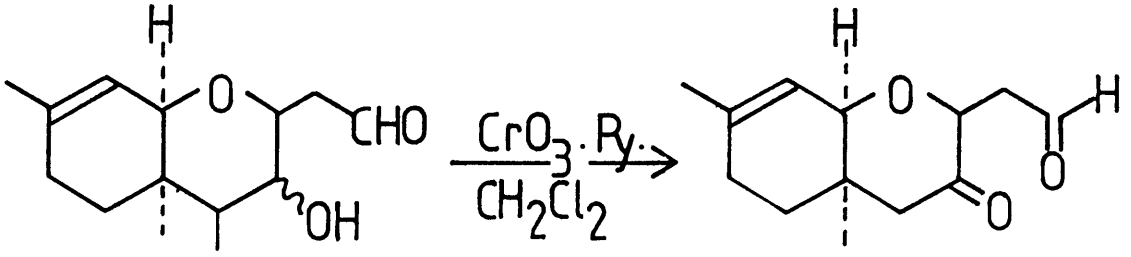

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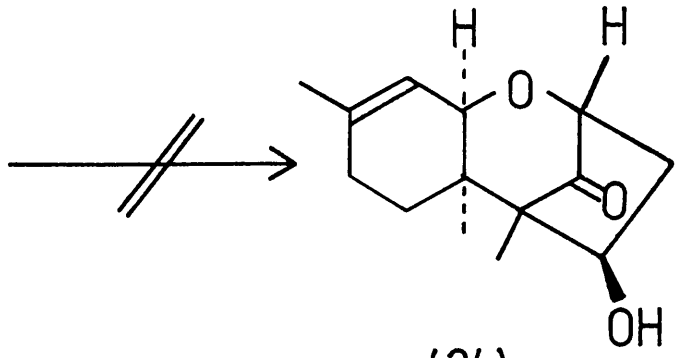

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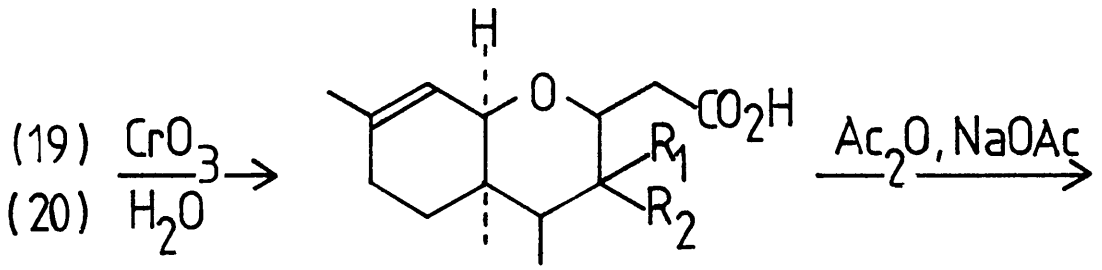
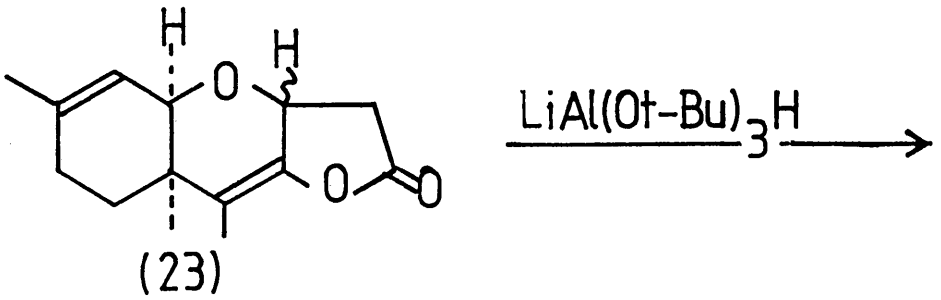
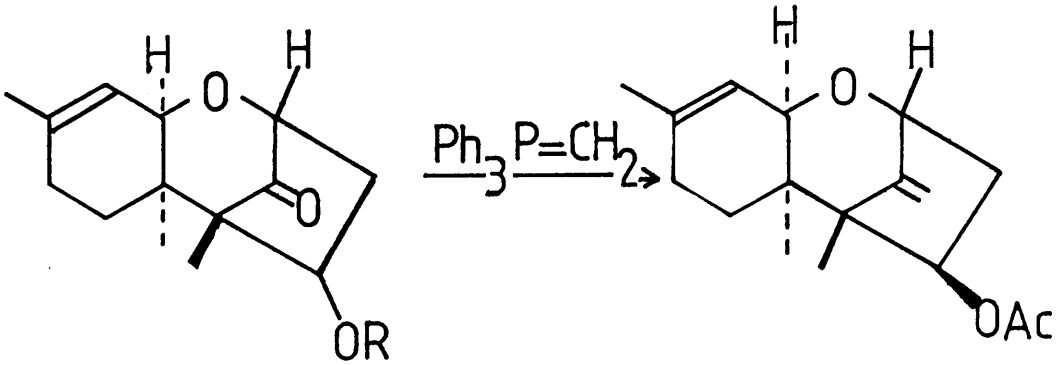


(21) R_1 , R_2 = O

(22) R_1 = H , R_2 = OH



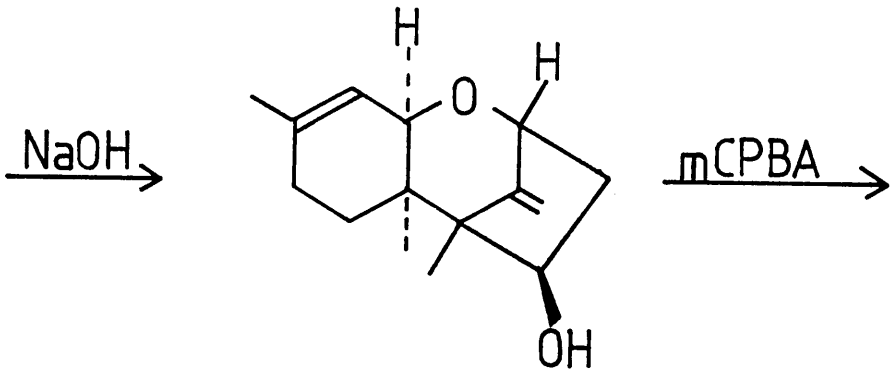
(23)



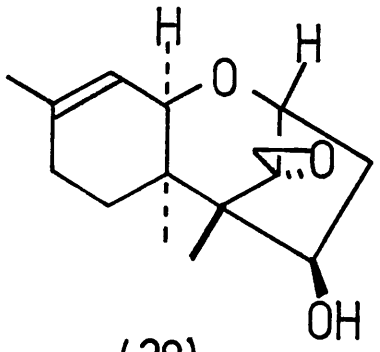
(24) R = H

(26) R = Ac

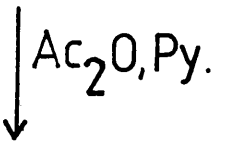
(27)

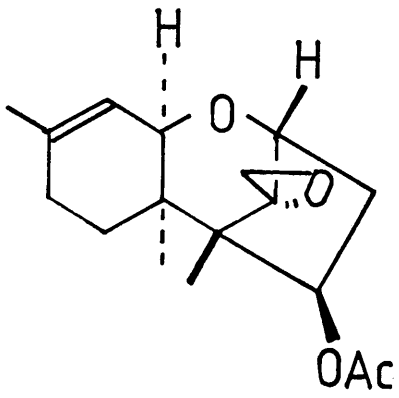


(28)



(29)





(30)

hydrolysis of the ethyl ester, followed by acidification-dehydration afforded only the expected cis-fused γ-lactone (14).

Subsequent transformation of γ-lactone (14) into trans-acetal (18) proceeded straightforwardly as shown. Accordingly, acetal (18) was smoothly converted into the corresponding cis-fused bicyclic hydroxy-aldehyde (19), which underwent selective oxidation to furnish the key intermediate keto-aldehyde (20).

Structural examination of keto-aldehyde (20) revealed that it potentially contained all of the requisite functionality for its eventual transformation into the target molecule, trichodermin (30). Conformational analyses carried out were encouraging and indicated that it should undergo the desired cyclisation to afford a product having the correct relative stereochemistry for trichodermin.

Unfortunately however, a major problem arose when contrary to the results obtained from conformational studies, numerous attempts to induce keto-aldehyde (20) to undergo the desired aldol reaction were unsuccessful.

To circumvent this somewhat unexpected problem the diastereoisomeric enol lactones (23) were prepared.

Extensive studies of complex hydride reduction of exocyclic enol-δ-lactones had revealed a highly stereoselective process[42]. Based upon this precedent, it was hoped that this method could be extended to the corresponding enol-γ-lactone (23) and that analogous hydride reduction would follow a similar stereoselective course, to afford a compound having a newly-formed hydroxyl group with the correct relative stereochemistry for trichodermin.

Accordingly, treatment of the diastereoisomeric mixture of enol-γ-lactones (23), with lithium tri-t-butoxyaluminium hydride

furnished two products. The major product proved to be keto-aldehyde (20); the other product, produced in only 7% yield was shown to be the desired tricyclic keto-alcohol (24).

Having successfully obtained the key trichodermin precursor (24), albeit in relatively low yield, all that remained for completion of the formal synthesis was introduction of the 12,13-epoxide function, along with the trivial step of acetylating the 4β-hydroxyl group.

Introduction of the requisite methylene function was successfully achieved by treatment of ketone (26) with methylene triphenylphosphorane, to afford, after reacetylation, intermediate (27).

Examination of molecular models suggested that epoxidation of compound (27) could be carried out stereoselectively to afford an epoxide having the required stereochemistry for trichodermin. However, the problem of regioselective epoxidation arose because tricyclic diene (27) contained two potential sites to epoxidation; furthermore the 9,10-double bond being trisubstituted would undergo epoxidation much more rapidly.

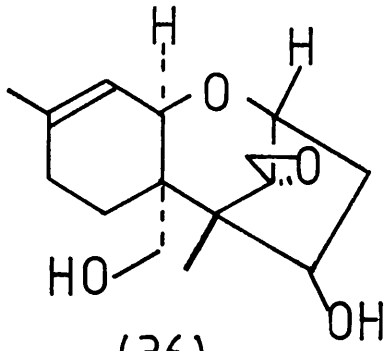
This problem was circumvented by deacetylating tricyclic diene (27) to the corresponding 4β-alcohol (28) and the hydroxyl group thus liberated was used as an anchor to direct the electrophilic epoxidising agent meta-chloroperbenzoic acid[43]. In such a way, both stereo- and regioselective epoxidation were accomplished.

Finally, acetylation of the resulting epoxide (29) yielded crystalline, racemic (±)-trichodermin (30) which was identical with naturally occurring (-)-trichodermin in all respects bar optical rotation.

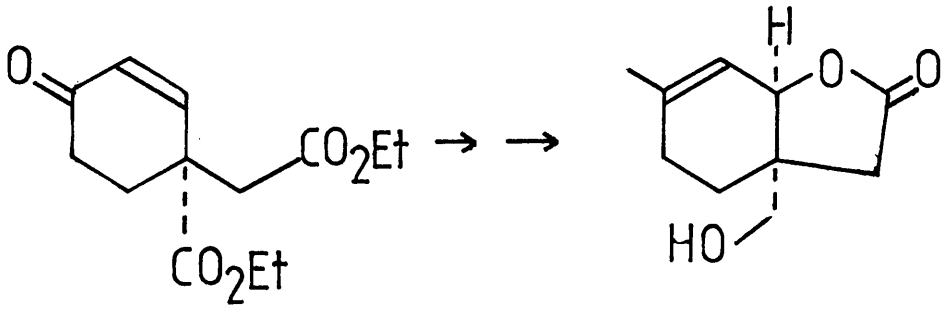
Attempts to extend this group 1 methodology and hence prepare the dioxygenated trichothecene, verrucarol (36) proved to be unsuccessful[37].

As outlined in Scheme 5, the key intermediates, enol esters (33) and

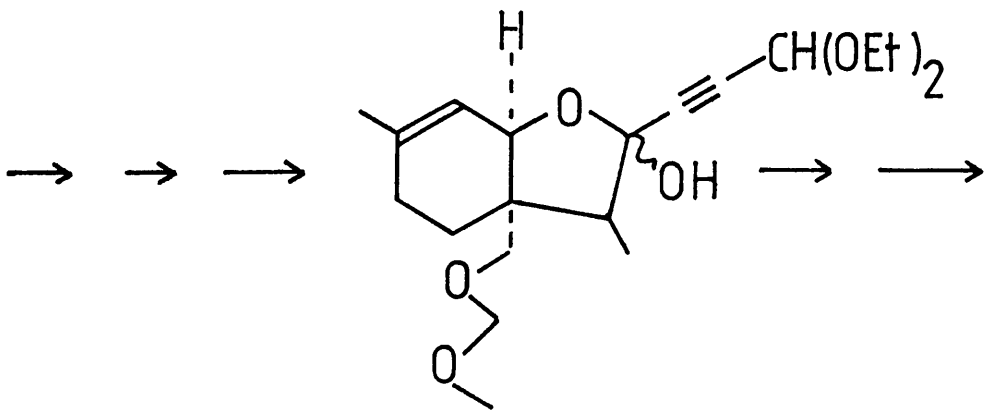
Scheme 5

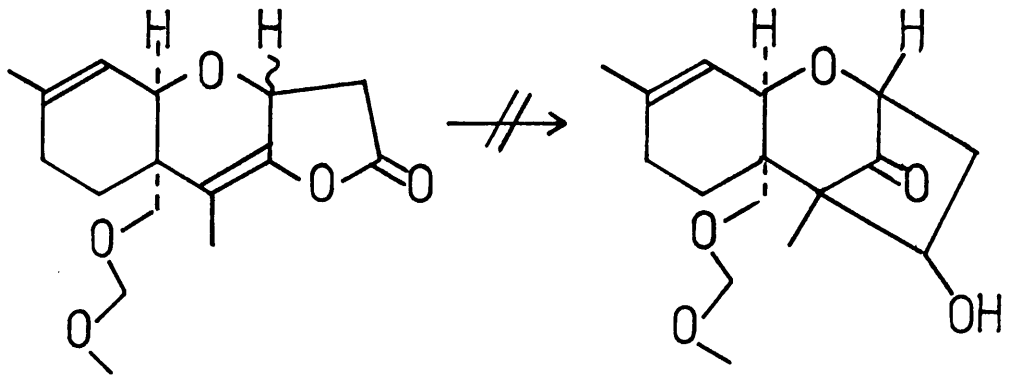


(36)



(31) (32)





(33) 3α-H

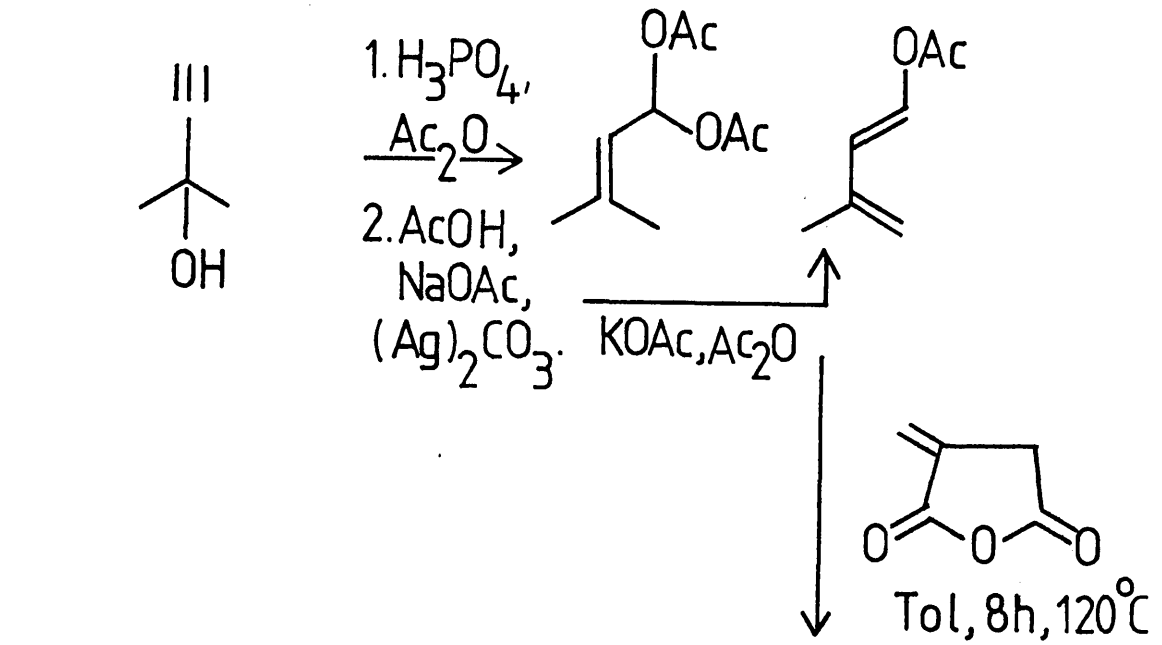
(34) 3β-H

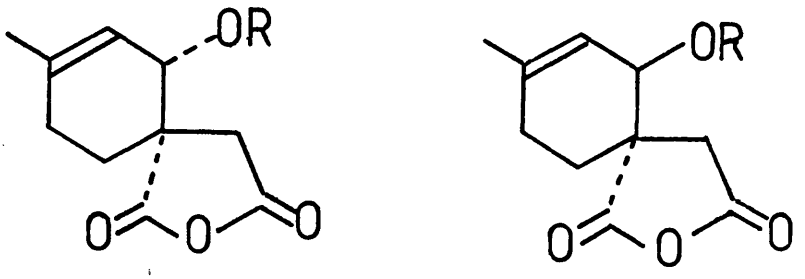
(35)

(34) were prepared from cyclohexenone (31) via a comparable route. In direct contrast however, numerous attempts to induce the racemic enol lactones to undergo reductive cyclisation to the desired hydroxy ketone (35) were unfruitful; even upon treatment with the previously successful lithium tri-t-butoxyaluminium hydride.

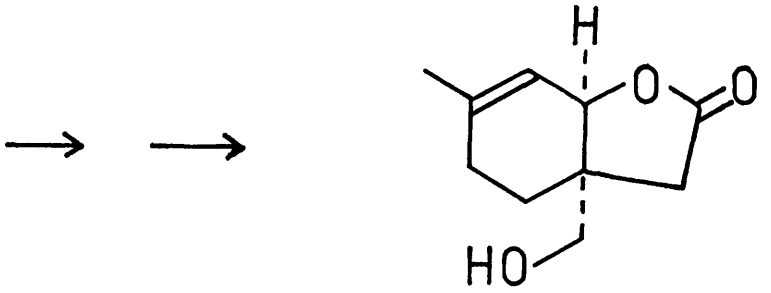
At approximately the same time, Snider and Amin independently published an alternative synthesis to the key intermediate (32)[44]. This efficient route allowed lactone (32) to be prepared in relatively high yield from readily available, inexpensive starting materials, namely 3-methyl-1-acetoxy-1,3-butadiene and itaconic anhydride, via a cycloaddition reaction as depicted in Scheme 6.

Scheme 6





3 : 1



(32)

GROUP 2 ALDOL

The concept of the group 2 aldol approach was pioneered by Fujimoto and his associates[29] in the total synthesis of 12,13-epoxytrichothec-9-ene (47), a fungal metabolite isolated from Trichothecium roseum.

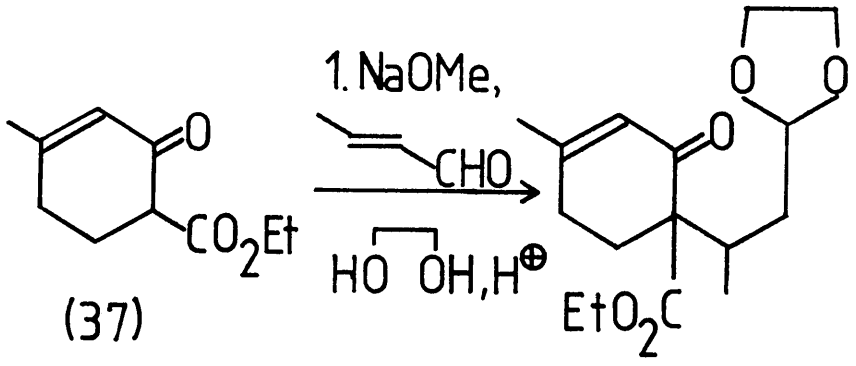
The group 2 aldol approach differs from the corresponding group 1 aldol approach, in that the C-ring is attached via carbanion formation at C-2 (i.e. C-2-C-3 bond formation), as opposed to carbanion formation at C-5, (C-4-C-5 bond formation) in the latter case.

Following Scheme 7, Michael reaction of keto-ester (37) with crotonaldehyde afforded the expected keto-aldehyde, which was subsequently transformed into the corresponding acetal (38). Meerwein-Ponndorf reduction of acetal (38) furnished the cis-fused pyrane derivative (39), which was reductively transformed into intermediate (40). Selective attack at the electron-rich enol ether double bond of (40) by meta-chloroperbenzoic acid produced a diastereoisomeric mixture of hydroxy esters (41), which underwent smooth pyrolysis to the corresponding ketone (42).

Allylation of (42) afforded the unexpected O-allylated product (43). However, this was turned to advantage in establishing the desired stereochemistry at C-5 by Claisen rearrangement of the formed enol ether (43). Experimentally, enol ether (43) underwent rearrangement to afford a 2:1 mixture of Claisen products (44a) and (44b) respectively, with the desired α-isomer predominating.

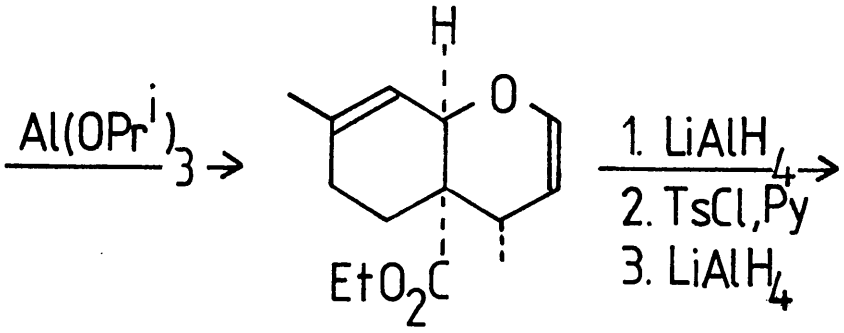
Osmylation of (44a), followed by cleavage of the resulting diol, yielded the keto-aldehyde monohydrate (45), which cyclised under basic conditions to furnish the diastereoisomeric tricyclic ketone(46), in an impressive 90% yield.

Scheme 7

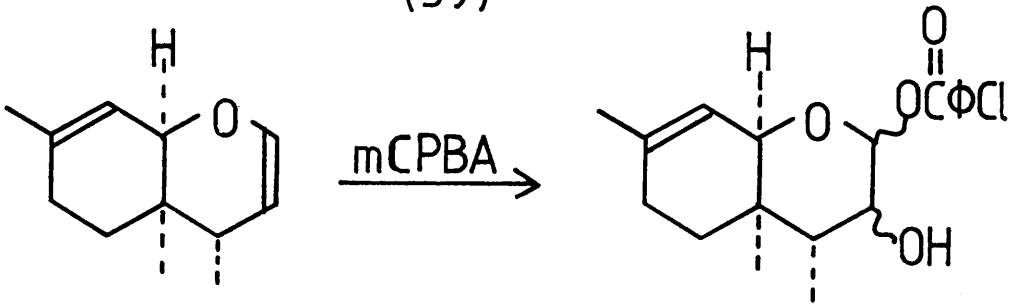


(37)

(38)

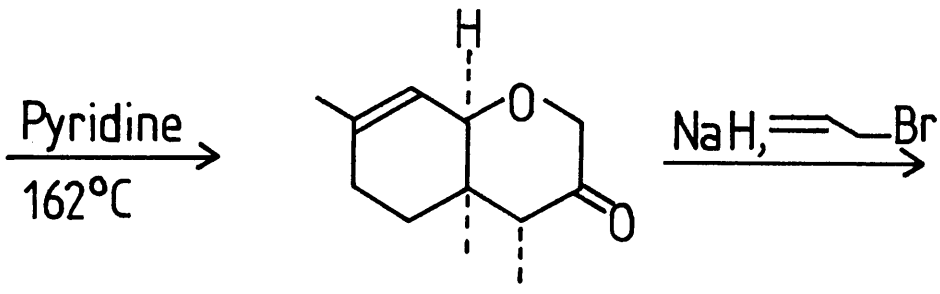


(39)

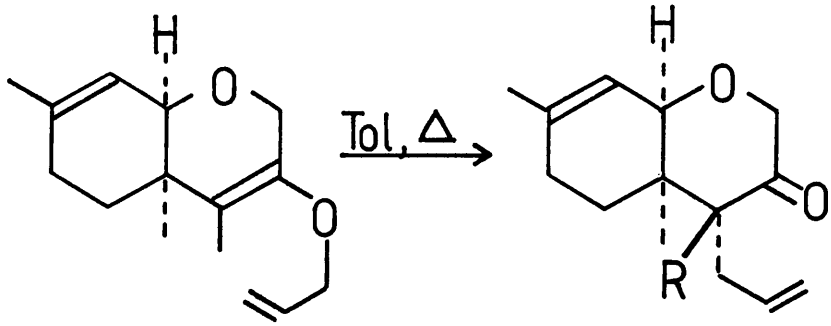


(40)

(41)



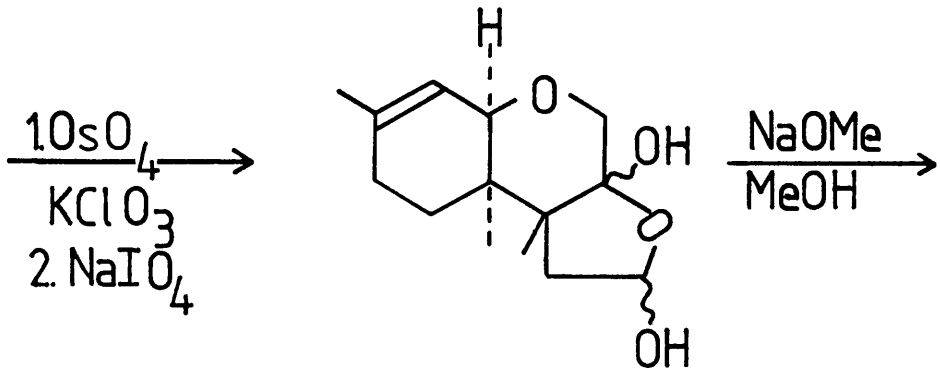
(42)



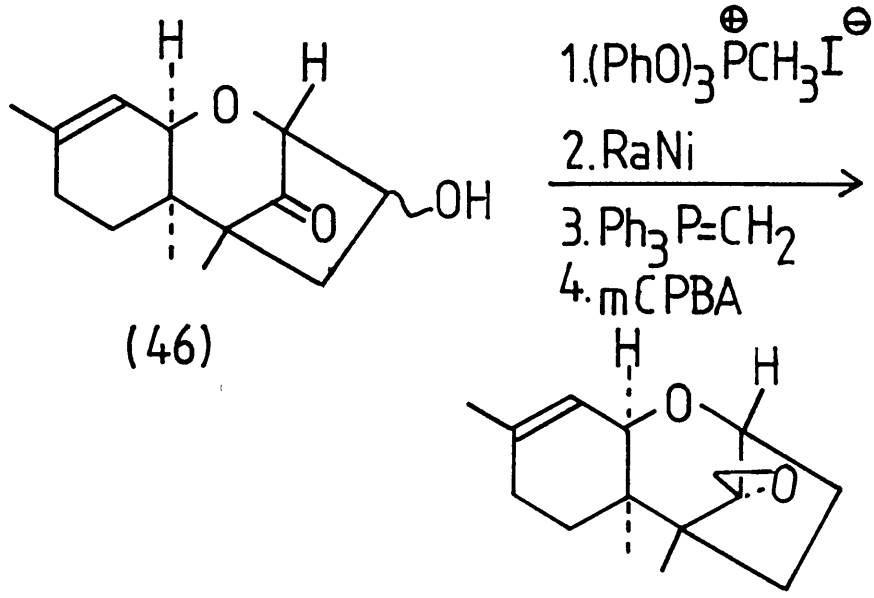
(43) (44)

R = Me

R = $CH_2CH=CH_2$



(45)



(46) (47)

The final stages of the synthesis required removal of the 3-hydroxy group, which was accomplished by reductive dehalogenation of the derived 3-iodo compound with Raney nickel. Stereoselective epoxidation was carried out using the method previously described by Colvin and Raphael[28]: it should be noted that although this ketone lacked the hydroxyl-direction described by Henbest[43], the desired stereoisomer (47) was obtained on epoxidation.

Scheme 8 outlines the route followed by Kraus and his coworkers in the preparation of the 3α,15-dihydroxytrichothecene, calonectrin (62)[32].

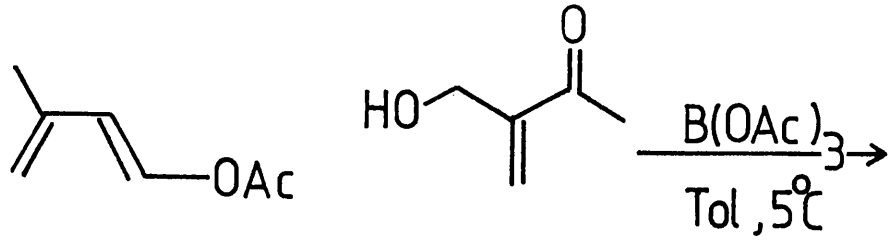
Lewis-acid catalysed cycloaddition between 1-acetoxy-3-methylbutadiene and 3-(hydroxy methyl)-3-buten-2-one cleverly served to establish a highly functionalised A-ring system. The Diels-Alder reaction proceeded with adequate stereocontrol to afford a 3.5:1 diastereoisomeric mixture of acetoxy ketones (48a) and (48b) respectively, with the desired isomer predominating; furthermore it also served to introduce regiospecifically the trisubstituted 9,10-olefin.

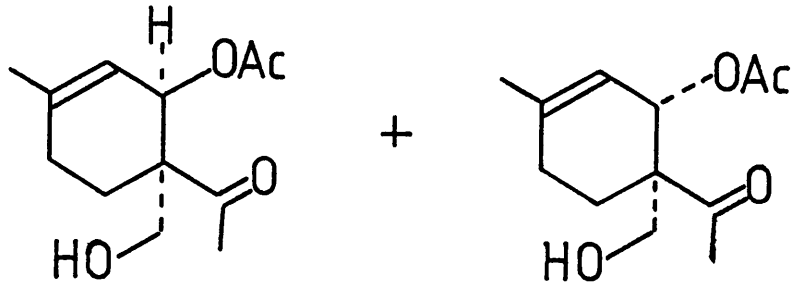
Acetoxy ketone (48a) was subsequently transformed into the synthetically-useful intermediate (54) via the key transformations of intramolecular Knoevenagel condensation to convert intermediate (49) into the corresponding cyanolactone (50) and Curtius degradation of acid (53) to yield hydroxy ketone (54), after desilylation.

Kraus improved Fujimoto's previous scheme[29] by introducing the quaternary C-5 centre with complete stereocontrol. This was accomplished by fluoride-induced intramolecular alkylation of silyl enol ether (55), to afford ketone (56), stereospecifically.

The all-important aldol cyclisation of keto aldehyde (58) proceeded successfully, to furnish the desired tricyclic alcohol (59), as a

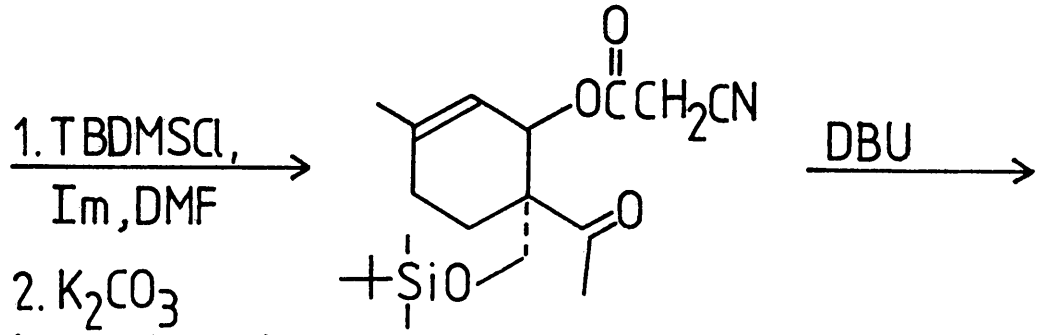
Scheme 8



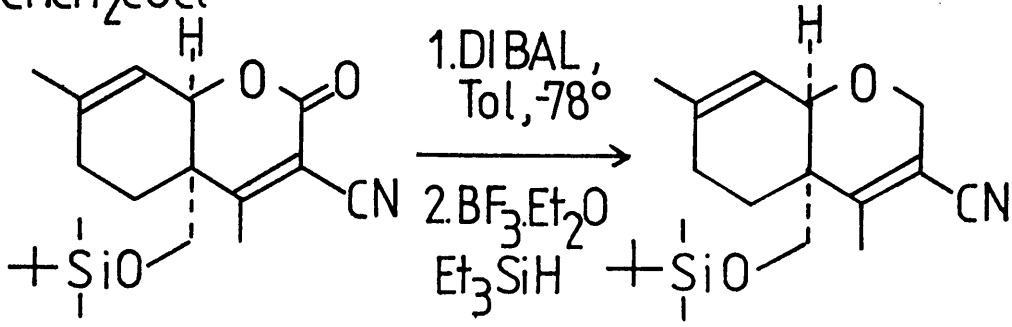


(48a) : (48b)

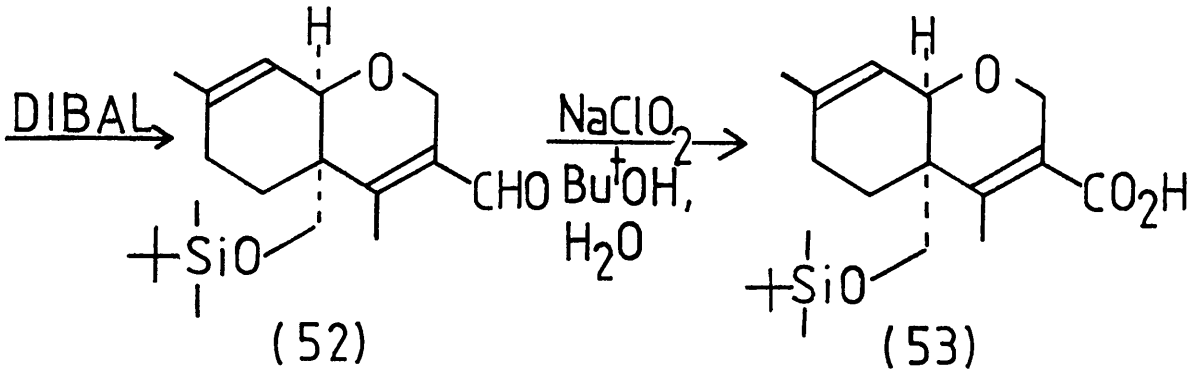
3.5 : 1

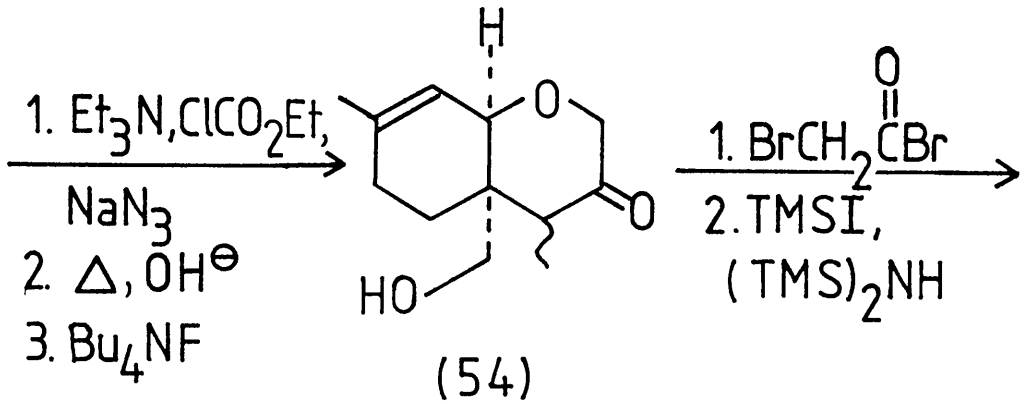


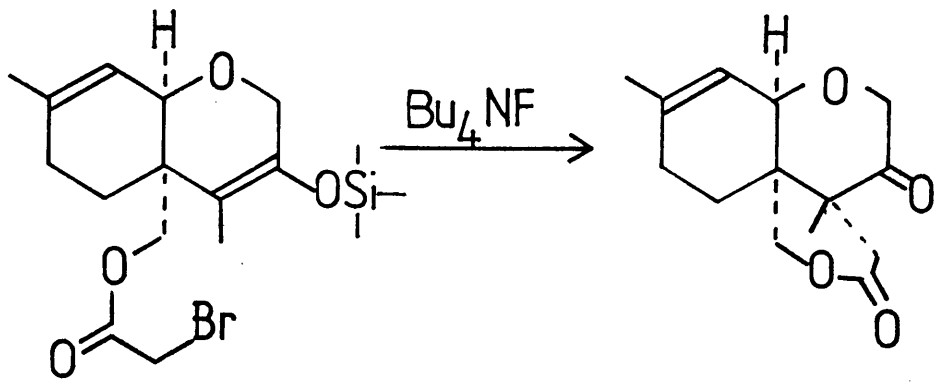
(49)

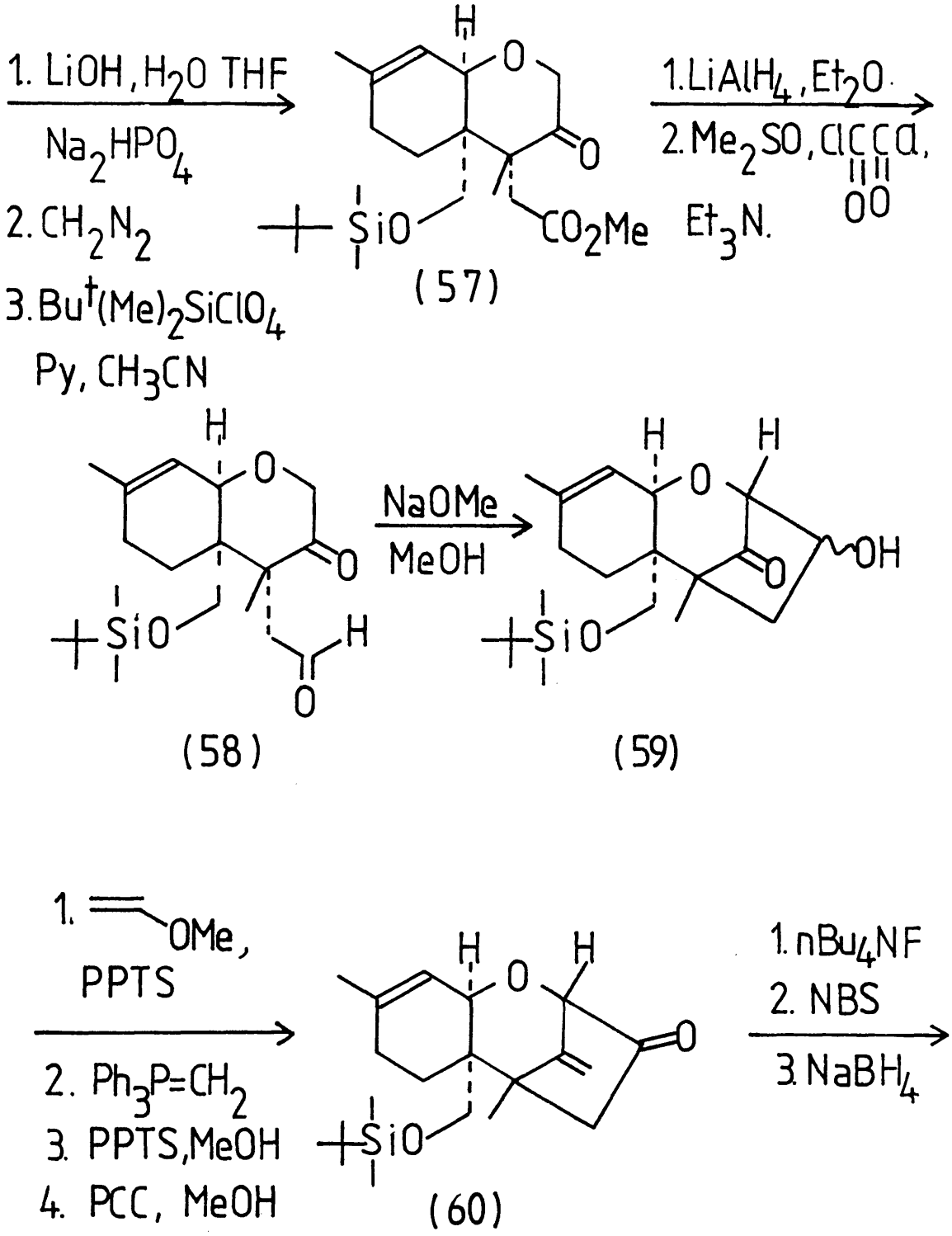


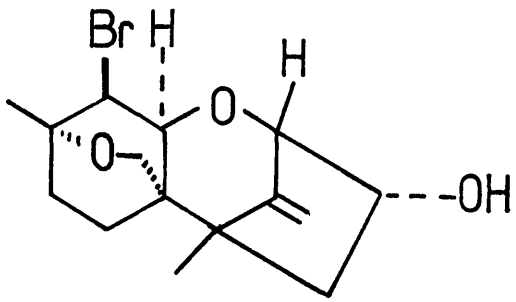
(50) (51)


DIBAL
H
O
CHO
+SiO
(52)
NaClO2
t-BuOH,
H2O
CO2H
(53)

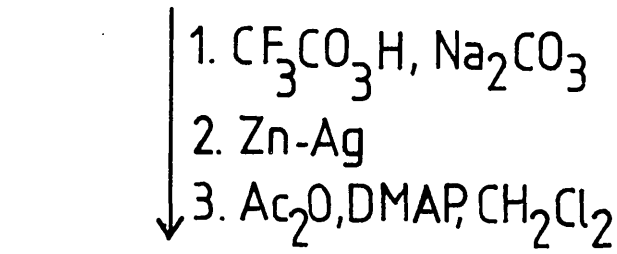

1. Et3N,ClCO2Et,
NaN3
2. Δ, OH⊖
3. Bu4NF
HO
(54)
1. BrCH2CBr
2. TMSI,
(TMS)2NH

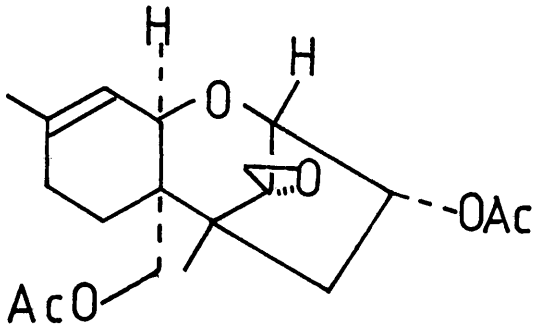

Bu4NF
OSi
Br
(55)
(56)


1. LiOH, H2O THF
Na2HPO4
2. CH2N2
3. But(Me)2SiClO4
Py, CH3CN
(57)
1. LiAlH4, Et2O
2. Me2SO, ClCCCl, Et3N.
NaOMe
MeOH
(58)
(59)
1. OMe, PPTS
2. Ph3P=CH2
3. PPTS, MeOH
4. PCC, MeOH
(60)
1. nBu4NF
2. NBS
3. NaBH4

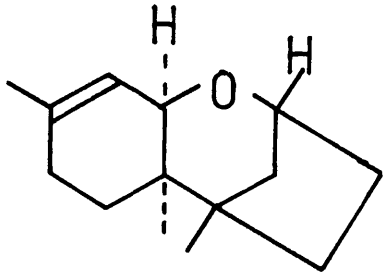

Br H
H
O
O
OH

(61)


1. CF_3CO_3H, Na_2CO_3
2. Zn-Ag
3. Ac_2O, DMAP, CH_2Cl_2


H
H
O
O
OAc
AcO

(62)


H
H
O

(63)

mixture of epimers in a respectable 63% yield.

Due to the non-selective nature of peracid epoxidation on certain trichothecadienes it was necessary to protect the trisubstituted olefin as the corresponding bromoether. Epoxidation of the remaining methylene group then proceeded stereoselectively.

Deprotection and finally acetylation of the 3α,14-hydroxyl groups completed this successful synthesis of calonectrin (62).

The group 2 aldol approach, investigated by Colvin and Thom[38], towards a total synthesis of vomitoxin, will be discussed at a later stage.

In conclusion, the group 1 aldol approach appears to be a much less efficient route towards trichothecenes than the corresponding group 2 aldol approach. In the former case, intermediates of type (20) are unwilling to undergo intramolecular aldol cyclisation to form the C-4-C-5 bond of the tricyclic system; and at best will cyclise only in very poor yields. Fortunately, the group 2 aldol cyclisation does not suffer similarly, and no difficulty was observed in the C-2-C-3 bond forming process.

BIOMIMETIC APPROACH

The group 3 biomimetic approach currently ranks as the most versatile entry into trichothecanoid systems.

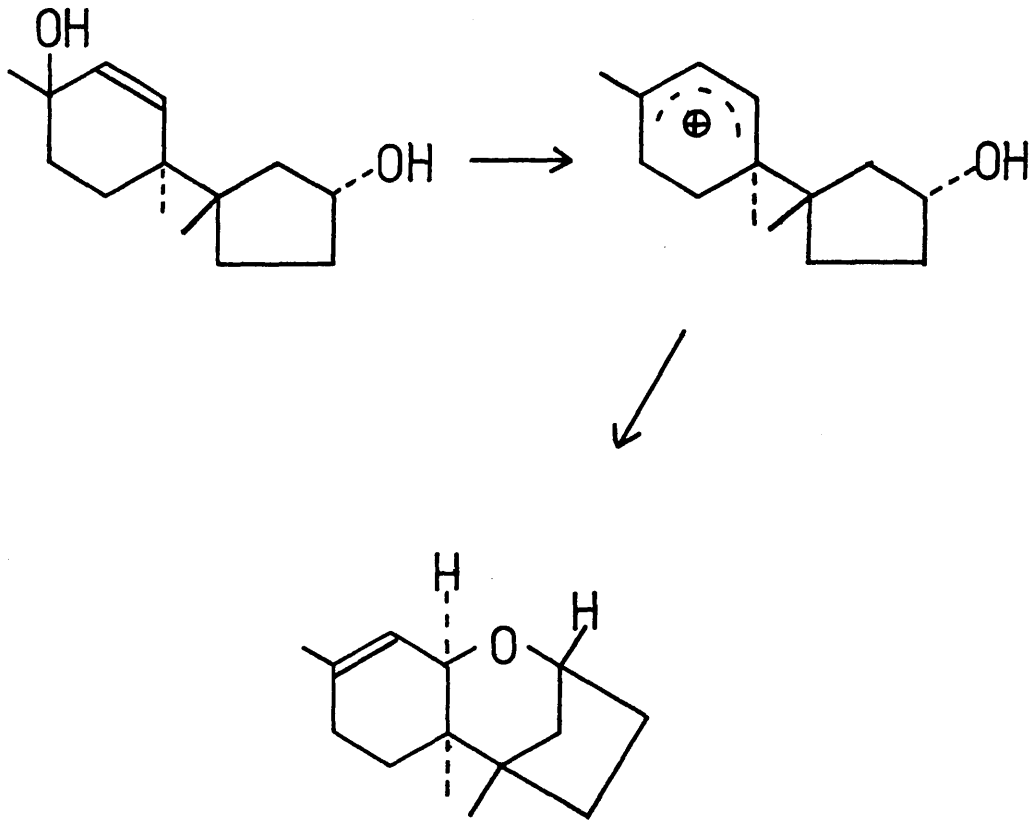
The group 3 cyclisation involves an O-1-C-11 bond forming process and this can proceed in two different ways: it can occur via an allylic carbonium ion as indicated in Scheme 9, thereby regiospecifically generating the trisubstituted olefin directly. Alternatively, the cyclisation can proceed by Michael addition of the cyclopentanol on to the double bond of the enone system, as shown in Scheme 10, to afford the corresponding ketone. This latter route is somewhat less attractive than the former, because it requires the additional steps of conversion of the ketone into the corresponding tertiary alcohol, followed by selective dehydration to furnish the 9,10-double bond.

A stereochemical problem which has to be considered is control of stereochemistry between the two isolated rings to effect stereocontrol over the quaternary C-5 and C-6 centres. A number of schemes have been devised for this and these shall be discussed in the context of individual syntheses.

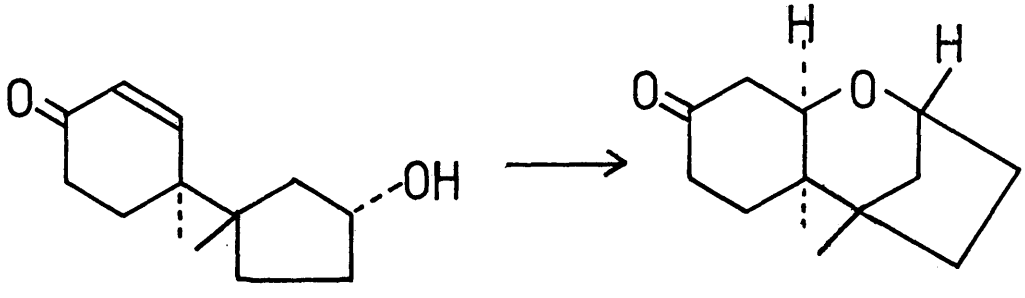
An attractive feature of this strategy is that it allows complete control over the relative configuration at the AB-ring junction, because biomimetic cyclisation always yields the desired cis-fused bicyclic system.

Initial studies into the group 3 approach were carried out at the laboratories of Masuoka and coworkers. In 1974, this strategy was successfully applied to the synthesis of a model 13-nortrichothec-9(10)-ene

Scheme 9



Scheme 10



system (63)[30].

Results from the model system were so encouraging that this methodology was subsequently used in an alternative synthesis of the naturally occurring 12,13-epoxytrichothec-9-ene system (70)[39].

As outlined in Scheme 11, the key step in the reaction sequence involved a [2+2] photoaddition reaction which afforded the desired cis-anti-cis tricycle (64) as the major adduct. The cycloaddition provided complete control over the C-5 and C-6 centres, simultaneously establishing both centres with the correct relative stereochemistry.

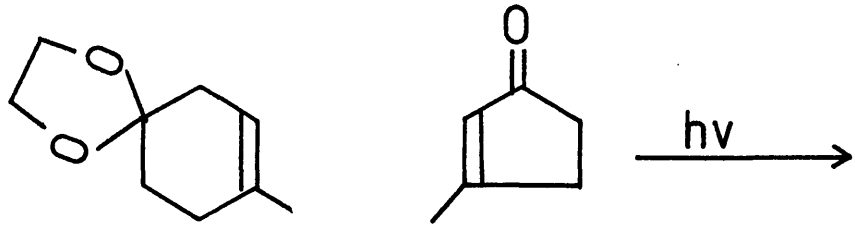
Acid hydrolysis of cycloadduct (64) gave the dione (65). Methylenation at C-12 was successfully accomplished as indicated. It was observed that borohydride reduction of enone (66) afforded an alcohol having the wrong stereochemistry at C-2. This problem was circumvented by alcohol inversion via the mesylate to afford alcohol (68), now with the correct stereochemistry for successful biomimetic cyclisation.

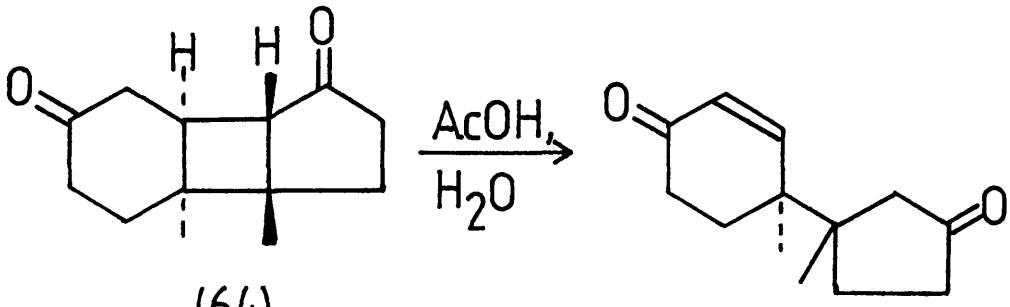
Acid-catalysed cyclisation of key intermediate (68) furnished the desired tricyclic compound (69), which underwent non-selective peracid epoxidation to afford the desired 12,13-epoxytrichothec-9-ene (70), along with the alternative 9,10-epoxy system.

Still and Tsai utilised the group 3 biomimetic approach in their elegant synthesis of trichodermol (84)[31]. The problem of relating the stereochemistry between the isolated A and C-rings was efficiently solved using a cycloaddition-fragmentation sequence.

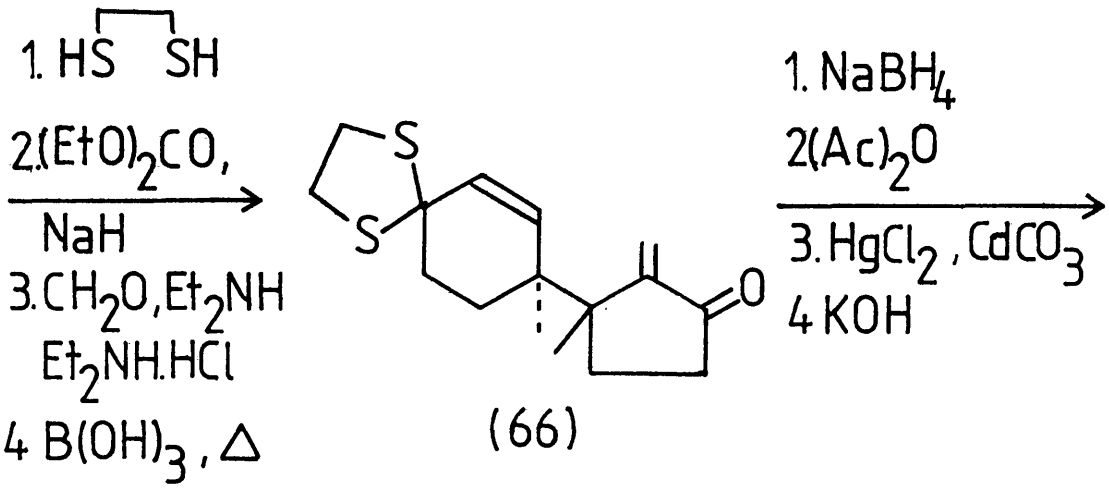
As outlined in Scheme 12, Diels-Alder reaction between the silyloxydiene (71) and quinone proceeded stereoselectively to afford cycloadduct (72) in very high yield. Epoxidation, followed by Herz-Favorskii ring

Scheme 11

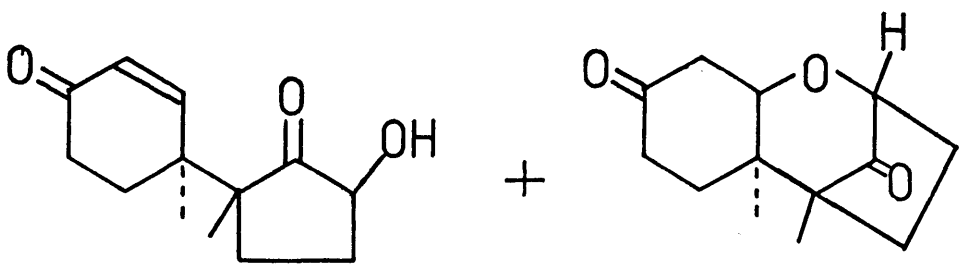




(64) (65)

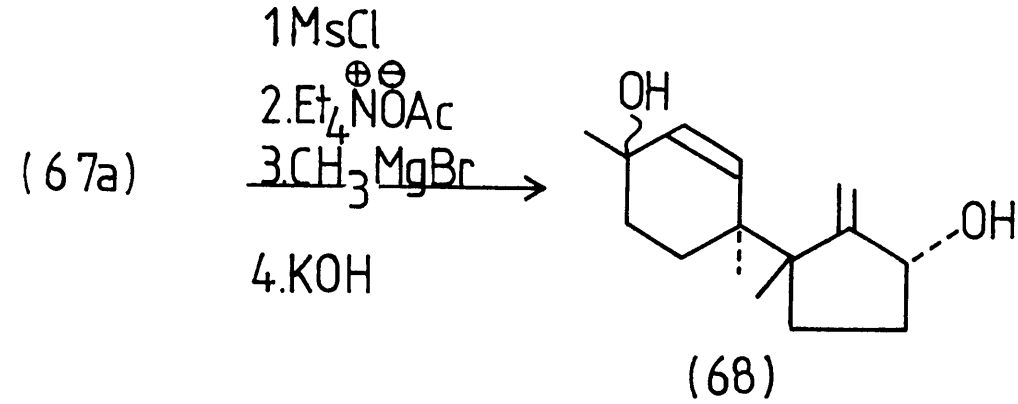


(66)

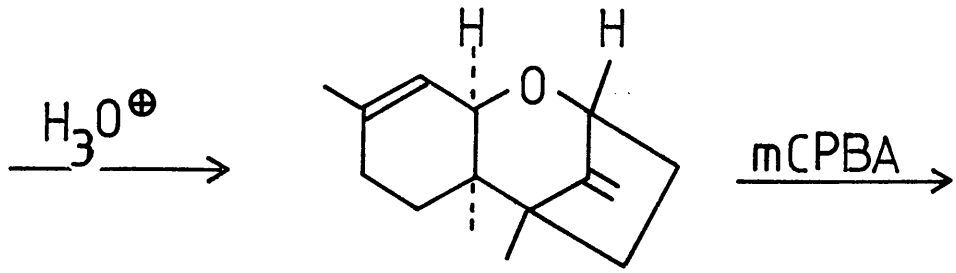


(67a) Major

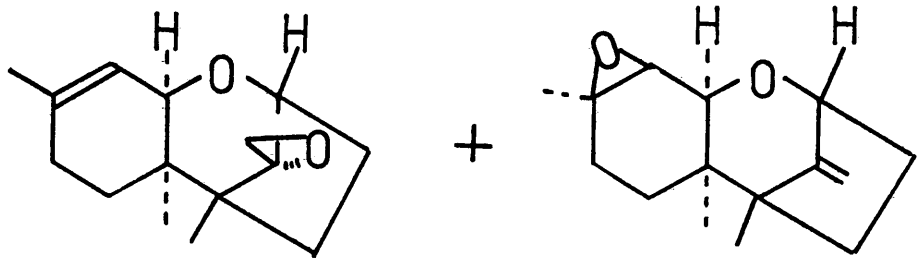
(67b) Minor


1MsCl
2.Et4N⊕O⊖Ac
3.CH3MgBr
4.KOH
(67a)
OH
OH

(68)

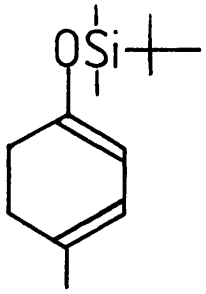

H3O⊕
H
H
O
mCPBA

(69)

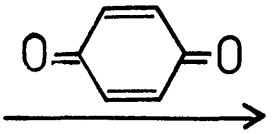

H
H
O
O
+
O
H
H
O

(70)

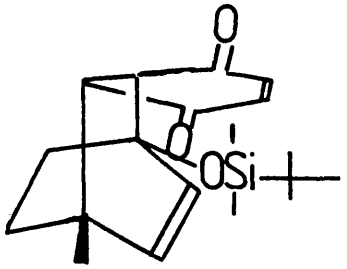
Scheme 12



(71)

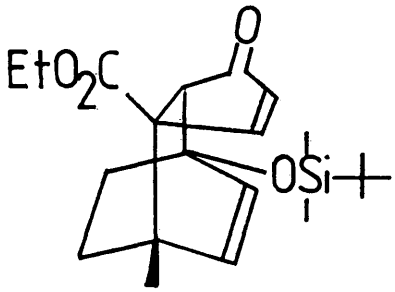


25°C, 5d



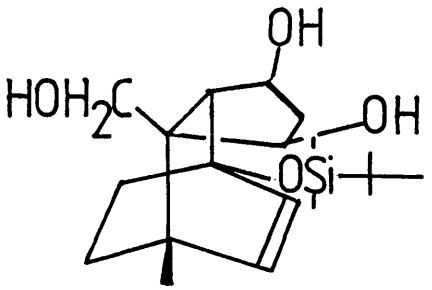
(72)

1. Triton B, Bu^tOOH
($PhCH_2NMe_3OH$)
2. NaOH, EtOH

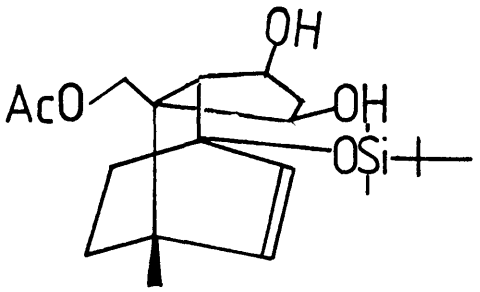


(73)

1. Triton B
Bu^tOOH
2. Li, NH_3, EtOH



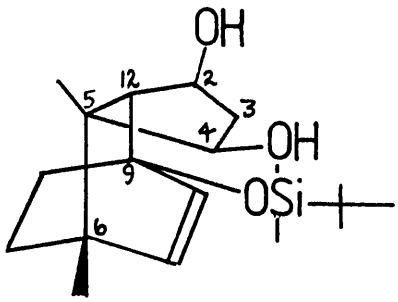
(74)



Ac_2O, Py

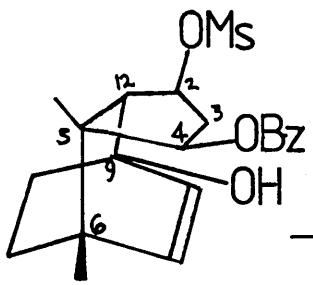
HMPA, hv

(75)



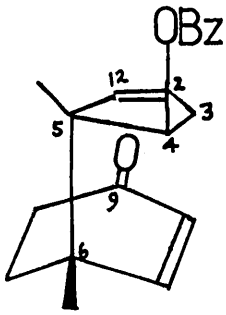
1. PhCOCl
2. Bu_4NF
3. K_2CO_3, MeOH
4. MsCl, Et_3N

(76)



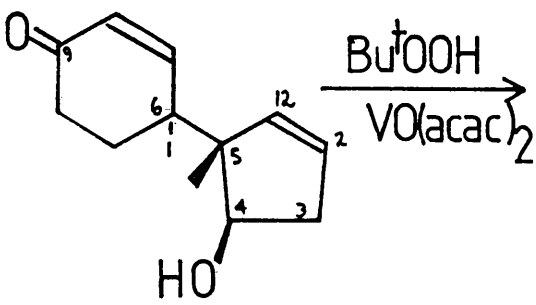
NaH, THF

(77)



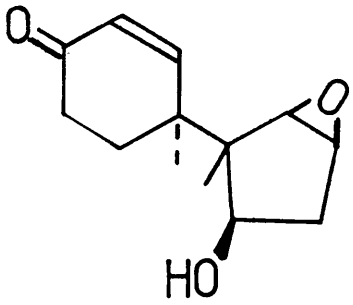
K_2CO_3, MeOH

(78)

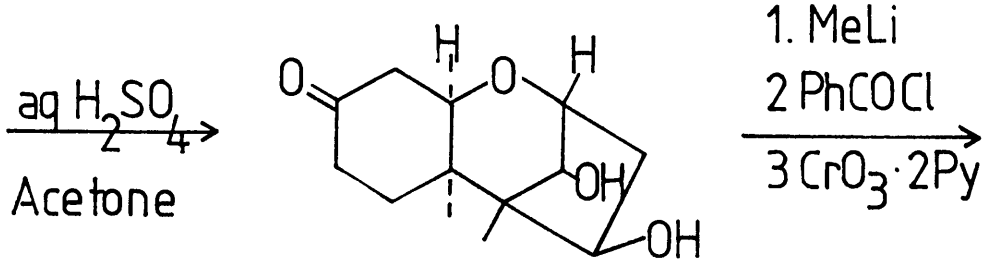


Bu^tOOH
$VO(acac)_2$

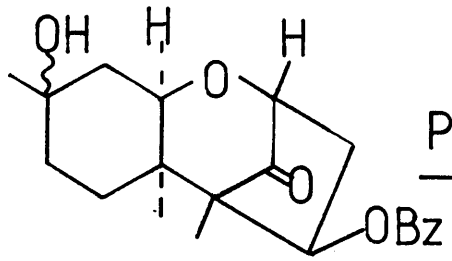
(79)



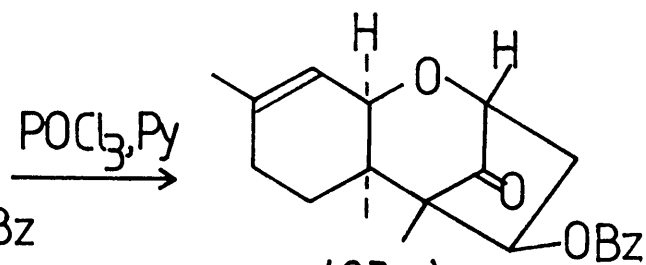
(80)



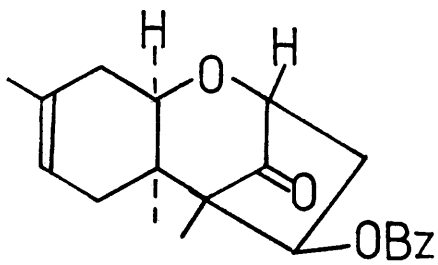
(81)



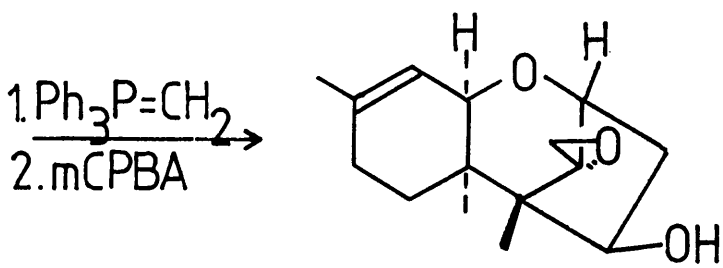
(82)



(83a)



(83b)



(84)

contraction, furnished cyclopentenone carboxylic ester (73) regiospecifically; the ring contraction served to establish both the C-5 and C-6 quaternary centres with complete stereocontrol. The requisite 4β-hydroxyl group was introduced stereospecifically by sequential epoxidation and dissolving-metal reduction.

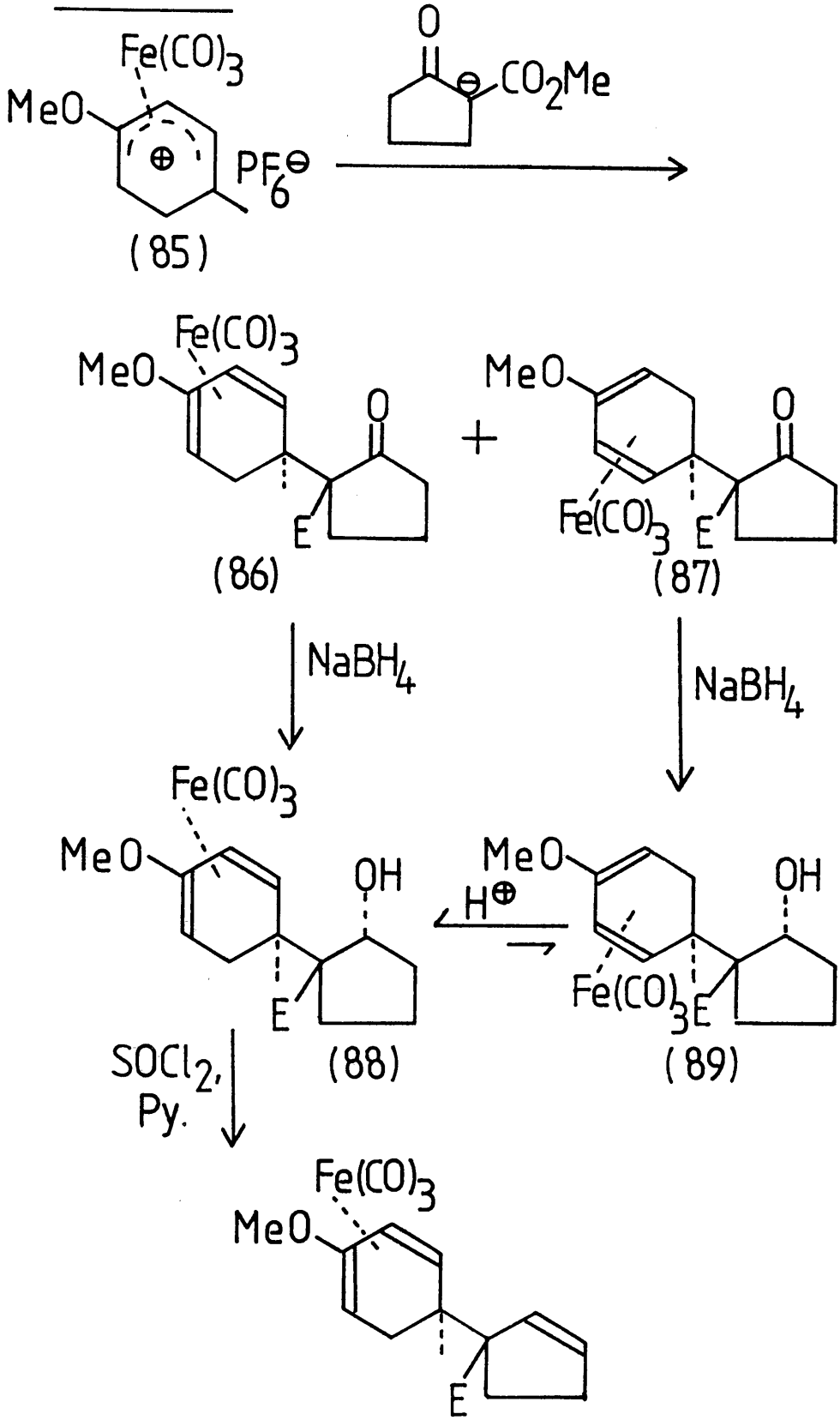
Subsequent Grob fragmentation of hydroxymesylate (77) unmasked intermediate (78), containing a 2,12-olefin and the correct relative stereochemistry for further elaboration into trichodermol. At this stage elaboration of the 2,12-double bond to give the 2α-hydroxyl group, required for biomimetic cyclisation was accomplished by hydroxyl-directed epoxidation. Acid hydrolysis of the resulting 2,12-epoxide and concomitant Michael addition, afforded the desired tricycle (81).

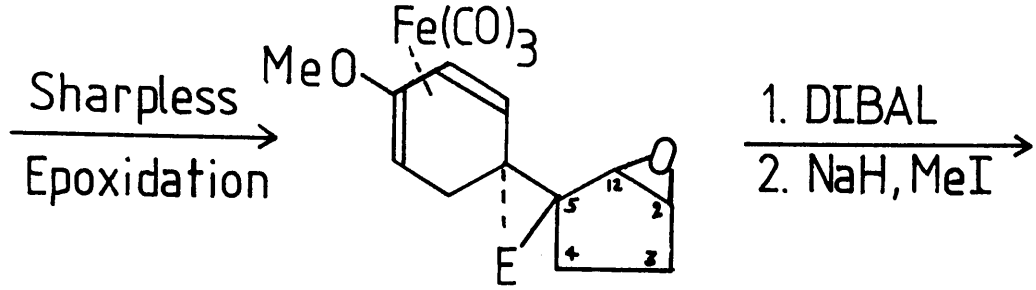
Further straightforward elaboration of tricycle (81) gave (±)-trichodermo

A short time later Pearson and Ong published a synthesis of 12,13-epoxy-14-methoxytrichothecene (95), a trichothecene analogue of potential pharmacological interest[45]. This synthesis also followed the group 3 biomimetic approach and was comparable to the previously discussed synthesis by Still and Tsai[31] in that it involved a 2,12-epoxy intermediate which underwent a tandem epoxide opening-cyclisation sequence. This synthesis is of particular interest because of its use of organoiron complexes to synthesise trichothecanoid systems, as shown in Scheme 13.

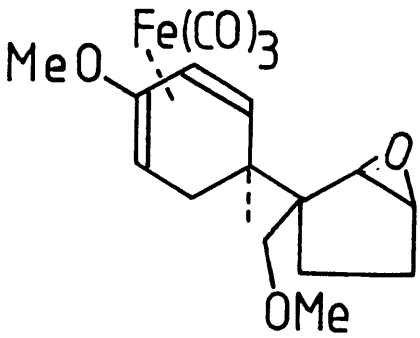
It has been observed that,generally, tricarbonyl(4-methoxy-1-methylcyclohexadienylium) iron hexafluorophosphate (85) reacts with a variety of stabilised enolate ions regio- and stereospecifically at the methylated dienyl terminus. Accordingly, upon reaction with the potassium enolate of methyl-2-oxo-cyclopentane carboxylate, a 1:1 mixture of diastereoisomers

Scheme 13

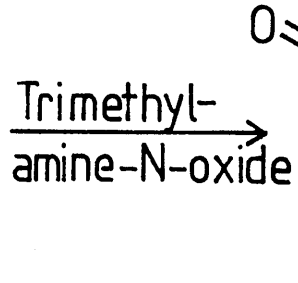

Fe(CO)3
MeO
PF6⊖
(85)
O
CO2Me
(86)
(87)
NaBH4
NaBH4
OH
H⊕
(88)
(89)
SOCl2,
Py.
(90)
E=CO2Me

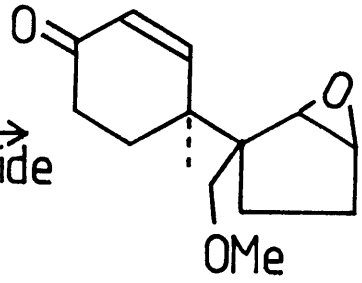

Sharpless
Epoxidation
MeO
Fe(CO)3
E
1. DIBAL
2. NaH, MeI

(91)

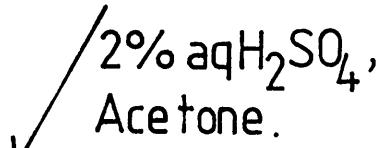

MeO
Fe(CO)3
OMe

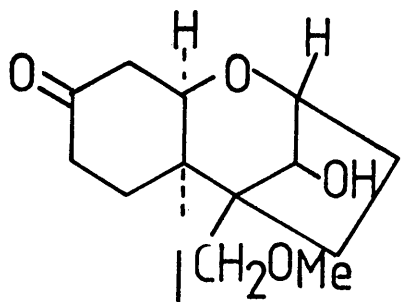
(92)


Trimethyl-
amine-N-oxide

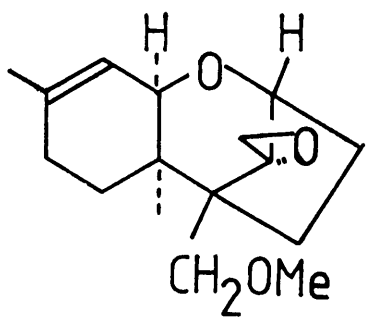

O
OMe

(93)


2% aqH2SO4,
Acetone.


H
O
H
O
OH
CH2OMe

(94)


H
O
H
O
CH2OMe

(95)

(86) and (87) was formed quantitatively, with diastereoisomer (87) having the incorrect relative stereochemistry between C-5 and C-6.

The diastereoisomeric mixture of keto esters (86) and (87) was reduced to the corresponding hydroxy esters (88) and (89), respectively: fortuitously diastereoisomer (89) underwent facile conversion into the desired diene isomer (88), upon mild acid treatment. This reaction sequence thus led to a high yielding preparation of an intermediate which had the correct relative stereochemistry between these two contiguous chiral centres.

Further synthetic manipulation towards stereoselective introduction of the 2α-hydroxyl group proceeded by selective dehydration of hydroxy ester (88) to yield the 2,12-olefin intermediate (90).

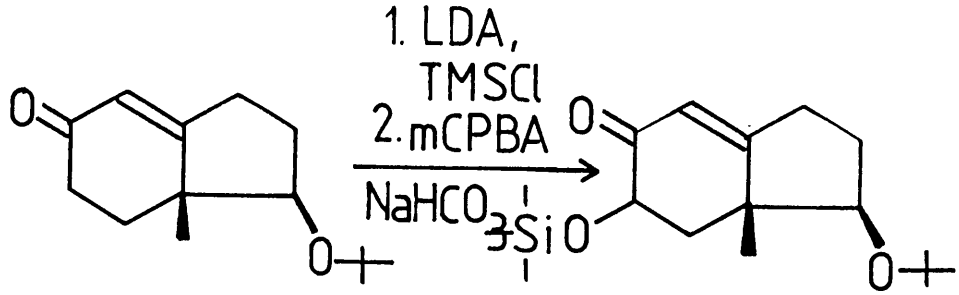
Sharpless epoxidation[46] of intermediate (90) afforded the 2,12-epoxide (91), which notably still contained the iron tricarbonyl group. This sequence of reactions illustrated the usefulness of the iron tricarbonyl function as a protecting group for diene and dienol ether systems.

Removal of this protecting group by treatment with trimethylamine-N-oxide afforded epoxy-enone (93), which was further elaborated to the aforementioned trichothecene analogue (95).

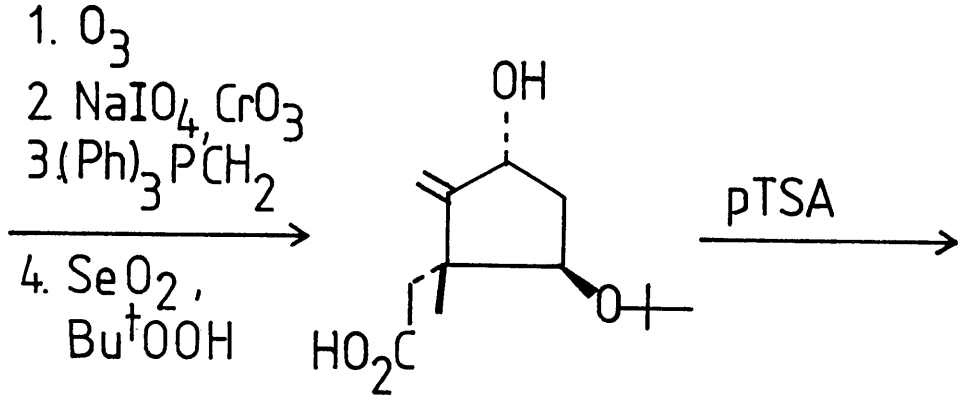
Schlessinger and Nugent successfully completed the first synthesis of the 4β,15-dihydroxytrichothecene, verrucarol (36), which followed the group 3 biomimetic strategy[33].

Starting from the readily available dione (96), key intermediate allylic alcohol (98) was obtained as outlined in Scheme 14. Lactonisation and methylenation afforded the synthetically useful α-methylene lactone

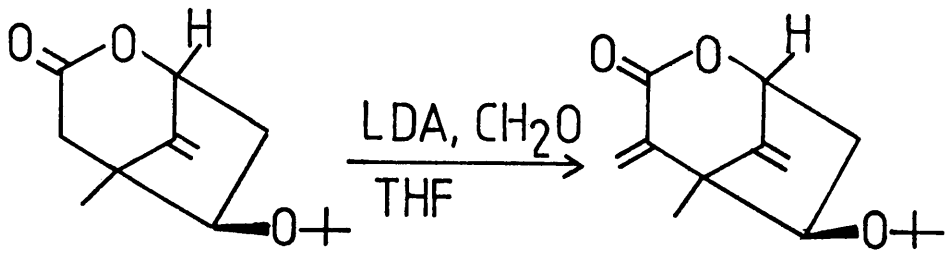
Scheme 14



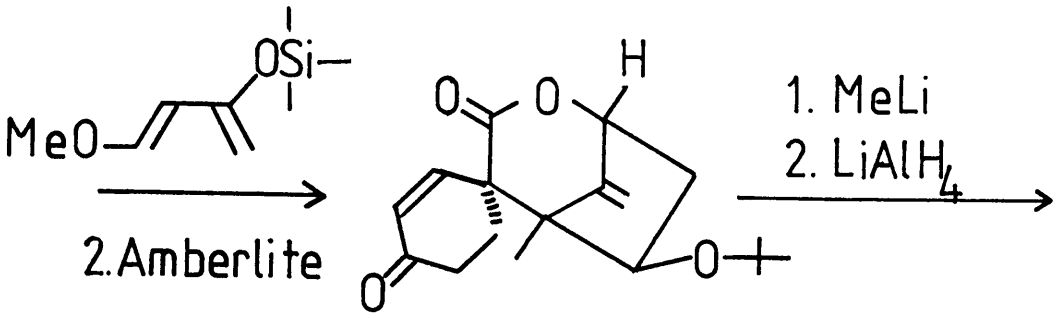
(96) (97)



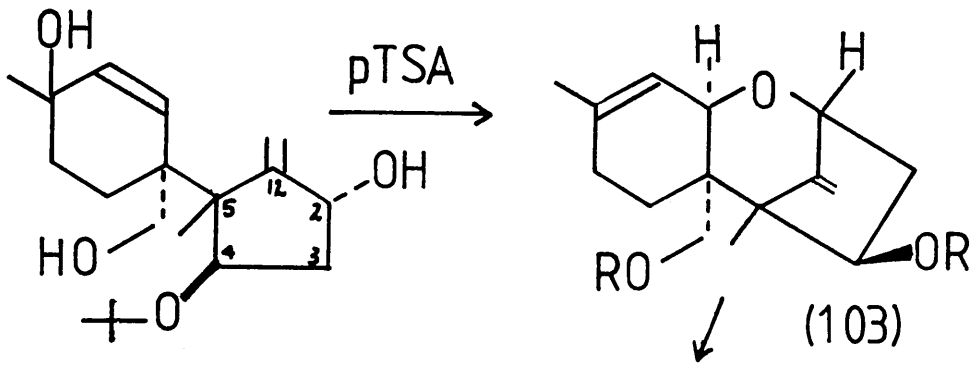
(98)



(99) (100)

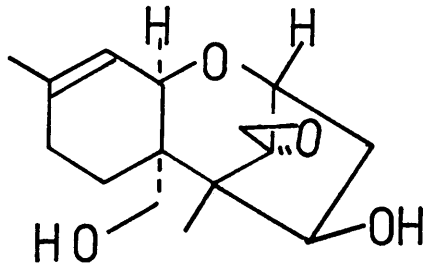


(101)



(102)

(103)



(36)

(100), in eight steps overall from dione (96).

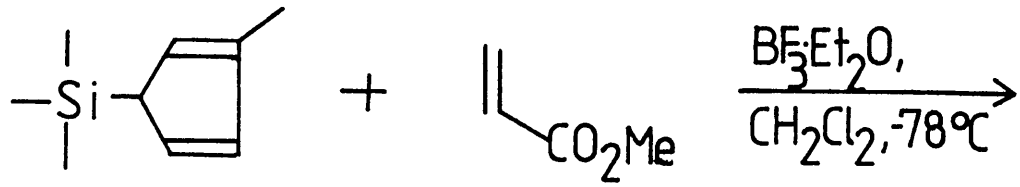
The problem of relating the stereochemistry between the C-5 and C-6 quaternary centres was solved using a [4+2] cycloaddition reaction, which annelated the A-ring on to a preformed BC bicyclic precursor. Examination of molecular models indicated that diene addition to methylene lactone (100) should occur exclusively from the β-face, due to the sterically biased nature of the bicyclic intermediate.

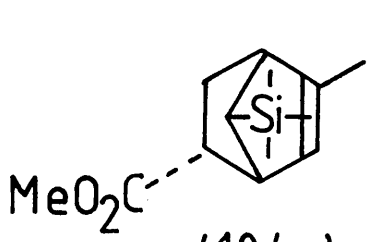
This was borne out experimentally: reaction of lactone (100) with 1-methoxy-3-trimethylsilyloxybutadiene furnished cyclohexenone (101) as a single diastereomer after acid hydrolysis. Treatment of cyclohexenone (101) with methyl lithium afforded an excellent yield of a single alcohol which was reductively cleaved to the corresponding triol (102); this intermediate readily cyclised in the presence of acid to furnish the desired tricycle (103). Further functionalisation to the target molecule verrucarol (36) was successfully achieved by a sequence similar to that described in previous syntheses.

An alternative second synthesis of verrucarol (36) was reported by Roush and D'Ambra[34]. Preparation of key intermediate (113), a bicyclic precursor possessing all of the functionality necessary for elaboration to the target molecule, was cleverly accomplished via a trimethylsilyl-controlled Diels-Alder reaction and subsequent Wagner-Meerwein rearrangement sequence.

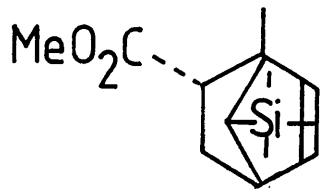
As shown in Scheme 15, reaction of methyl(cyclopentadienyl) trimethylsilane with methyl acrylate, in the presence of $BF_3.Et_2O$ afforded the desired bicyclo[2.2.1] heptene (104a) as the major product. Peracid treatment, followed by exposure of the resulting epoxide to Lewis acid, furnished the corresponding bicyclo[2.2.1]

Scheme 15

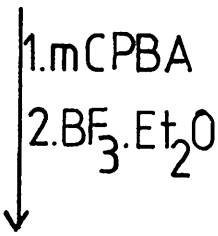


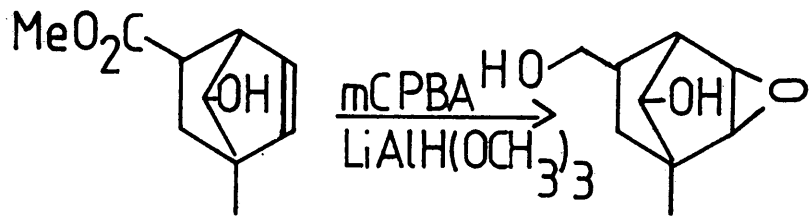


(104a)



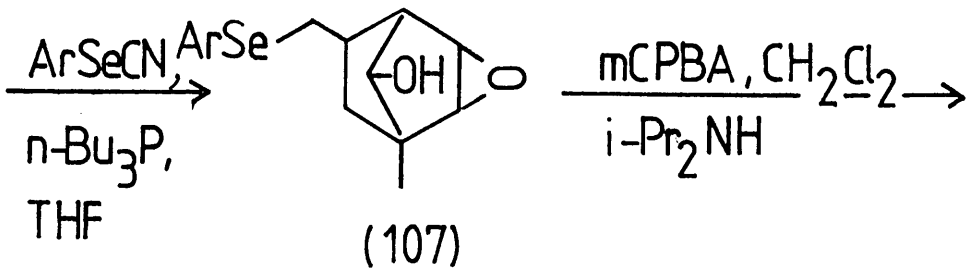
(104b)



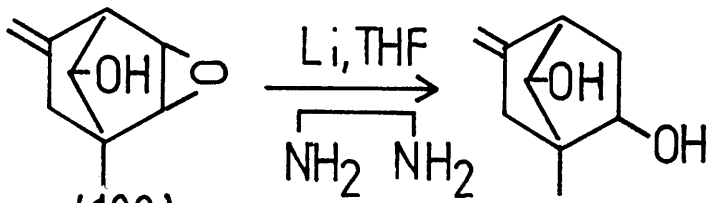


(105)

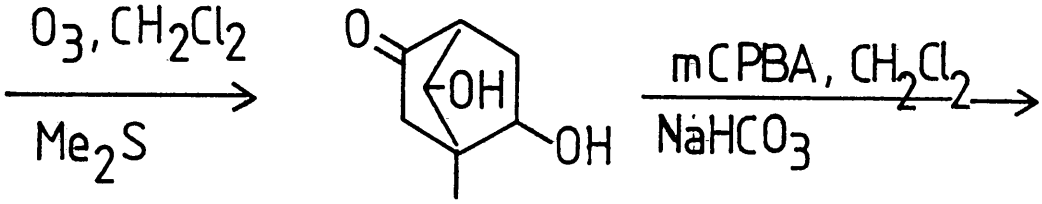
(106)



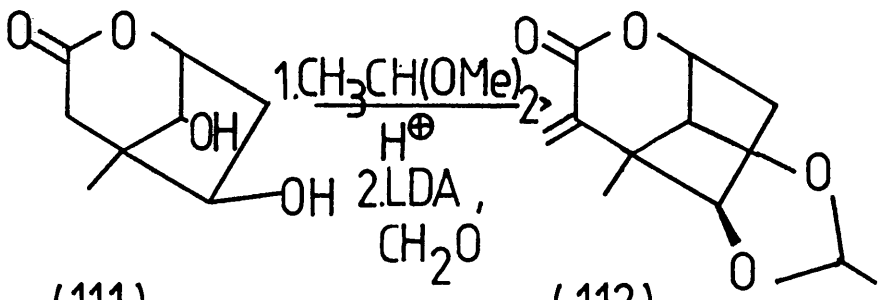
(107)



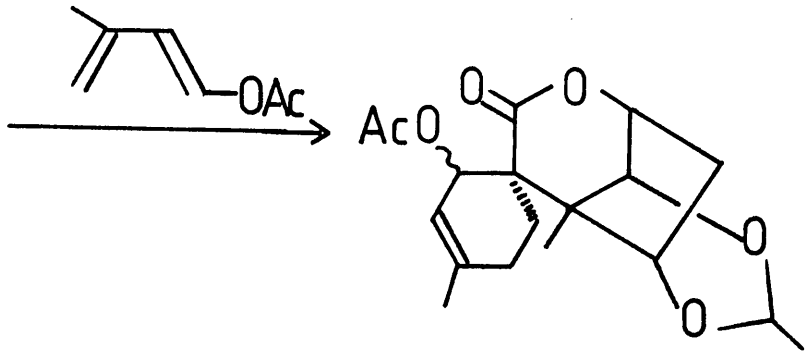
(108) (109)



(110)

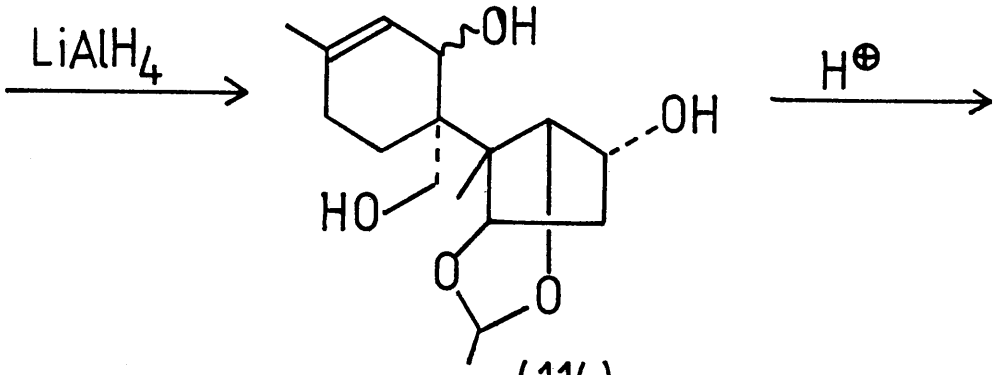


(111) (112)

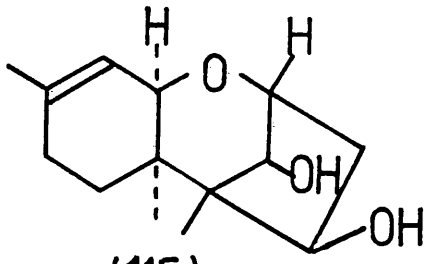


(113a) α = OAc 3 : 1

(113b) β = OAc



(114)



(115)

↓

↓

VERRUCAROL

heptenol (105) via a silyl-controlled Wagner-Meerwein rearrangement, utilising silicon's ability to stabilise β-carbonium ions. Further synthetic manipulation furnished diol (111), which was protected as the ethylidene derivative and subsequently converted into the desired α-methylene lactone (112).

The critical C-5 - C-6 stereochemistry and requisite A-ring were introduced via a Diels-Alder reaction in an analogous manner to that reported by Schlessinger and Nugent[33]. Reaction of α-methylene lactone (112) with 3-methyl-1-acetoxy butadiene gave a 3:1 mixture of adducts (113a) and (113b) respectively. Hydride reduction afforded the corresponding triol (114), which underwent smooth acid-catalysed ring closure to the desired tricycle (115), and thence to (±)-verrucarol (36)

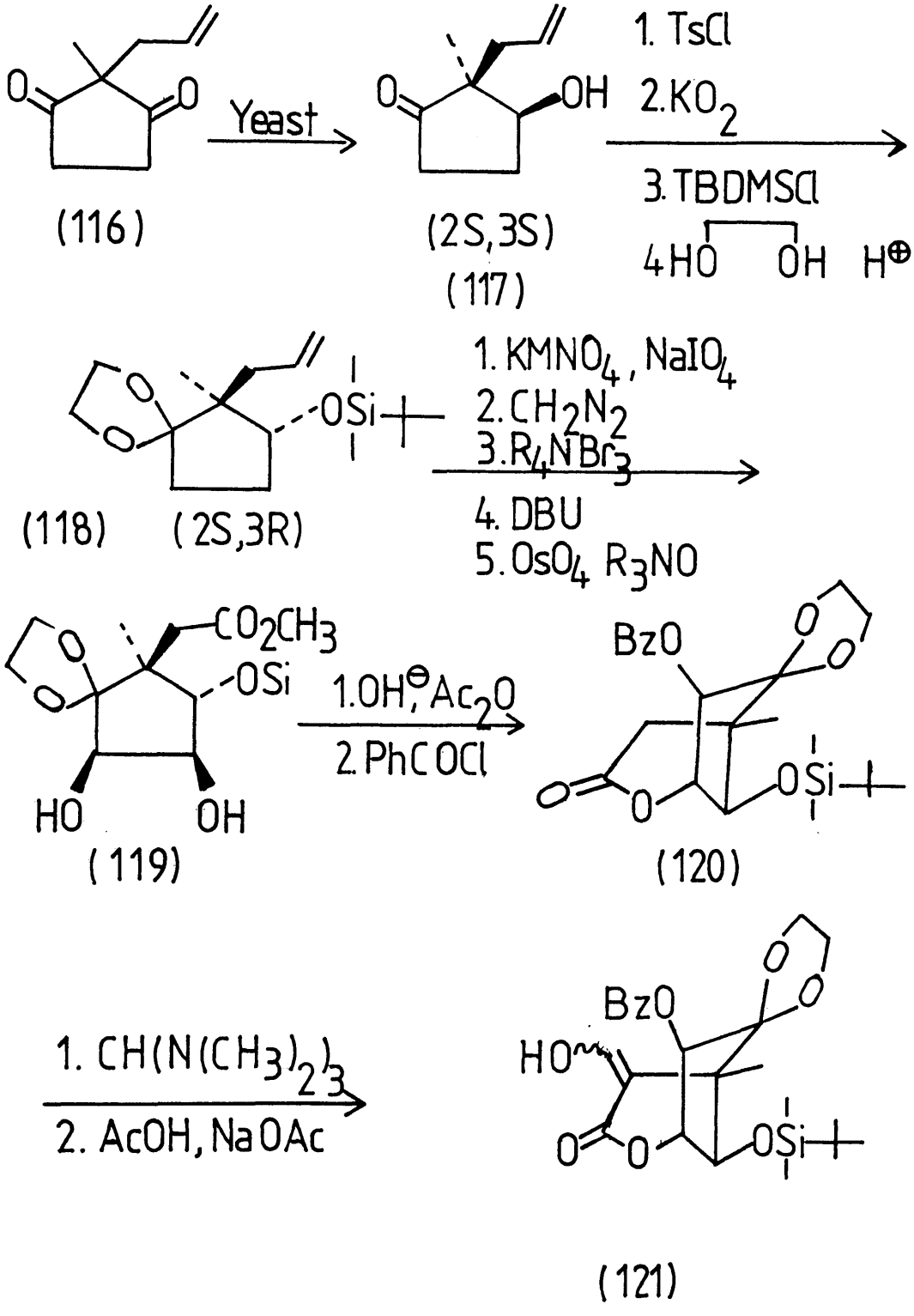
Brook's synthesis of the cytostatic agent, anguidine (127)[36], represented the first total synthesis of a trihydroxylated trichothecene, and also the first enantioselective synthesis of a trichothecene.

The overall strategy chosen for assembly of the trichothecene skeleton involved addition of an A-ring unit on to a fully functionalised C-ring synthon; introduction of the B-ring was then achieved by the now familiar biomimetic cyclisation pathway.

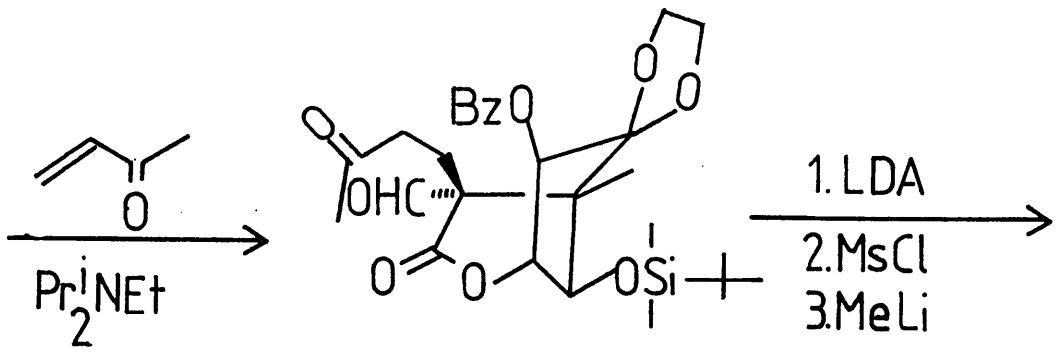
As outlined in Scheme 16, the synthesis began with an asymmetric microbial reduction of 2-allyl-2-methyl-1,3-cyclopentanedione (116), furnishing (2S,3S)-2-allyl-3-hydroxy-2-methylcyclopentanone (117). The resulting alcohol (117) possessed incorrect stereochemistry at C-4 for further elaboration to anguidine, but this was easily rectified by a facile alcohol inversion process to afford the desired (2S,3R)-isomer (118). Further synthetic manipulation afforded key intermediate, hydroxy methylene lactone (121).

At this stage, the A-ring was introduced via a Robinson annelation

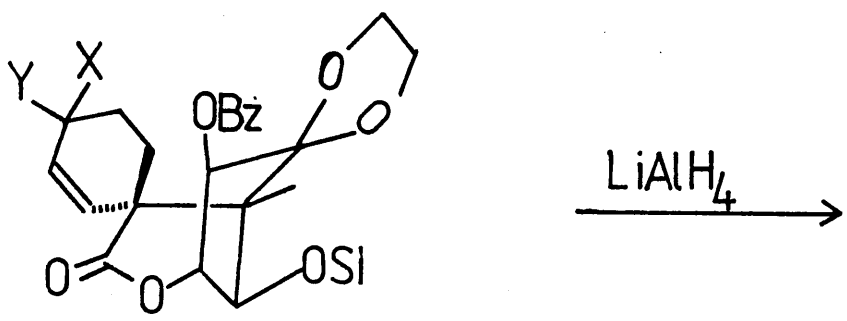
Scheme 16



(116) (2S,3S) (117) (118) (2S,3R) (119) (120) (121)

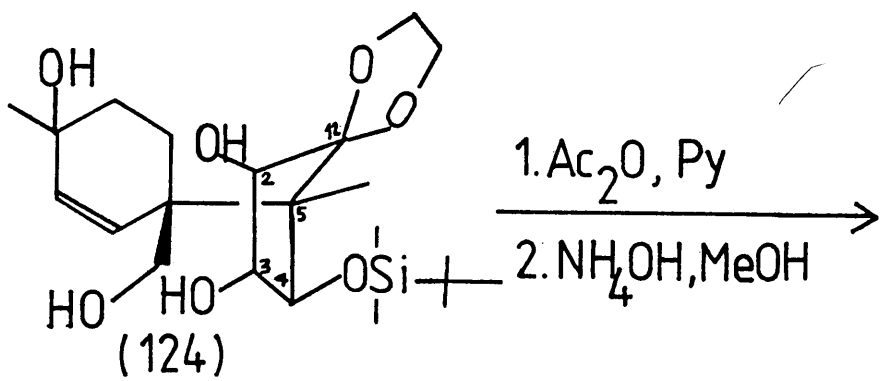


(122)

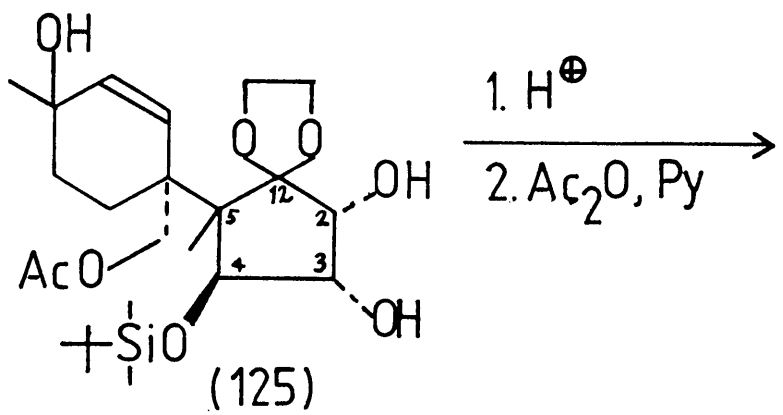


(123a) X,Y= O

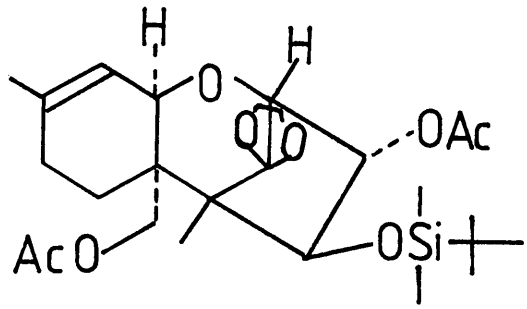
(123b) X=Me ,Y=OH



(124)



(125)

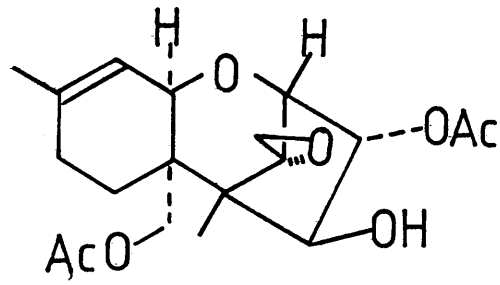


(126)

↓

↓

↓



(127)

ANGUIDINE

sequence. Reaction of methyl vinyl ketone with the enolate of (121) was observed to take place from the less hindered exo face of the bicyclic precursor, which was consistent with earlier observations made by Roush[47].

Intramolecular aldol condensation furnished the desired A-ring system (122); subsequent hydride reduction of intermediate (123b) gave tetraol (124).

Attempts to cyclise tetraol (124) directly were unsuccessful, due to cyclisation of the C-15 hydroxyl group. To circumvent this problem it was necessary to protect the C-15 hydroxyl group as the corresponding acetate, whereupon acid-catalysed cyclisation readily took place. Further synthetic transformation afforded anguidine (127) which was identical with a natural sample.

GROUP 4 BIOMIMETIC APPROACH

The Group 4 biomimetic strategy, outlined in Scheme 17, was developed by Anderson and coworkers, interested in devising efficient syntheses of A-ring aromatic trichothecene analogues, for potential therapeutic application[40,41].

As shown in Scheme 3, application of this methodology depends upon the key O-1-C-2 bond formation, which generally involves cyclisation of a cyclohexanol A-ring on to a C-ring synthon which possesses a suitable leaving group. This route was modified to one involving cyclisation of a phenol on to a suitably functionalised C-ring unit, which served to introduce the desired aromatic A-ring and effectively eliminated the problem of introducing the C-6 and C-11 chiral centres.

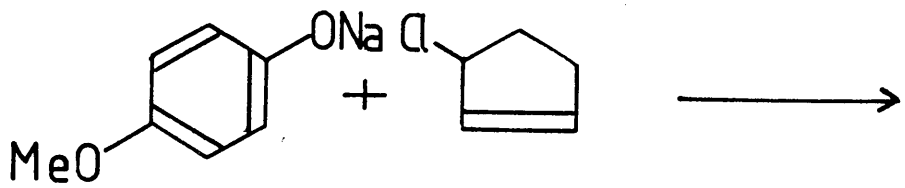
The target molecule for the synthesis of 6,9-bis-normethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (136) was bromohemiketal (134), which contained all the required functionality.

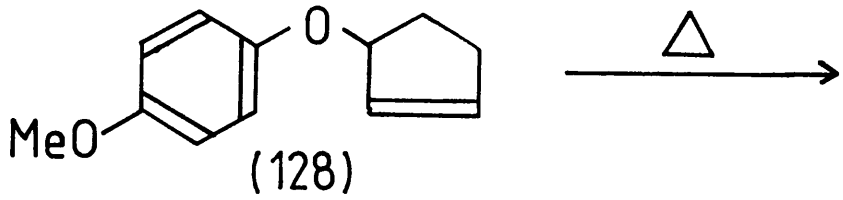
Reaction of sodium p-methoxyphenoxide with 3-chlorocyclopentene furnished arylallylether (128), which underwent Claisen rearrangement to the corresponding phenol (129a). Protection and a subsequent isomerisation-epoxidation sequence afforded epoxide (131), which was readily transformed into ketone (132a) upon Lewis acid treatment.

α-Methylation, α-bromination and deprotection were carried out sequentially to provide an isomeric mixture of two bromohemiketals (134a) and (134b). Both hemiketals underwent base-catalysed cyclisation to tricycle (135).

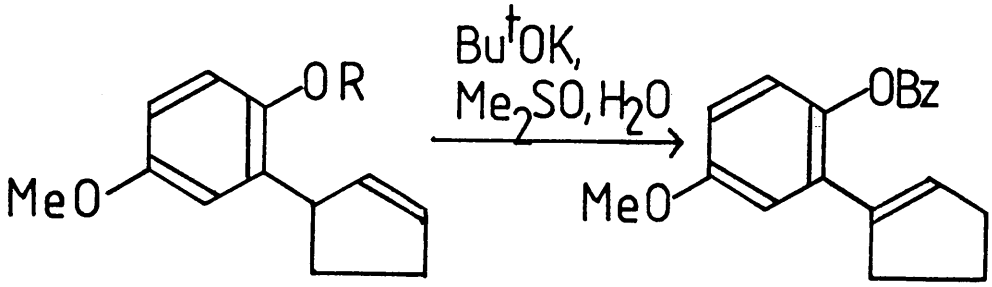
Finally, epoxidation of tricyclic ketone (135) was carried out using dimethylsulphonium methylide, to afford the target molecule (136), with the epoxide having undefined stereochemistry. In the light of former

Scheme 17





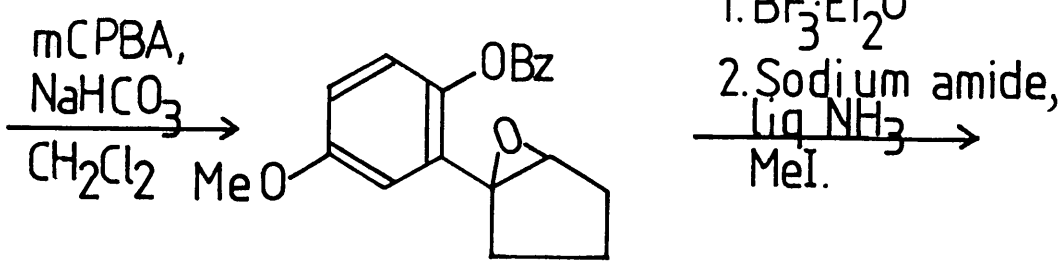
(128)



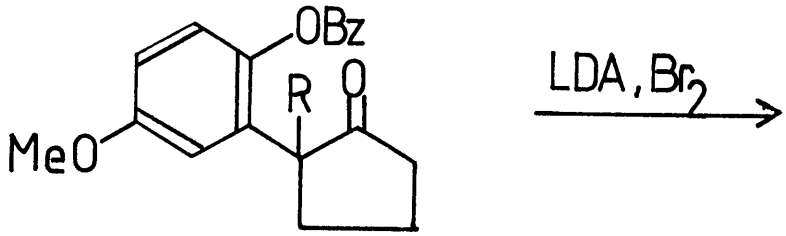
(129a) R=H

(129b) R=Bz

(130)

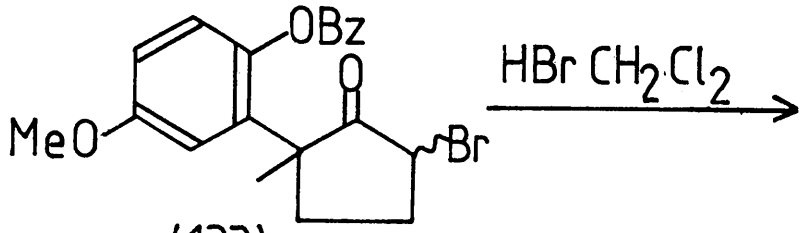


(131)

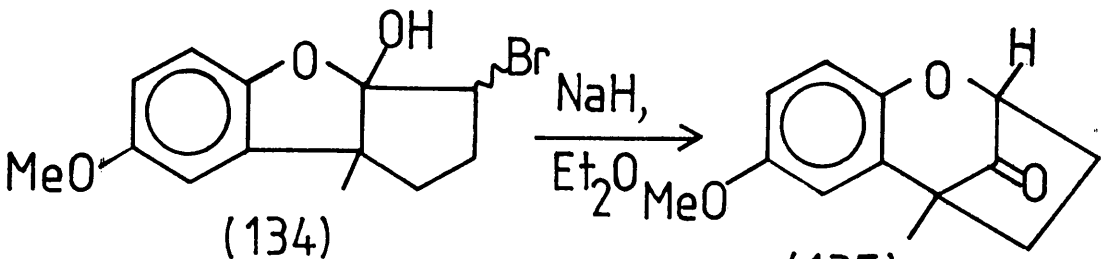


(132a) R=H

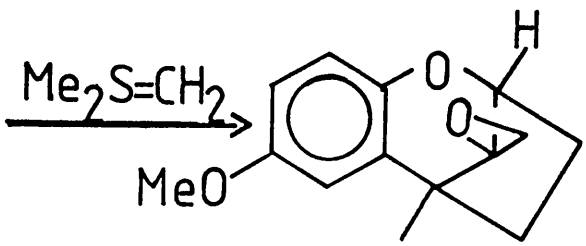
(132b) R=Me



(133)



(134) (135)



(136)

studies involving epoxidation of trichothecene precursors with dimethyl sulphonium methylide[28,29], it would seem likely that this epoxide was the unnatural 12,13-epoxide. Interestingly, this aromatic trichothecene analogue (136) exhibited significant in vivo antileukemic activity.

More recently the group 4 approach featured in a third synthesis of verrucarol (36), carried out by Trost and McDougal[35,48]. (Scheme 18).

A key step in this elegant synthesis involved Diels-Alder reaction between a C-ring dienophile (138) and diene (139), which served to assemble the A-ring and to introduce a number of the desired chiral centres of the target molecule (36).

Dienophile (138) was prepared from 2-methyl-1,3-cyclopentanedione in 4 steps. Subsequent cycloaddition between silyloxydiene (139) and the derived dienophile afforded the expected adduct (140) as the exclusive product. Inspection of intermediate (140) revealed that it contained two diastereotopic carbonyl groups, C-4 and C-12. Further elaboration of precursor (140) to verrucarol required differentiation between these two carbonyl groups; such that the C-12 carbonyl group which would ultimate become the 12,13-epoxide function could be temporarily protected, while the C-4 carbonyl group was selectively reduced.

Fortuitously, it was discovered that heating adduct (140) triggered an intramolecular ene-reaction to furnish tricycle (141), which arises because only the C-12 carbonyl group can align itself in the proper orientation to undergo the ene-reaction.

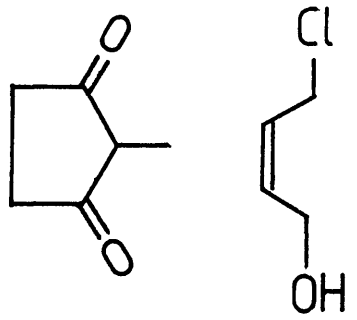
Having effectively differentiated between the two carbonyl groups, hydride reduction of the remaining C-4 carbonyl group gave the 4α-hydroxy compound, which was protected as the corresponding lactone (142). A subsequent retro-ene sequence then regenerated the C-12 carbonyl group to

afford ketone (143a). Introduction of the requisite α-bromine was achieved by quenching the ketone enolate derived from (143a) with trimethylsilylchloride, and subsequent α-bromination of the resulting intermediate silyl enol ether with bromine-dioxane. The derived α-bromoketone (143b) had incorrect stereochemistry at C-11; inversion was achieved by treatment with trifluoroacetic acid at 35-50°C, to afford the thermodynamic hemiketal (144). Fluoride-catalysed cyclisation of hemiketal (144) furnished the desired tricycle (145).

All that remained for completion of the formal synthesis of verrucarol (36) was Wittig introduction of the 12,13-methylene group, inversion of the 4α-hydroxyl group and finally selective molybdenum-catalysed epoxidation, to afford racemic (±)-verrucarol (36).

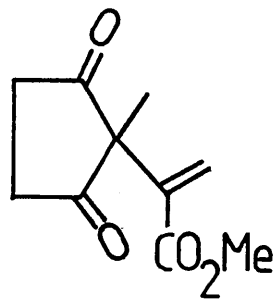
In conclusion, both the group 3 and group 4 strategies represent efficient entries into trichothecene systems.

Scheme 18

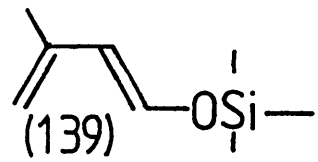


1. pTSA, toluene
$-H_2O$

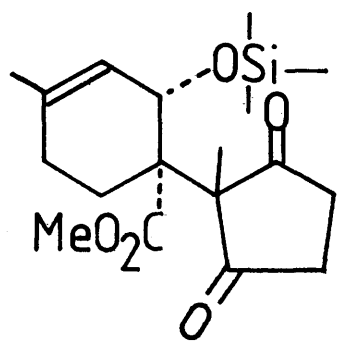
2. Mesitylene, reflux
3. $KMnO_4$
4. CH_2N_2
5. DBU



(138)

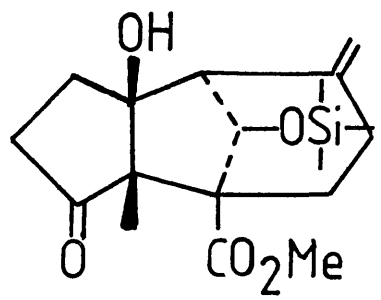


(139)



(140)

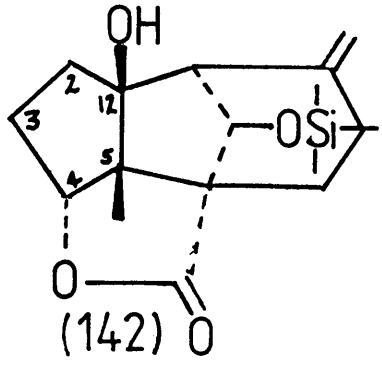
Mesitylene
155°C, 9h



(141)

1. $NaBH_4$, MeOH

2. $CrO_3 \cdot 2Py$

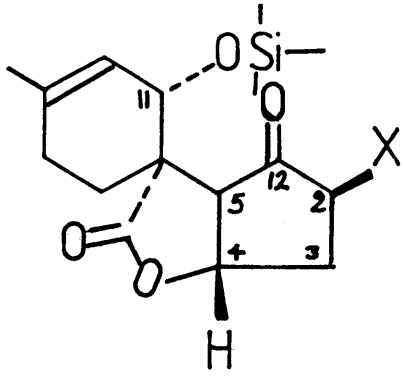


(142)

1. 4 70°C, 1·2 mm

2. $LiNR_2$, TMSCl

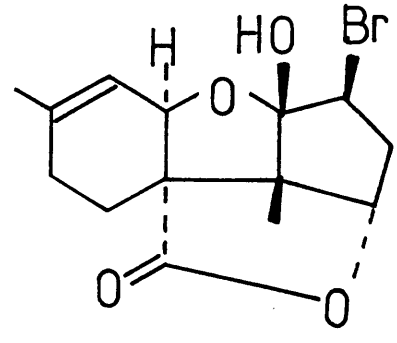
3. Br_2. Dioxane, Py, CH_2Cl_2



(143a) X = H

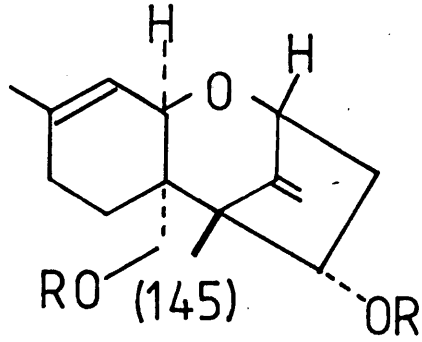
(143b) X = Br

CF_3CO_2H



(144)

n-Bu_4NF



(145)

VERRUCAROL (36)

DISCUSSION

Several efficient strategies towards the preparation of the tricyclic epoxy trichothecenes have been developed. In particular, over the past seven years, much activity has been directed towards devising Diels-Alder approaches to the AB ring system of these compounds.

The Diels-Alder methodology applied can be divided into two distinct approaches. The first involves assembly of a highly functionalised A-ring system via cycloaddition, with the requisite B-ring being assembled subsequently by intramolecular cyclisation. This strategy has been discussed in a comprehensive review article by McDougal and Schmuff[23] and will not be discussed further here. Alternatively, the AB ring synthon can be assembled directly by Diels-Alder reaction between a suitably functionalised buta-1,3-diene and coumalic acid derivative. Cycloaddition reactions which employ methyl coumalate or its derivaties as the dienophile are particularly attractive synthetic strategies in that they allow rapid access to molecules having a suitably functionalised B-ring. Moreover, the functionality of the A-ring in such systems can be varied by the choice of diene. This methodology also defines unambiguously the stereochemistry of the AB ring junction as cis-fused, and it also circumvents some of the problems encountered in forming the AB ring system by intramolecular cyclisation.

It should be stressed, however, that having thus assembled the cis-fused benzopyran ring system, a number of synthetic manipulations are still needed to convert it into a useful intermediate. This methodology has been used to prepare many advanced compounds en route to target trichothecene molecules,[38,49,50,51] and it was hoped that such an approach could be applied to a planned synthesis of T2 toxin.

The Diels-Alder approach towards formation of an AB ring synthon first featured in a synthesis of 12,13-epoxytrichothec-9-ene (47), by Nakahara and Tatsuno[49].

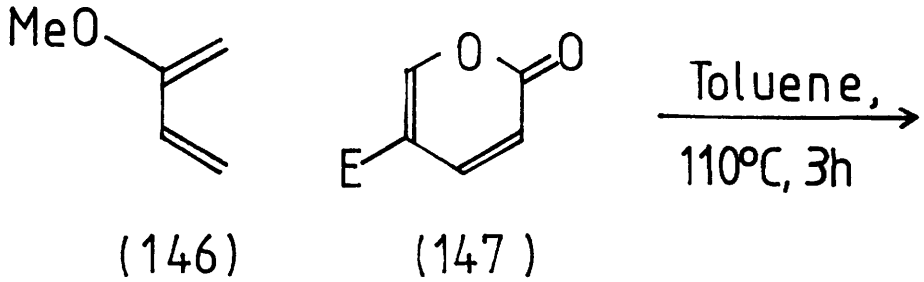
As shown in Scheme 19, cycloaddition between 2-methoxy-buta-1,3-diene (146) and methyl coumalate (147) afforded the enol ether (148), as a single regioisomer. Conjugate addition of dimethyl copper lithium to the enone system of adduct (148) furnished saturated lactone (149), which was subsequently reduced to the corresponding lactol (150). Acid hydrolysis gave the expected ketone (151), which was then converted into acetal (152). Careful Grignard treatment of intermediate (152) afforded tertiary alcohol (153), which on exposure to acid gave hemiacetal (154). Acetylation and pyrolysis then provided the key intermediate (40)'.

Intermediate (40)' was also employed in an earlier synthesis of 12,13-epoxytrichothec-9-ene by Fujimoto and coworkers[29], as shown in Scheme 7.

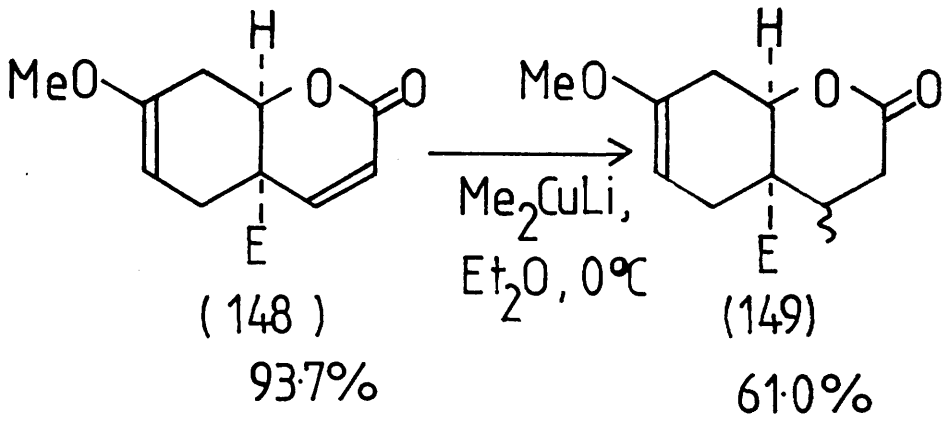
Kraus and coworkers used Diels-Alder methodology to assemble the AB ring system in their synthetic studies towards verrucarol (36)[50]. As outlined in Scheme 20, cycloaddition between isoprene (156) and methyl coumalate (147) afforded an inseparable regioisomeric mixture of adducts (157a) and (157b), in a ratio of 85:15 respectively, in a modest overall yield.

With the AB ring system in hand, a number of synthetic transformations were then carried out on the adduct (157a) in an attempt to convert it into the target molecule. Conjugate addition to the enone system of adduct (157a) afforded the corresponding cuprate product (158). Subsequent α-hydroxylation using the method of Vedejs[52], followed by

Scheme 19

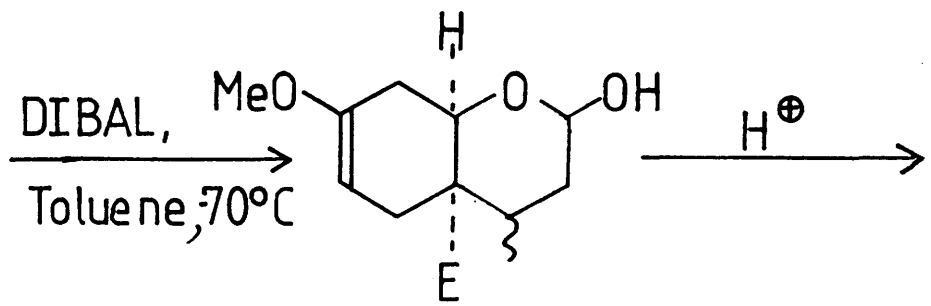


(146) (147)

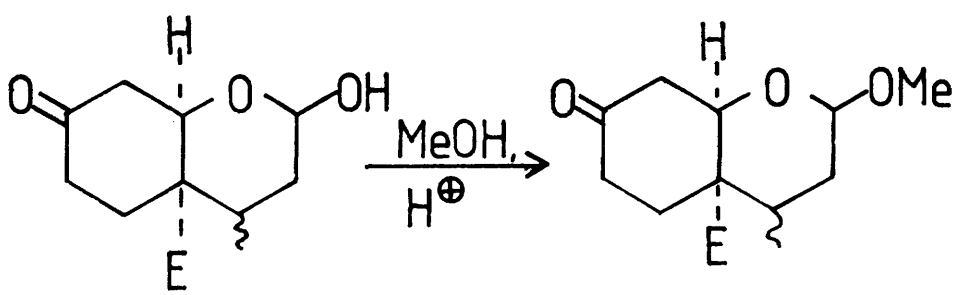


(148) 93·7%

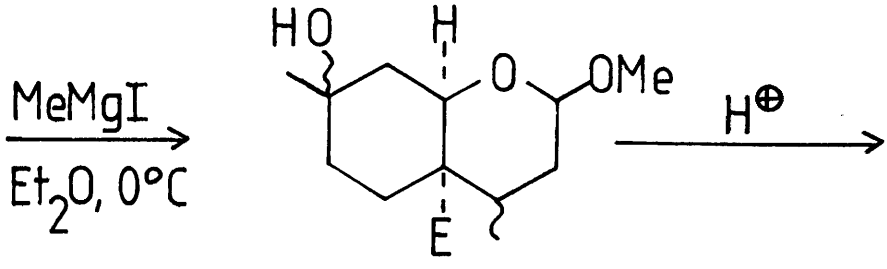
(149) 61·0%



(150) ; 90·8%

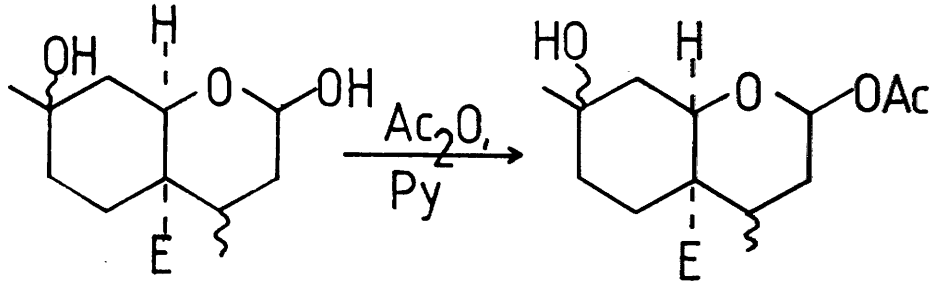


(151) ; 90·7% (152) ; 87·3%



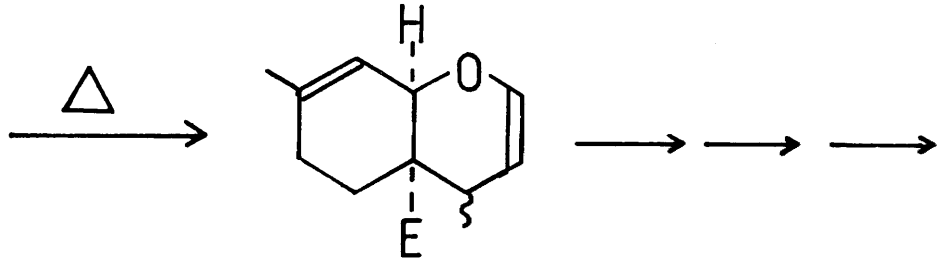
(153)

66·4%

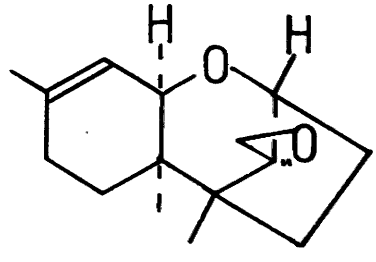


(154)

(155); 58·2%



(40)' ; 24·4%



(47)

N-chlorosuccinimide/dimethyl sulphide oxidation of the derived hydroxy lactone (159) furnished enol lactone (160). Diisobutyl aluminium hydride reduction of the O-methylated enol lactone (161) followed by reductive deoxygenation of the unstable lactol with triethylsilane and boron trifluoride etherate provided enol ether (162). Finally lithium aluminium hydride reduction of the remaining ester function and acid hydrolysis of the enol ether afforded the advanced intermediate keto alcohol (54)'. It should be noted that intermediate (54) appeared in an earlier synthesis of calonectrin, by Kraus and coworkers[3] where this intermediate was previously prepared by the alternative Diels Alder methodology as outlined in Scheme 8.

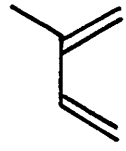
This synthetic scheme demonstrates the utility of the Diels-Alder methodology, providing rapid access to a useful, highly-functionalised intermediate, which ideally lends itself to further synthetic manipulati

White and coworkers[51] have published a novel synthesis of the tricyclic nucleus of verrucarol (36) which also features the Diels-Alder approach. As outlined in Scheme 21, this strategy employed cycloadditi between 2-ethoxy-buta-1,3-diene (163) and methyl coumalate (147).

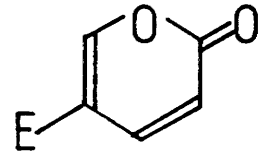
This proved to be a much more satisfactory [4+2] cycloaddition reaction than the aforementioned using isoprene[50]. The desired enol ether (164), was obtained as a single regioisomer in a very respectable yield of 79%. Adduct (164) was subsequently ketalised and then transfo into the saturated lactone (165), by a conjugate addition process. Regeneration of the α,β-unsaturated enone system of ring B was accomplis by a process of α-phenylselenylation and subsequent syn oxidative elimination to furnish the unsaturated lactone (166).

The 2-carbon bridge required for C ring formation was cleverly

Scheme 20

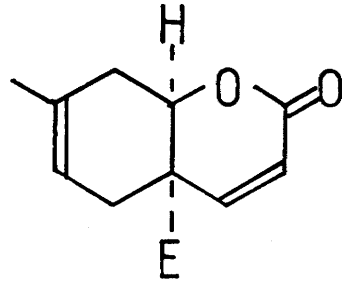


(156)

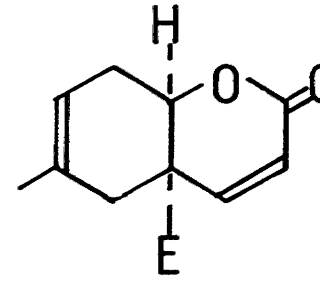


(147)

Benzene,
110°C, 48h

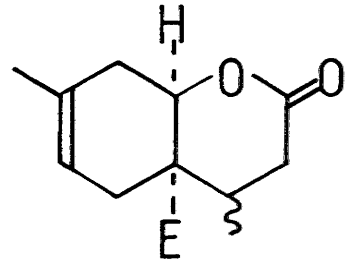


(157a)



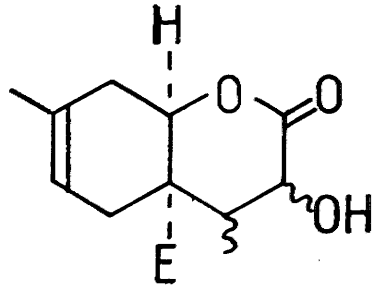
(157b)

Me_2CuLi
Et_2O, 0°C



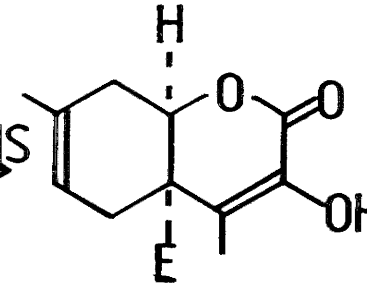
(158)

LDA
MoO_5·py·HMPA

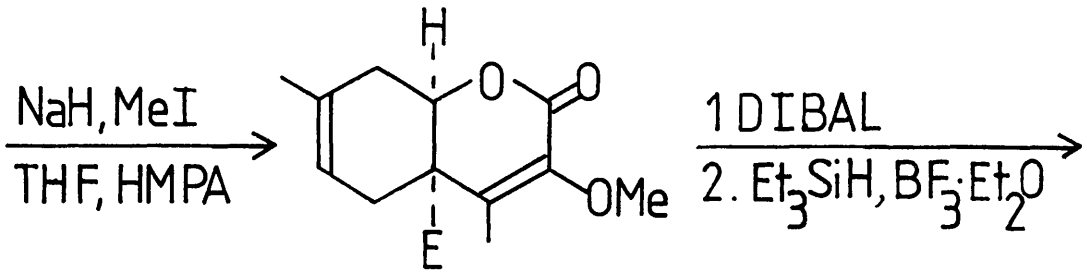


(159); 75%

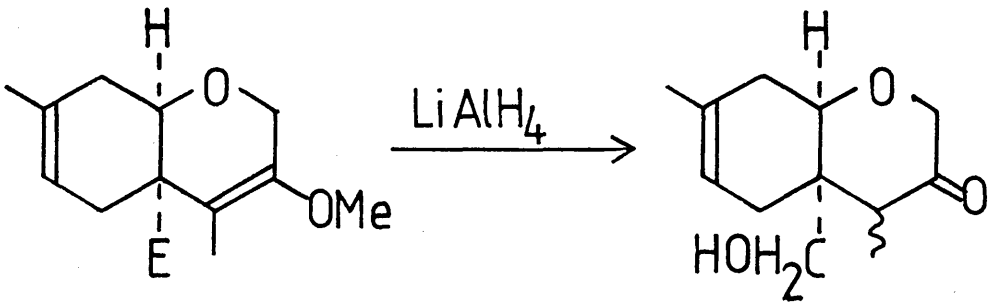
1. NCS, DMS
2. NEt_3



(160); 100%



(161) ; 72%

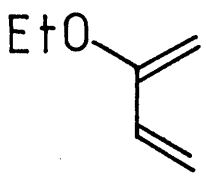


(162) ; 94%

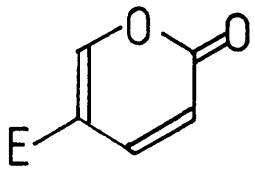
(54)' ; 98%

[E = CO_2Me]

Scheme 21

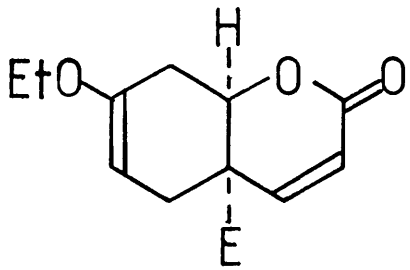


(163)



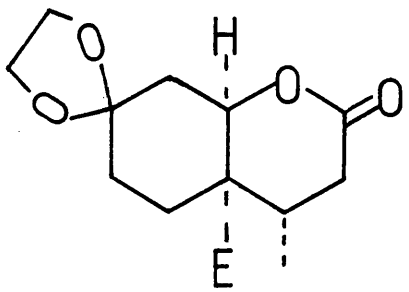
(147)

Benzene,
100°C, 20h



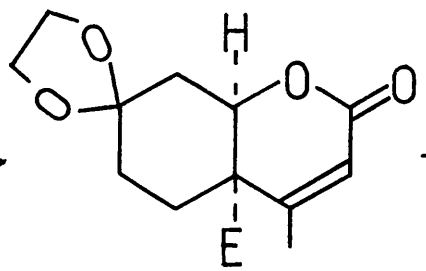
(164)

1. HO OH, p-TsOH
2. Me_2CuLi, THF



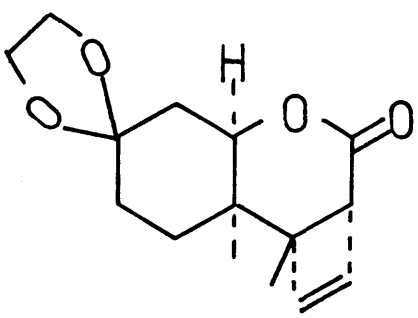
(165)

LDA, PhSeCl
2. H_2O_2, AcOH



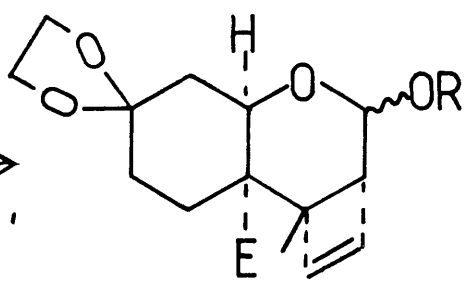
(166)

$HC{\equiv}CH$
hv, CH_3CN



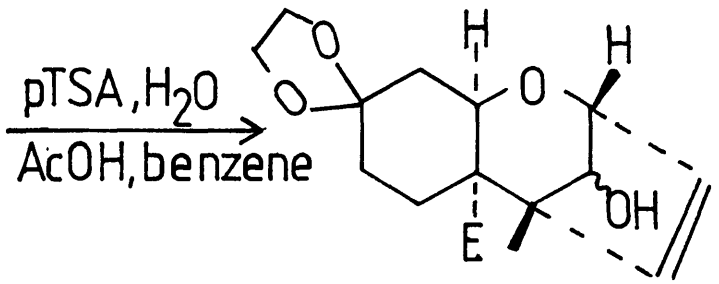
(167); 62%

DIBAL,
Toluene,
-70°C

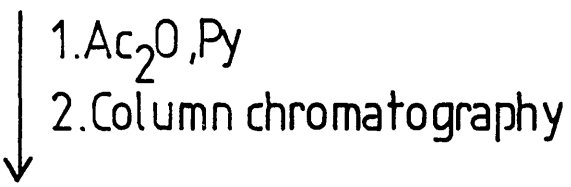


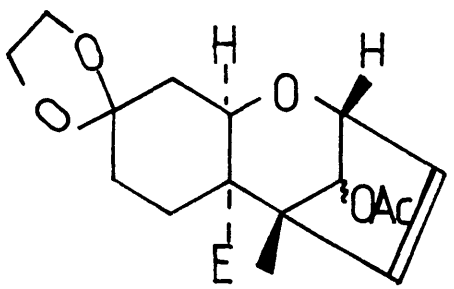
(168a) R=H

(168b) R=OAc


pTSA, H_2O
AcOH, benzene
O
O
H
O
H
OH
E

(169)


1. Ac_2O, Py
2. Column chromatography


O
O
H
O
H
OAc
E

(170)

introduced by a photolytic [2+2] cycloaddition reaction between lactone (166) and acetylene. The derived cyclobutene intermediate (167) was subsequently reduced to afford the key cyclobutenylcarbinol system (168a) and thence the corresponding acetoxy compound (168b). Under optimised reaction conditions intermediate (168b) rearranged to tricycle (169), a potentially useful synthetic intermediate en route to verrucarol.

In our own research laboratories Colvin and Thom[38] have studied potential routes towards vomitoxin (deoxynivalenol),(184). Structural examination of vomitoxin reveals that, in addition to the characteristic trichothecene features, it also possesses a 7α-hydroxyl group and an 8-keto function. Therefore, in devising a strategy towards vomitoxin, it was concluded that a Diels-Alder reaction between the 1-trimethylsilyl-oxy butadiene (171) and methyl coumalate (147) would be an attractive synthetic plan. Such a scheme would assemble a highly functionalised AB ring system possessing the requisite 7-hydroxyl group. In addition, the methyl cyclohexene system so-created could conceivably be transformed into the required A ring enone system by a base induced epoxide allyl alcohol rearrangement process[53]. To complete the synthetic scheme towards the target molecule it was envisaged that the C-ring could be formed using the now familiar group 2 aldol approach[29,32].

As shown in Scheme 22, cycloaddition between the 1-trimethyl silyloxy buta-1,3-diene (171) and methyl coumalate (147) proved to be a regiospecific process. The desired adduct (172a) was obtained as a single regioisomer, having mainly the undesired β-stereochemistry at the 7-position.

Fortunately it was discovered that the 7β-silyloxy compound could be easily equilibrated to furnish a 1:1 mixture of α- and β-alcohols

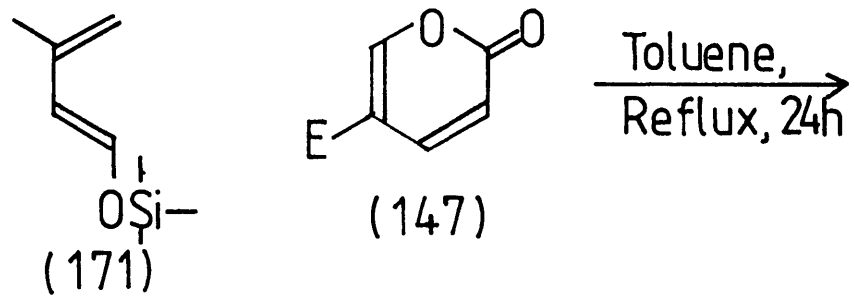
through a sequence of acid-catalysed desilylation and stirring of the resulting 7β-alcohol in ethyl acetate over chromatographic silica gel. Following column chromatography the recovered 7β-alcohol could be recycled through this process, to afford, after resilylation, large quantities of the desired 7α-silyloxy intermediate (172b).

1,2-Transposition of the lactonic carbonyl group of intermediate (172b) was achieved using the method developed by Kraus[50], as outlined in Scheme 20, such that silyloxy compound (172b) was transformed into enol ether (179). O-Alkylation of enol ether (175) with allyl bromide gave allyl enol ether (176). Subsequent diisobutyl aluminium hydride reduction of (176) afforded an unstable lactol, which was immediately reduced with boron trifluoride etherate and triethylsilane to furnish enol ether (178). Reduction of intermediate (178) to the corresponding diol (179), followed by a highly stereoselective [3,3] Sigmatropic rearrangement afforded the key intermediate, ketone (180), which possessed a highly functionalised B ring.

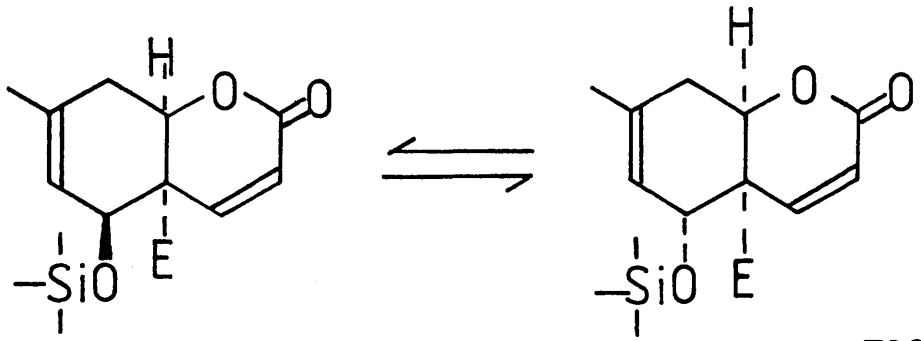
At this stage in the synthesis, attention was turned towards elaboration of the A ring system. Model studies on the base induced epoxide allyl alcohol rearrangement were very encouraging, so much so that epoxide (181) was prepared regio- and stereospecifically by the Sharpless epoxidation procedure[55]. It was envisaged that epoxide (181) would undergo a similar rearrangement process at a relevant stage in the synthesis to afford an intermediate possessing the requisite 9,10-double bond and a masked keto group at the 8-position.

Oxidative cleavage of the allyl side chain of epoxide (181) afforded nor-aldehyde (182), which underwent the key aldol cyclisation reaction to furnish tricycle (183). Having successfully prepared the tricyclic

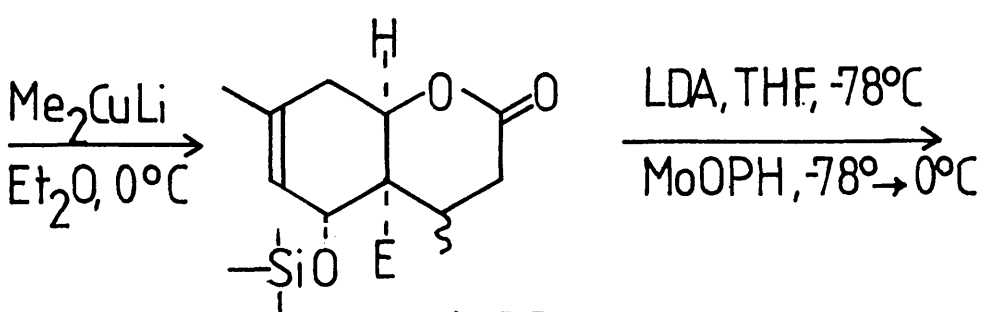
Scheme 22



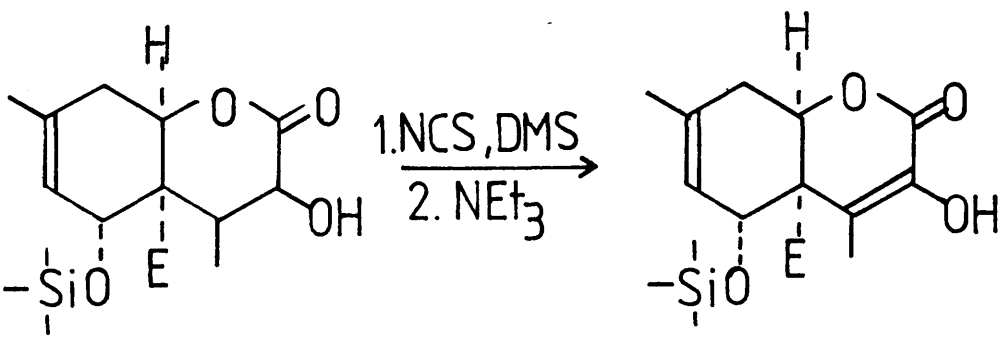
(171) (147)



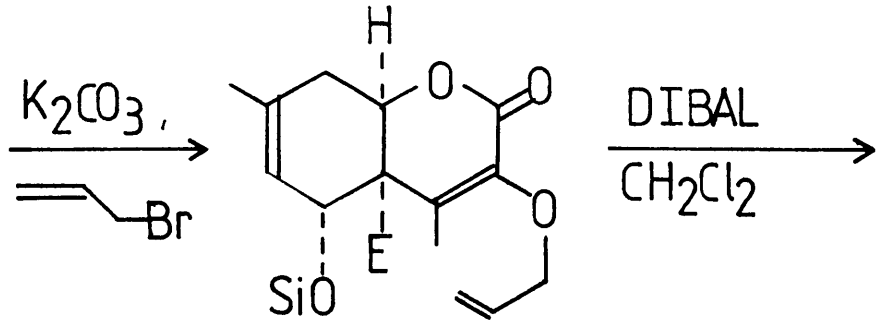
(172a) (172b) ; 59%



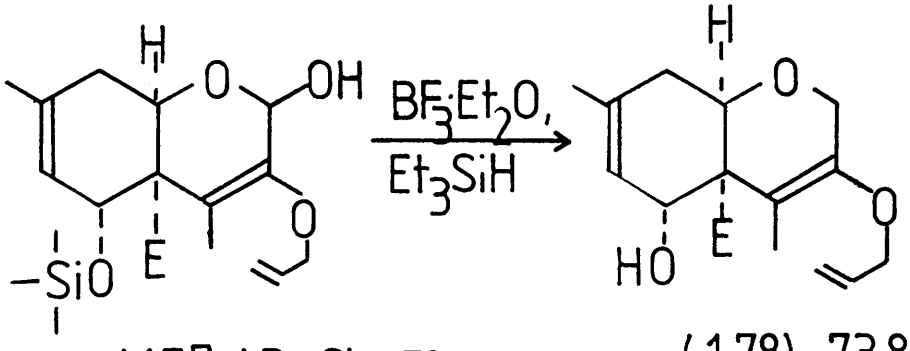
(173) ; 73%



(174) ; 73% (175) ; 77%

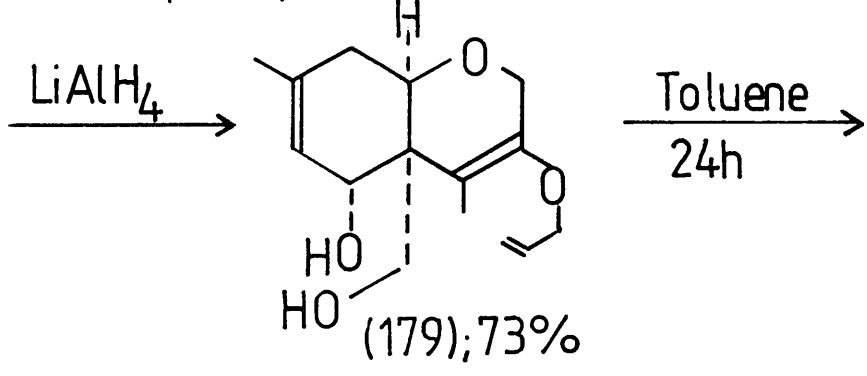


(176)

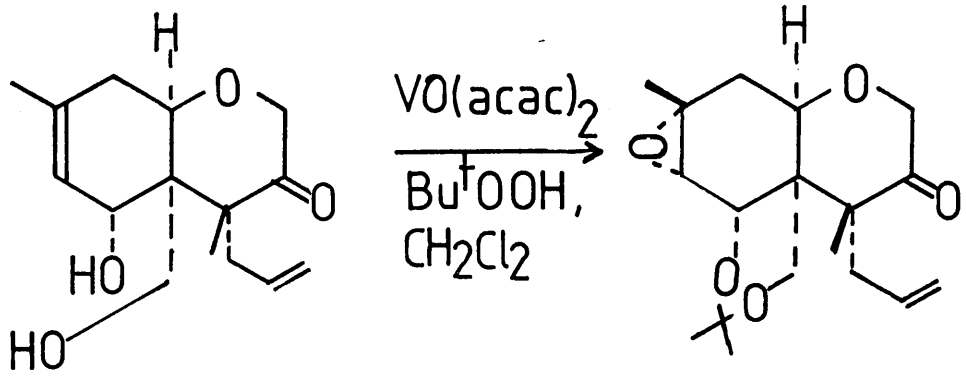


(177a) R=Si ; 50%
(177b) R=H 23%

(178) ; 73%

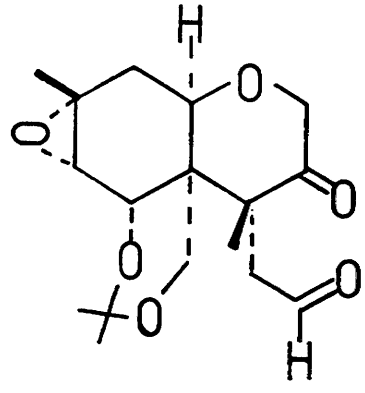


(179); 73%

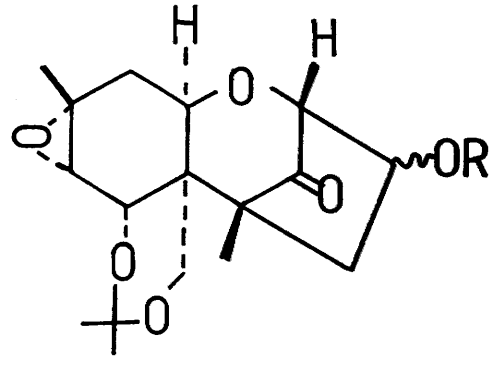


(180) ; 71%

(181) ; 76%

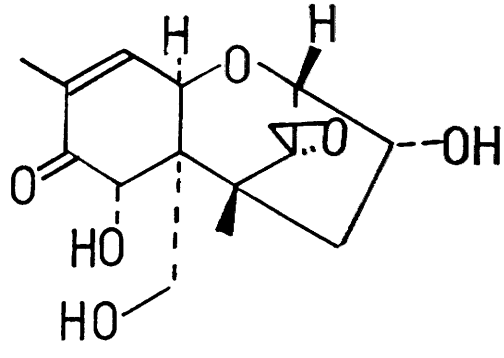


(182)



(183a) R=H

(183b) R=OAc



(184)

intermediate (183), all that remains for completion of the total synthesis of vomitoxin includes Wittig introduction of the C-12 - C-13 methylene function and thence regio- and stereoselective epoxidation to furnish the 12,13-epoxide group. The penultimate step requires rearrangement of the A-ring epoxy alcohol and subsequent oxidation of the resulting 8-hydroxyl group to the corresponding ketone.

In conclusion, it would appear that the Diels-Alder reaction has enjoyed significant success in preparing trichothecene precursors. Although the syntheses of vomitoxin and verrucarol via this approach are still incomplete, investigations towards completion of these syntheses are very encouraging.

As has been previously stated the trichothecene T2 toxin served as the target molecule for this study, the main objective of which was to devise a general route towards this trichothecene which could forseeably be extended to the preparation of related members of the group.

T-2 Toxin is a formidable synthetic challenge because of the structural complexity it offers: it has not yet been prepared by total synthesis. Structural features which have to be incorporated into the proposed synthetic plan include the cis-anti-cis tricyclic system, 9,10-double bond, 3α,4β,8α- and 15-hydroxyl groups and finally the 12,13-epoxy function.

In devising a route towards this target molecule Diels-Alder approaches were considered promising. Accordingly, it was decided that cycloaddition between a suitable functionalised 1,3-butadiene and an alkyl coumalate would be a logical place to begin the synthetic route.

The Diels-Alder reaction between isoprene (156) and methyl coumalate (147) appeared to be very attractive, provided both reasonable regioselectivity and yield could be attained. Such a scheme would allow rapid access to an intermediate having a cis-fused benzopyran system. Furthermore, the requisite 9-methyl group would result directly and the 8,9-double bond would allow functionalisation of the A ring. It was envisaged that elaboration of the B ring would follow a similar route to that previously described by Colvin and Thom[38] (Scheme 22) and therefore the C ring would be attached using the group 2 aldol approach.

Introduction of the requisite 4β-hydroxyl group could conceivably be accomplished by oxidation of the resulting 3-hydroxyl group and thence formation of the corresponding silyl enol there. Peracid oxidation of the silyl enol ether could be expected to afford the α-hydroxy or

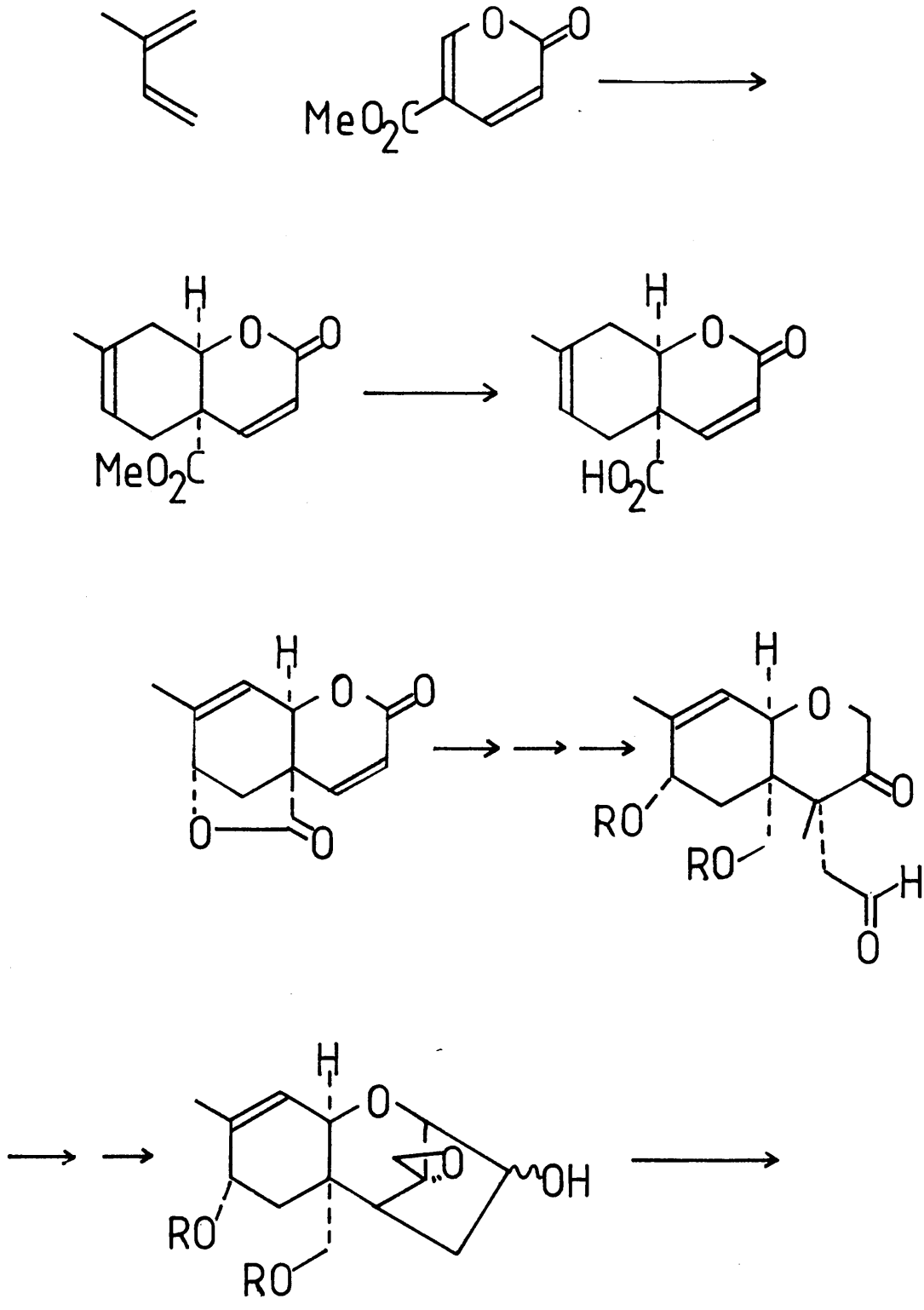
α-silyloxy ketone. Having introduced a hydroxyl function at the 4-position, subsequent stereoselective reduction should regenerate the 3-hydroxyl group. An idealised synthetic scheme towards T2 toxin (185) is outlined in Scheme 23.

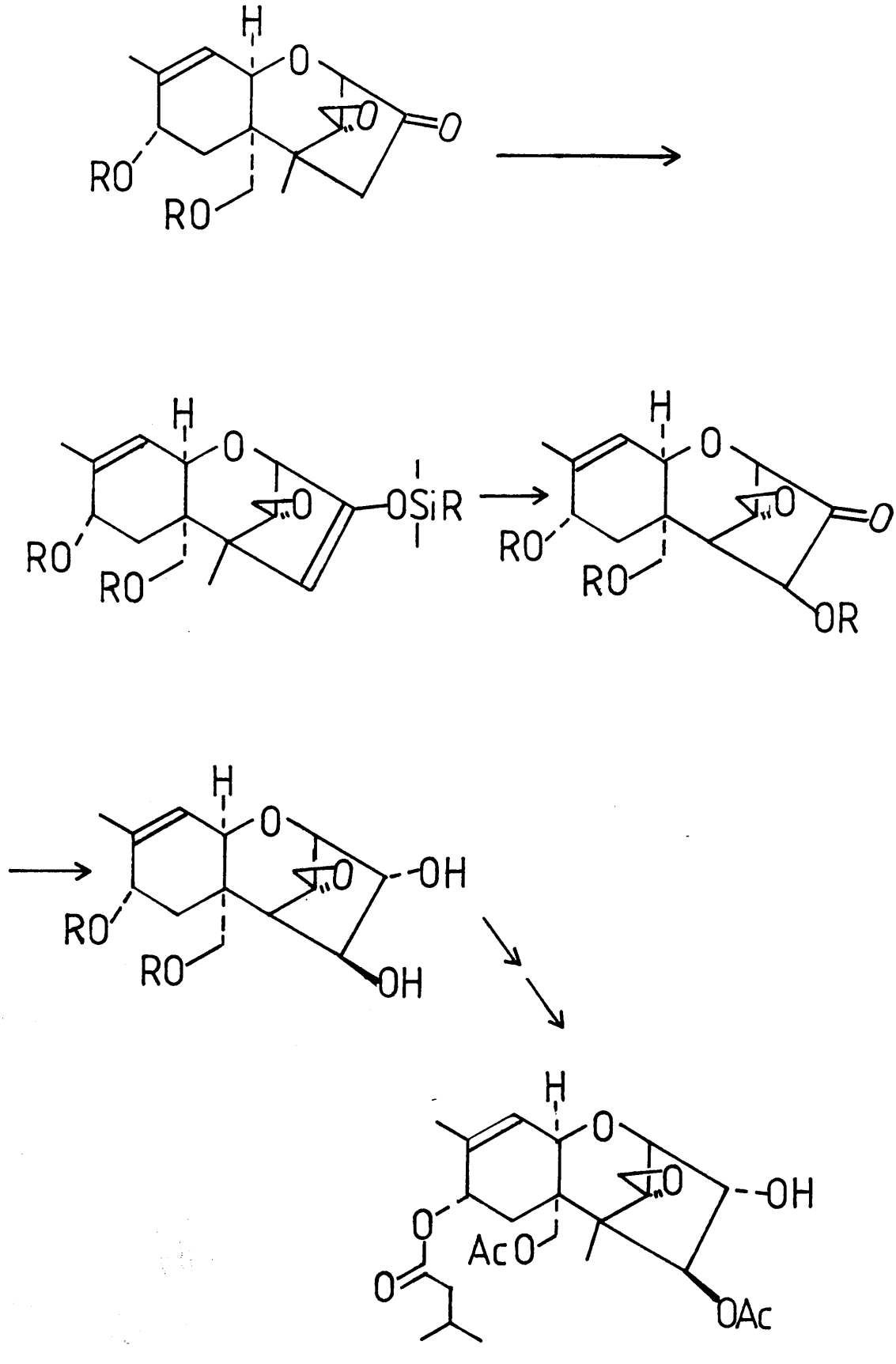
The cycloaddition reaction between isoprene and methyl coumalate is well documented[50,56,57]. In 1983 a report was published by White and coworkers[57] which appeared to be particularly relevant to the proposed scheme to T2 toxin. As outlined in Scheme 24, this cycloaddition reaction reportedly gave an inseparable 10:1 mixture of regioisomeric Diels-Alder adducts (157a) and (157b) respectively. The resulting modest 32% yield of the desired adducts could easily be endured because the regioselectivity of the reaction favoured the desired adduct (157a); moreover the diene and dienophile can be obtained readily in multigram quantities.

According to this study, base hydrolysis of the mixture of Diels-Alder adducts (157a) and(157b) quantitatively afforded carboxylic acids (186a) and (186b), which were subsequently transformed into the corresponding five-membered iodolactones (187a) and (187b). It was anticipated that dehydrohalogenation of the bicyclo [3.2.1]octane system (187a) would furnish the corresponding bicyclo [3.2.1] octene derivative (189), which possessed ideal functionality for further elaboration to T2 toxin.

To this end, iodolactones (187a) and (187b) were separated by column chromatography; iodolactone (187a) was reported to have infra-red absorptions at 1760 and 1740 cm^{-1}, whereas iodolactone (187b) had infra-red absorptions at 1785 and 1740 cm^{-1}, 1785 cm^{-1} being a

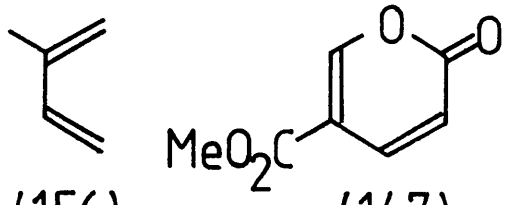
Scheme 23





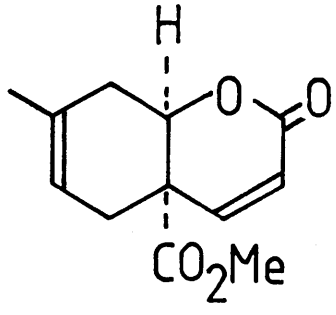
T2 TOXIN
(185)

Scheme 24

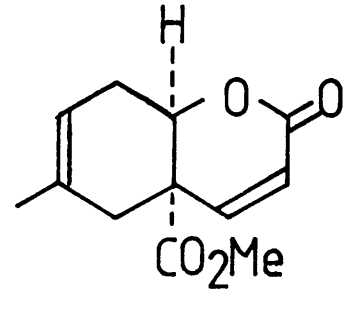


(156) (147)

Benzene,
110 - 120°C,
18h



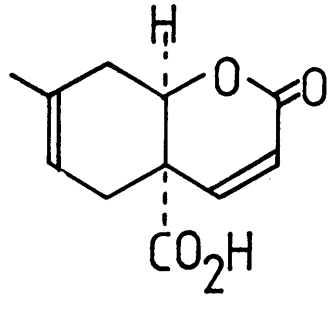
(157a)



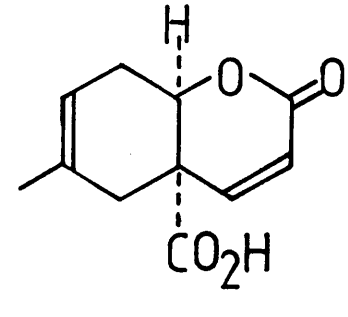
(157b)

10 : 1 ; 32%

aq NaOH

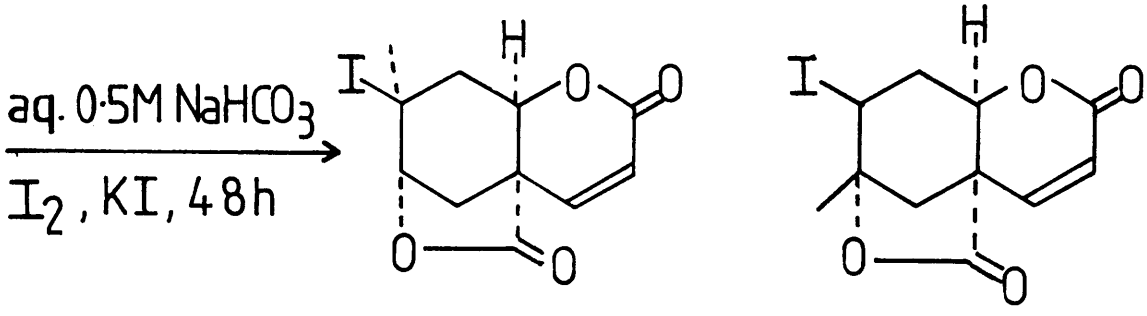


(186a)



(186b)

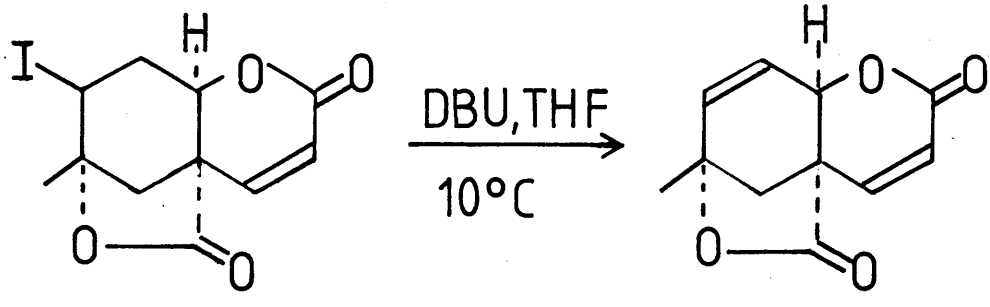
100 %



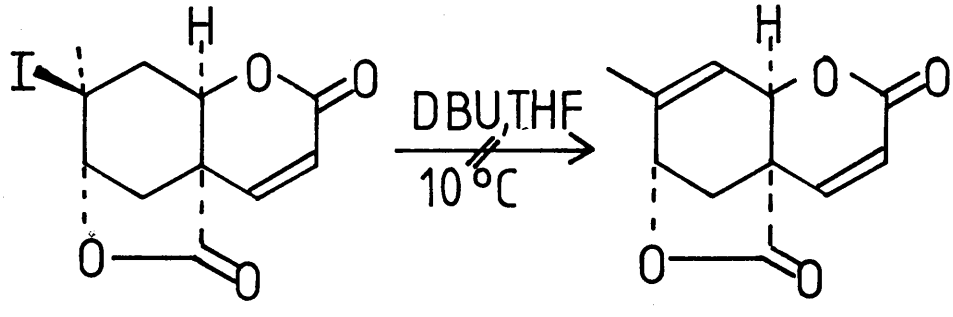
(187a) (187b)

66%

Separate by column chromatography



(187b) (188), 91%



(187a) (189)

characteristic value for a 5-membered lactone. Treatment of the undesired γ-lactone (187b) with DBU resulted in elimination of HI to afford the expected bicyclo [3.2.1] octene system (188). Surprisingly, however, similar treatment of the regioisomeric iodolactone (187a) with DBU did not effect the desired dehydrohalogenation and either starting material, or decomposition products, on exposure to more vigorous conditions were recovered.

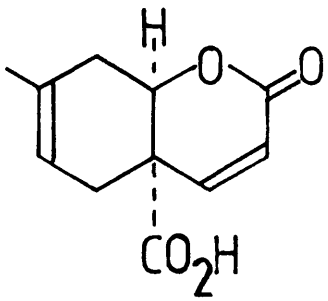
The explanation offered for this observation was that the anti-proton at C-10 of lactone (187a) was difficult to abstract by the base due to steric shielding by the C-9 methyl group. Examination of a molecular model of the structure proposed for iodolactone (187a) indicates that this is not the case; the iodine and adjacent proton on C-10 appear to be quite unhindered and indeed ideally alligned for the necessary E2 elimination.

The unsaturated γ-lactone (189) appears to be a particularly promising intermediate towards a total synthesis of T2 toxin. In an attempt to prepare this precursor, it was decided to parallel this route (Scheme 24) and circumvent the problems encountered at the E2 elimination step by modifying the scheme to one of selenolactonisation[58].

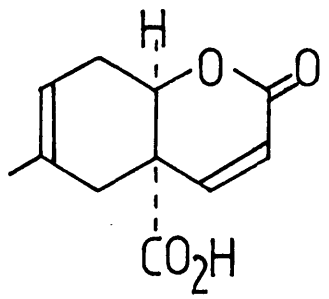
As outlined in Scheme 25, selenolactonisation of the original mixture of carboxylic acids should afford the desired five-membered selenolactones (190a) and (190b). Subsequent syn oxidative elimination of intermediate (190a) would be expected to furnish the desired bicyclo [3.2.1] octene derivative (189)' and thereby effect regiospecific introduction of the 9,10-double bond.

In our hands however, the Diels-Alder reaction between methyl coumalate (147) and an excess of isoprene (156), (toluene, 110^{o}C, 18h)

Scheme 25

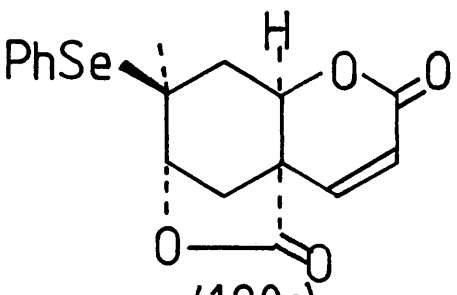


(186a)

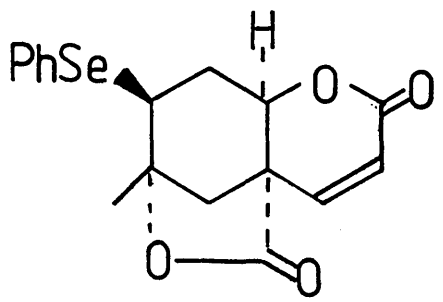


(186b)

$\xrightarrow[CH_2Cl_2, -78°C]{PhSeCl, NEt_3}$



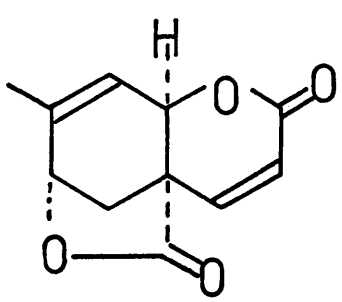
(190a)



(190b)

1. Column chromatography

2. 30% H_2O_2, Py, CH_2Cl_2

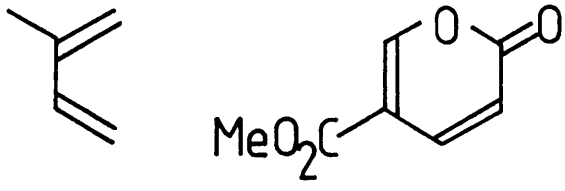


(189)'

afforded an inseparable mixture of regioisomers (157a) and (157b) in a total yield of only 15.7%; the regioisomeric ratio as determined by ^{13}C-n.m.r. spectroscopy was 5:2, with the desired regioisomer predominating. The major product, obtained in 45% yield, proved to be the hitherto unisolated, alternative Diels-Alder adduct (157c), which arises from methyl coumalate acting as the 4π component in the cycloaddition reaction. (Scheme 26). The conditions employed for the cycloaddition reaction left little room for experimental manipulation, and were followed as closely as possible to those described[57]. Although toluene was the solvent of choice for our Diels-Alder reaction, benzene was also used but was observed to give identical results.

It was patently necessary to improve both the regioselectivity of the reaction and the yield of the desired adduct (157a) before continuing with the proposed reaction scheme. The results obtained from the Diels-Alder reaction indicated that methyl coumalate was acting as a reasonably efficient diene in its reaction with isoprene; it was therefore necessary to improve its dienophilicity by converting it into a better 2π component. To this end, frontier molecular orbital theory was invoked (and considered in its simplest terms!). To improve the efficiency of the cycloaddition reaction the energy difference (ΔE), between the HOMO of the diene and the LUMO of the dienophile has to be reduced (Fig. 1)[59]. This can be accomplished either by raising the energy of the HOMO, or alternatively by lowering the energy of the LUMO. It was desirable to continue to use isoprene as the 4π component in the Diels-Alder reaction, and therefore the energy of its HOMO was considered to be a constant; the energy difference had to be reduced by lowering the energy of the LUMO of the coumalate.

Scheme 26

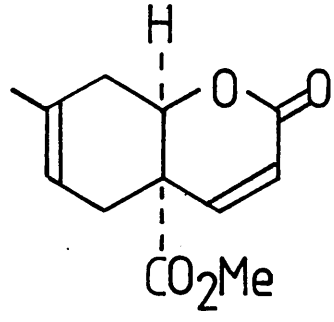


(156) (147)

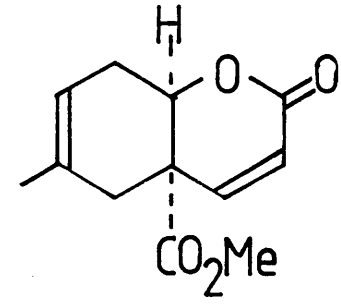
Toluene, 110°C

Hydroquinone,

18h

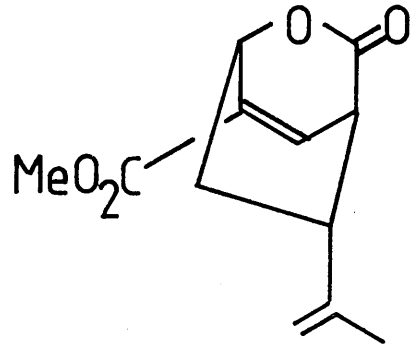


(157a)



(157b)

5 : 2 ; 15·7%



(157c); 45%

+ POLYMERISED ISOPRENE

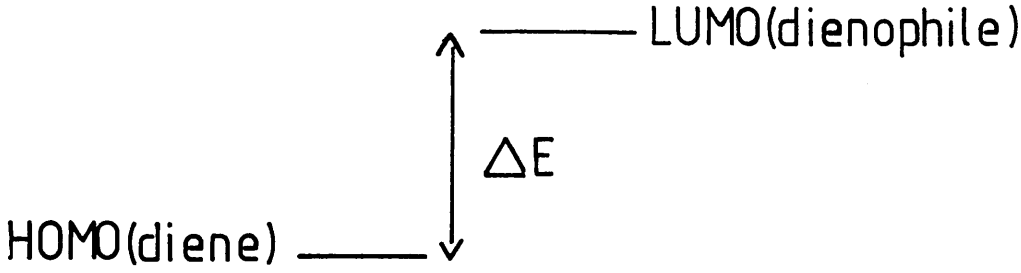


Fig.1

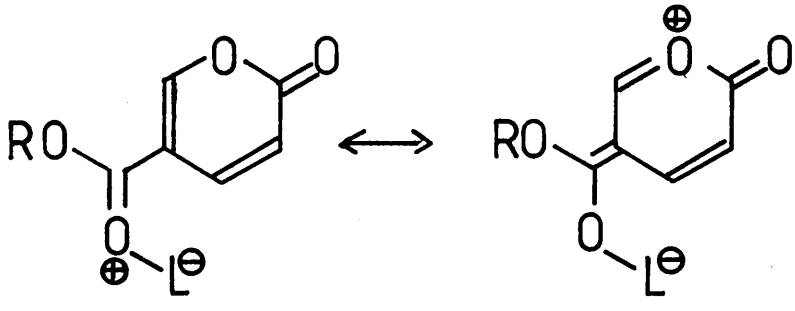


Fig.2

Generally speaking, the energy of the LUMO of a dienophile can be lowered by employing Lewis acid catalysts (Fig. 2). However as shown in table 4, neither the yield nor the ratio was improved by use of a range of Lewis acid catalysts; such reactions yielded only polymerised isoprene and unreacted methyl coumalate.

A study of the effect of various carboxyl protecting groups on the yield and the ratio was carried out. These groups included the t-butyl-dimethylsilyl and trimethylsilyl ester groups, the N,N-dimethyl amide and the tetrahydropyranyl ester; these were all uniformly unsuccessful and gave disappointing results, as listed in table 4.

Alternatively, the energy of the LUMO of a dienophile can be lowered if an electron-withdrawing group is attached. It was therefore decided to employ coumalyl chloride (191) as the 2π component.

The acid chloride (191) was prepared in an improved yield of 86%, as compared with the reported literature[60] yield of 67%, and it was subsequently reacted with an excess of isoprene in a sealed reaction vessel (toluene, 110°C, 18h), as shown in Scheme 27. The crude reaction mixture was esterified with methanol in the presence of triethylamine and then purified by column chromatography. A substantially improved yield of 39% of the desired adducts (157a) and (157b) was obtained as an inseparable 4:1 mixture of regioisomers. The alternative adduct was also obtained in a reduced yield of 21%.

Having improved both the yield and the regioisomeric ratio of the desired adduct (157a), the 4:1 mixture of adducts was subjected to basic hydrolysis to furnish the corresponding carboxylic acids (186a) and (186b) in 98% yield. Selenolactonisation of the mixture of acids afforded a mixture of lactones in 67% overall yield, from which the major component

Table 4

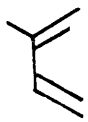
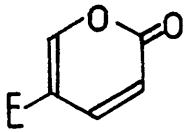
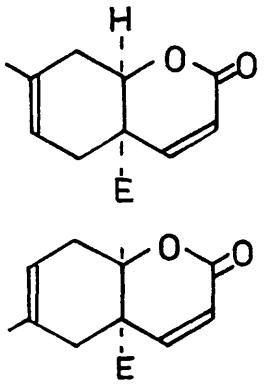
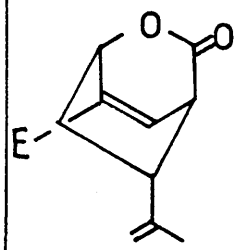
Diene	Dienophile	Conditions	Lewis Acid	Desired Adduct	Alternative Adduct	Polymerised Isoprene	Methyl Coumal
		Toluene, 110°C, 18h, hydroquinone	—	 15·7%, 5:2	 45·4%	✓	—
〃	〃	CH_2Cl_2 0°C - RT	$AlCl_3$ 5,10, 15%	—	—	✓	✓
〃	〃	〃	$TiCl_4$ 25%	—	—	✓	✓
〃	〃	〃	$Ti(OPr^i)_4$ 25%	—	—	✓	✓

Table 4 (contd.)

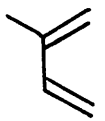
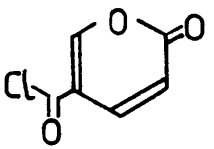
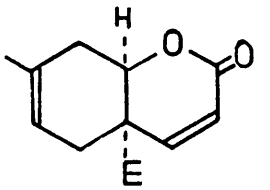
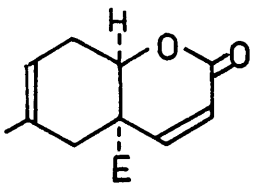
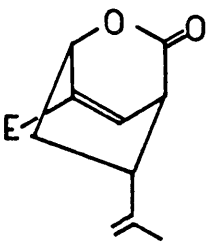
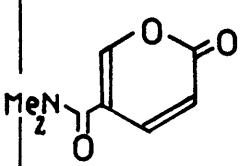
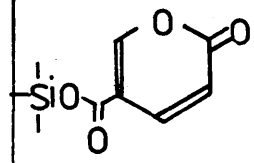
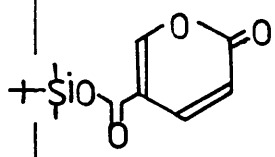
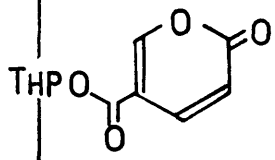
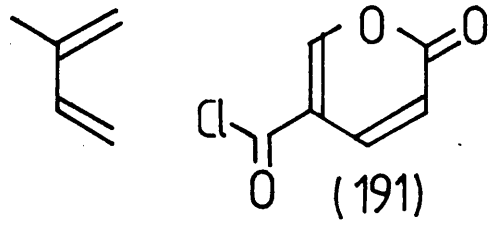
〃	〃	〃	$TiCl_4$ + $Ti(OPr^i)_4$ 1:1, 20%	Small amount (less than 5%)	—	✓	✓
		1. Toluene, hydroquinone, 110°C, 18h 2. NEt_3, MeOH		  39%, 4 : 1	 21%	✓	—
		Toluene, hydroquinone 110°C, 18h	—	—	—	✓	—

Table 4 (contd.)

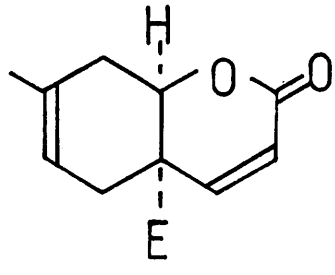
"	80 	"	—	—	—	✓	Coumalic Acid
"	80 	"	—	—	—	✓	"
	81 	"	—	—	—	✓	"

Scheme 27

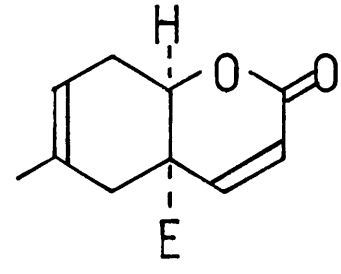


(191)

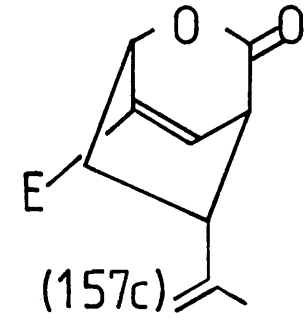
1. Toluene, 110°C
Hydroquinone
2. MeOH, NEt_3



(157a)



(157b)



(157c)

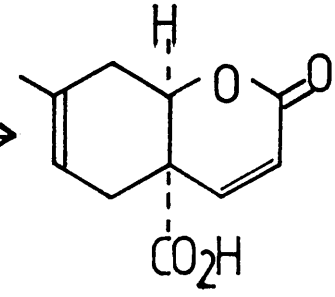
4 : 1

39 %

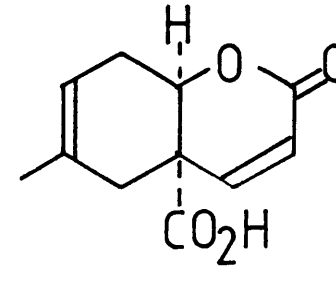
21%

[E=CO_2Me]

1. Column chromatography
2. aq NaOH



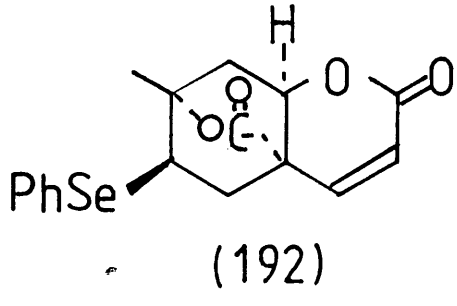
(186a)



(186b)

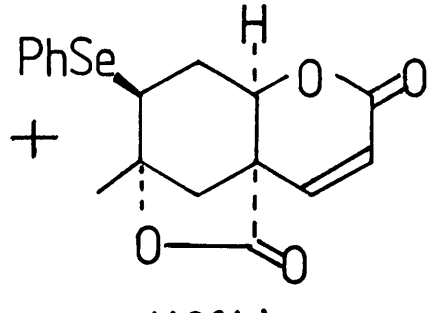
98·3 %

PhSeCl
CH_2Cl_2
-78°C



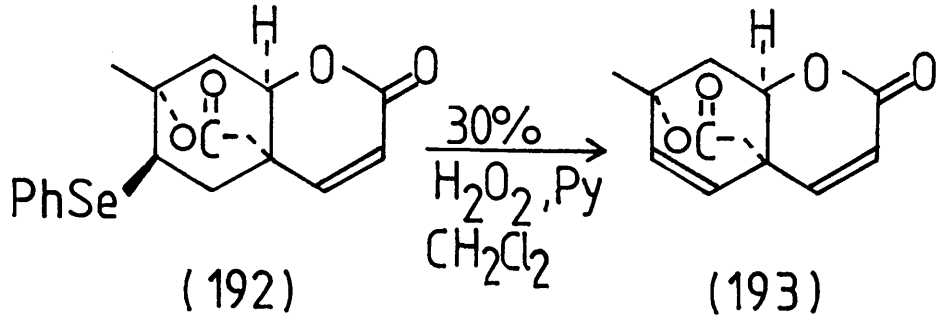
(192)

+



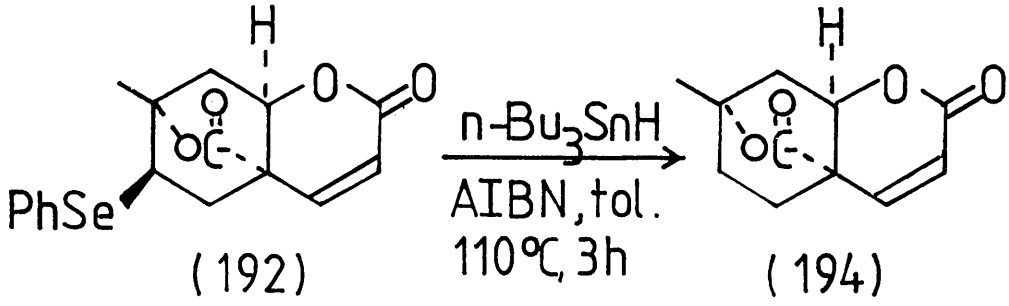
(190b)

67%



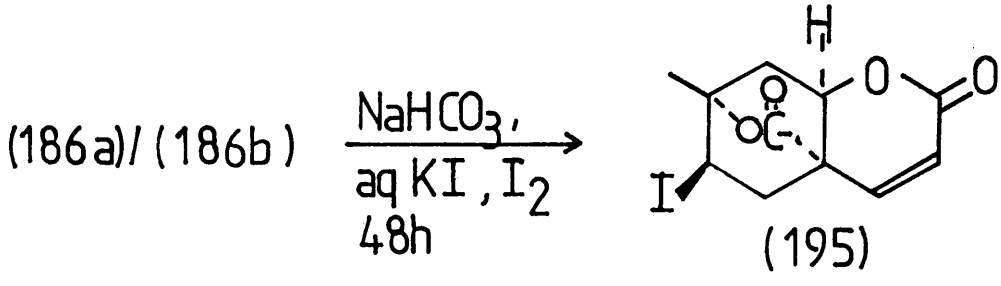
(192) (193)

83%

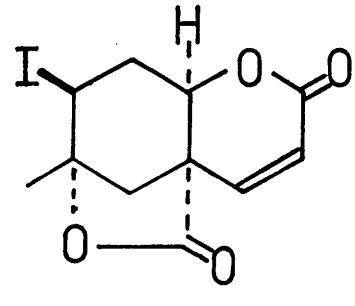


(192) (194)

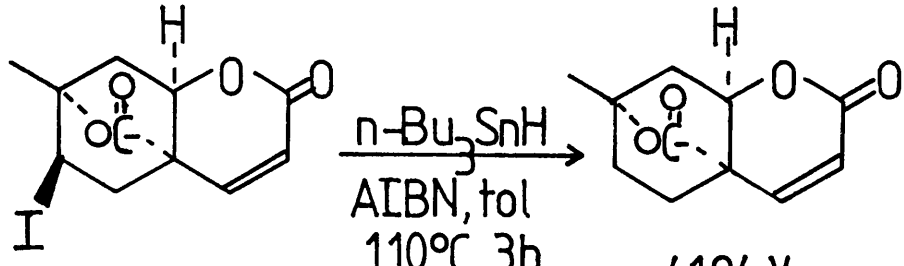
79%



(195)



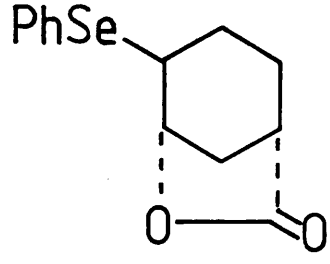
(187b); 46·6%



(195)

(194)'

67%



(196)

could readily be obtained pure by column chromatography. The structure of the major product was shown unambiguously to be the unexpected bicyclo[2.2.2] octane derivative (192); which showed a characteristic infra-red absorption at 1765 cm^{-1} for the δ-lactone. ^{13}C-n.m.r. spectroscopy confirmed this structure [δ24.4(q,CH_3-C), 43.6(d,CH-Se), 85.1(s,C-O)]. The minor product proved to be the bicyclo [3.2.1] octane derivative (190b), which had an infra-red absorption at 1790 cm^{-1} as expected for a γ-lactone.

The structure of selenolactone (192) was further proven by its smooth oxidative elimination[58] to the unsaturated lactone (193) and by its reductive cleavage[61] on treatment with tributyl tin hydride to saturated lactone (194).

Iodolactonisation of the original mixture of carboxylic acids (186a) and (186b) was repeated as reported[57]. Purification of the crude mixture of iodolactones and full characterisation of the major lactone component proved that the structure was also the bicyclo [2.2.2] octane derivative (195) and not the five-membered lactone as had previously been reported. Iodolactone (195) absorbed in the infra-red region at 1760 cm^{-1} which was characteristic for the six-membered lactone. Furthermore, its ^{13}C-n.m.r. spectrum [δ22.5 (d,CH-I), 26.3(q,CH_3-C), 84.3(s,C-O)] was in complete agreement with this proposed structure. The bicyclo [2.2.2] octane derivative (195) underwent smooth reductive dehalogenation on treatment with tributyl tin hydride to afford 67% of the corresponding saturated lactone (194), which was identical to lactone (194) in every respect.

Examination of a molecular model of the six-membered iodolactone (195) revealed that there was no appropriate antiperiplanar C-H bond

adjacent to the carbon carrying iodine, which explained why this iodolactone did not undergo elimination of HI on treatment with DBU.

Throughout our experimental studies no evidence was detected to support the formation of the five-membered lactone (187a). Our observations were subsequently communicated to the White group which is now in agreement with our corrected structural assignments[62].

In conclusion, both iodo- and selenolactonisation of carboxylic acid (186a) give lactones arising from carboxyl trapping of the more stable, more substituted carbocation, with the resulting formation of the bicyclo [2.2.2] octane framework. This system appears to be the thermodynamically more stable, in contrast to other, unsubstituted cases, where a bicyclo [3.2.1] octane system with a five-membered lactone ring is preferred[63], for example compound (196).

All attempts to induce the bicyclo [2.2.2] octane intermediate (192) to undergo rearrangement to the desired five-membered lactone (190a) were uniformly unsuccessful. The six-membered lactone (192) could not be converted into a useful trichothecene precursor and hence this route towards T2 toxin was subsequently abandoned.

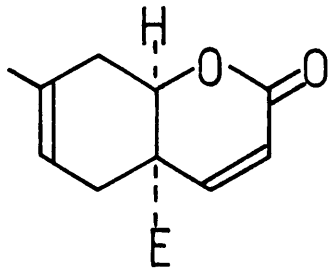
α-Allylic alcohol (200a) and the corresponding γ-lactone (203) were considered to be such promising trichothecene precursors that they became the prime target molecules. If these compounds could be obtained in substantial amounts this would contribute significantly towards the successful preparation of T2 toxin. Accordingly, attention was directed towards devising facile, efficient syntheses of these intermediates.

As outlined in the proposed reaction Scheme 28, it was expected that bromination of cuprate product (158) would afford a 1:1 mixture of the two possible 1,2-trans dibromides, resulting from trans diaxial addition of bromine to the remaining 6,7-double bond of intermediate (158). It was envisaged that subsequent acetolysis of the mixture of trans dibromides would furnish a mixture of the corresponding allylic acetates (198a) and (198b). Furthermore, because formation of the allylic acetates proceeds via the allylic carbonium ion no stereocontrol could be expected and it was anticipated that up to 50% of the undesired β-allylic acetate (198b) would also be obtained.

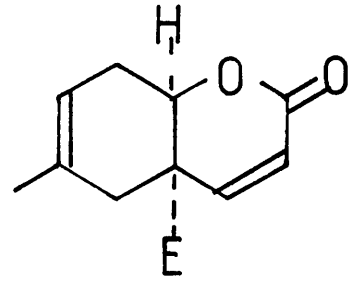
β-Allylic acetate (198b) could conceivably be transformed into the desired α-allylic alcohol by sequential hydrolysis of the mixture of acetates to the corresponding alcohols, and oxidation of the allylic alcohols to afford enone intermediate (201). Examination of a molecular model of enone (201) indicated that hydride reduction should occur preferentially from the β-face of the molecule to afford predominantly the desired α-allylic alcohol (200a).

The resulting configuration of the hydroxyl group could be established, unequivocally by hydrolysis of α-hydroxy ester (200a) to the corresponding α-hydroxy acid (202a), followed by formation of γ-lactone (203) via the Corey-Nicolaou lactonisation procedure[64].

Scheme 28

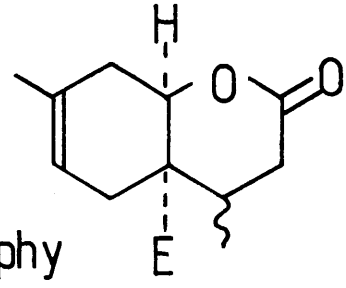


(157a)



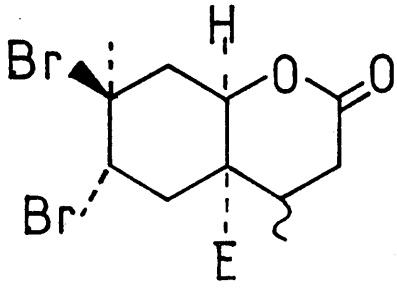
(157b)

1. Me_2CuLi, Et_2O, 0°C
2. Column chromatography



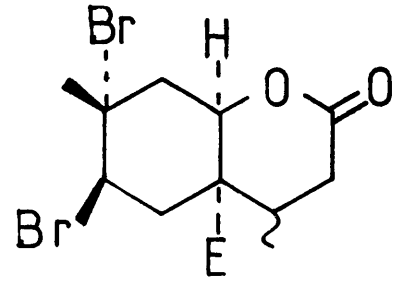
(158)

Br_2, Et_2O, 0°C



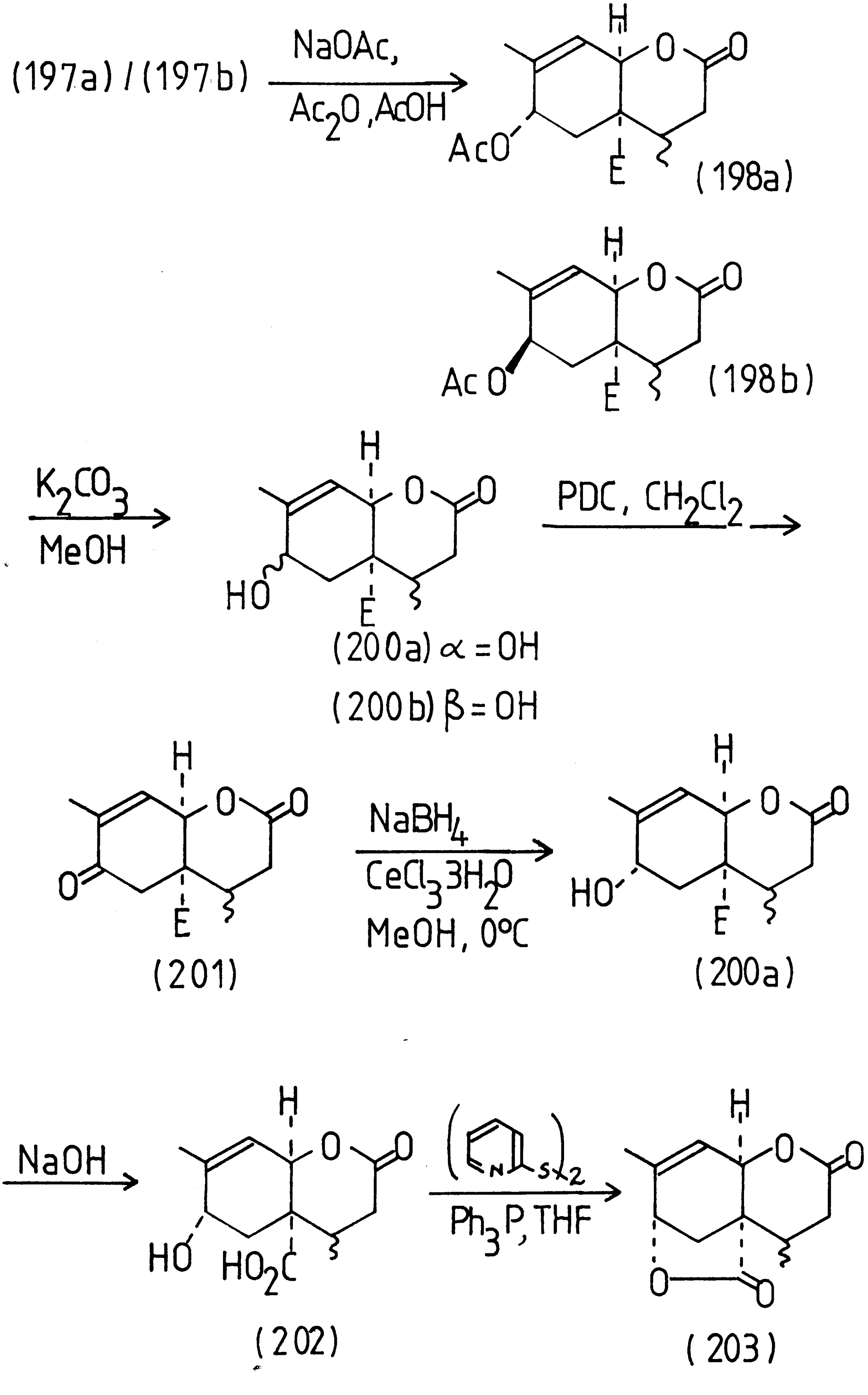
(197a)

+



(197b)

[E = CO_2Me]


(197a) / (197b)
NaOAc,
Ac2O, AcOH
AcO
H
O
O
E
(198a)
AcO
(198b)
K2CO3
MeOH
HO
(200a) α = OH
(200b) β = OH
PDC, CH2Cl2
(201)
NaBH4
CeCl3 3H2O
MeOH, 0°C
(200a)
NaOH
HO
HO2C
(202)
Ph3P, THF
(203)

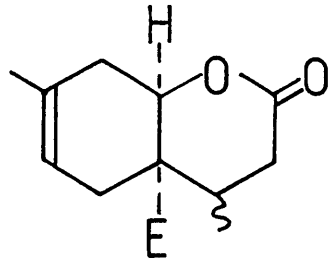
As outlined in Scheme 29, conjugate addition of dimethyl copper lithium to the enone system of adduct (157a) afforded 78% of crystalline cuprate product (158), as mainly one epimer. Subsequent bromination of the cuprate product afforded 94.3% of a 1:1 mixture of the two possible 1,2-trans dibromides (197a) and (197b).

The crude mixture of dibromides was stirred at 110°C for 24 hours in a solution of glacial acetic acid, acetic anhydride and anhydrous sodium acetate[65]. Purification of the acetolysis mixture by column chromatography gave 46.2% of the desired allylic acetates (198a) and (198b) as an oily, inseparable 1:1 mixture of epimers. In addition, 41.4% of a crystalline dibromide was recovered, along with 8.2% of a more polar isomeric acetate (199).

As shown in Scheme 30, a proposed mechanism for the formation of the allylic acetates (198a) and (198b) involves an initial E2 elimination of HBr from the diaxial dibromide to furnish the corresponding allylic bromide. The allylic bromide then undergoes loss of bromide ion to afford the allylic carbonium ion, which is subsequently attacked by acetate anion to furnish the resulting 1:1 mixture of α-allylic acetate (198a) and β-allylic acetate (198b).

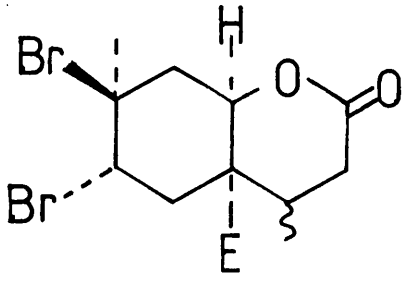
Alternatively, the isomeric acetate (199) can be formed via a mechanism involving an E2 elimination of HBr to afford the exomethylene compound shown in Scheme 31. Loss of Br^- from this allylic bromide gives the alternative allylic carbonium ion which is then attacked by acetate to afford the rearranged product (199).

Scheme 29



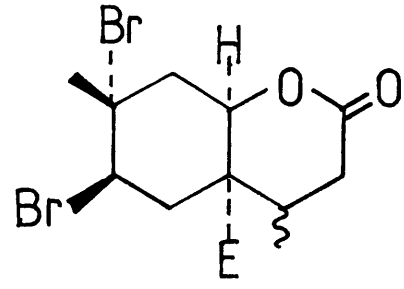
(158); 78%

Br_2, Et_2O, 0°C, 5m



(197a)

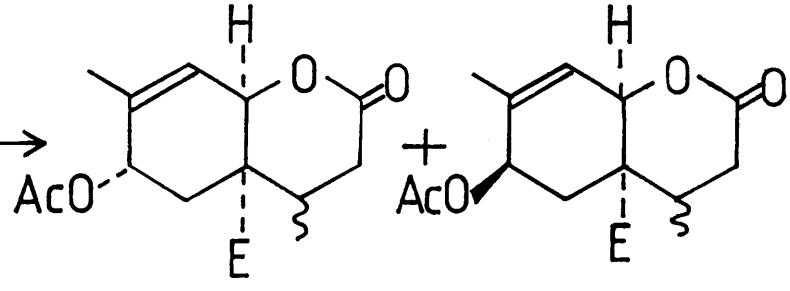
1 :



(197b)

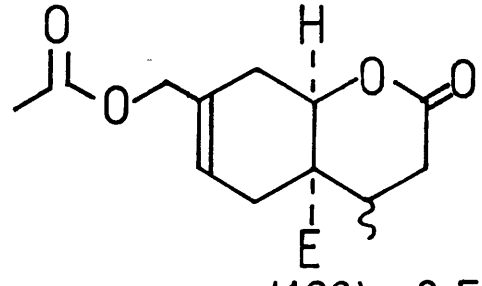
1 ; 94·3%

Ac_2O, AcOH, NaOAc



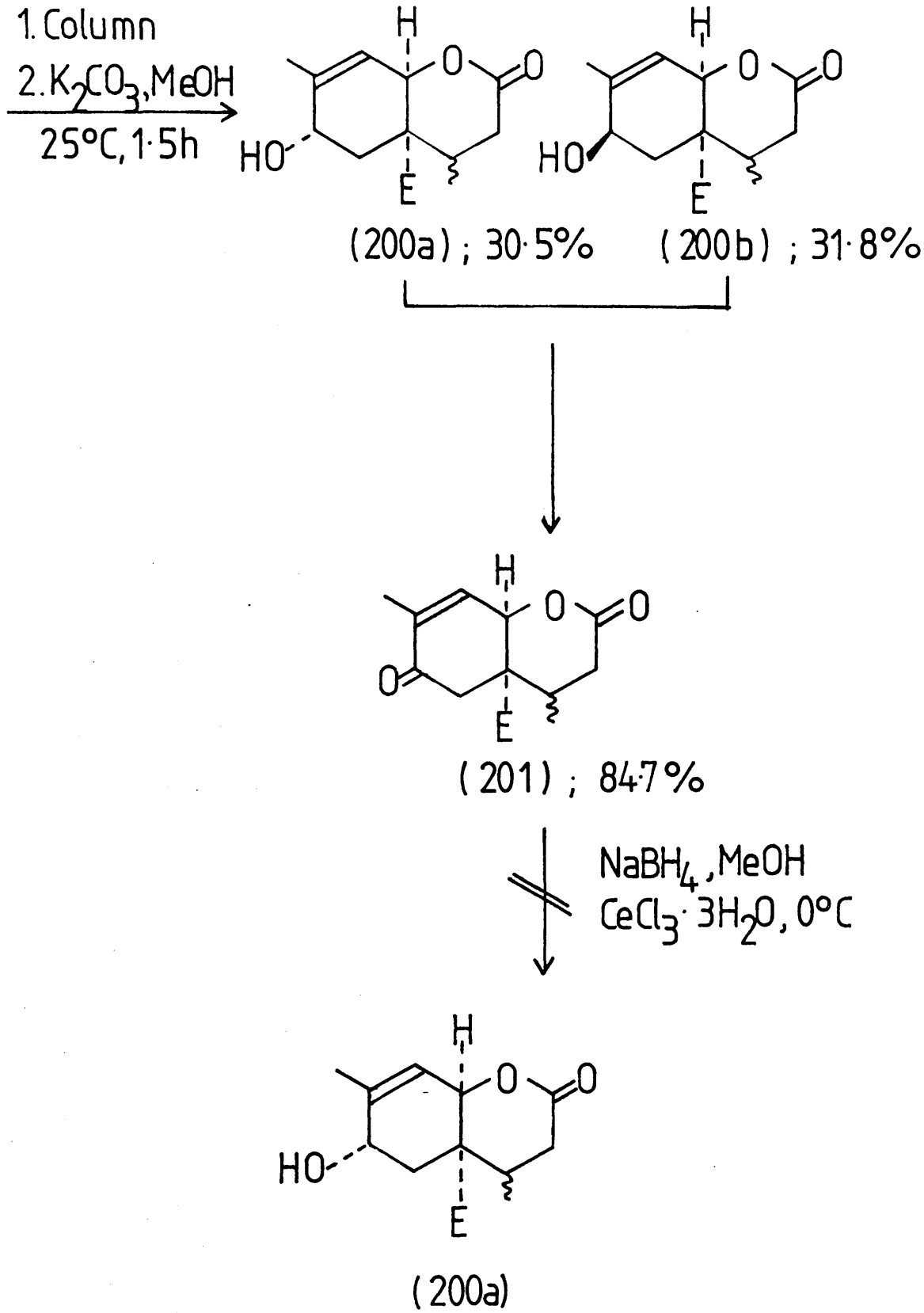
(198a) 1 : (198b) 1; 46 %

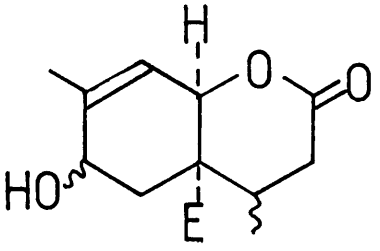
+



(199); 8·5%

+ 41·4% DIBROMIDE (197c)


1. Column
2. K_2CO_3, MeOH
25°C, 1·5h
H
O
O
HO
E
(200a) ; 30·5%
(200b) ; 31·8%
(201) ; 84·7%
$NaBH_4$, MeOH
$CeCl_3 \cdot 3H_2O$, 0°C
(200a)



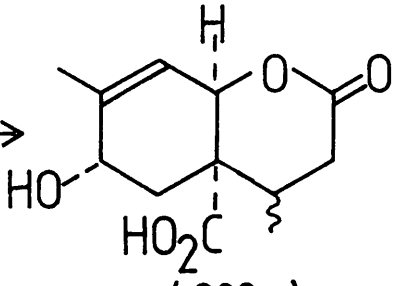
(200a) α = OH

(200b) β = OH

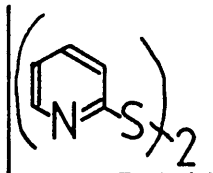
1 : 1

1. Column

2. NaOH

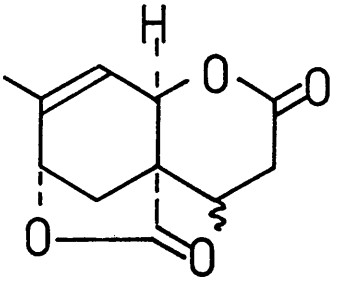


(202a)

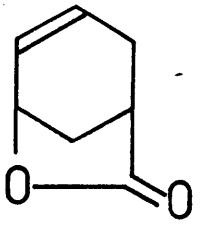


Ph_3P, THF

25°C 24h

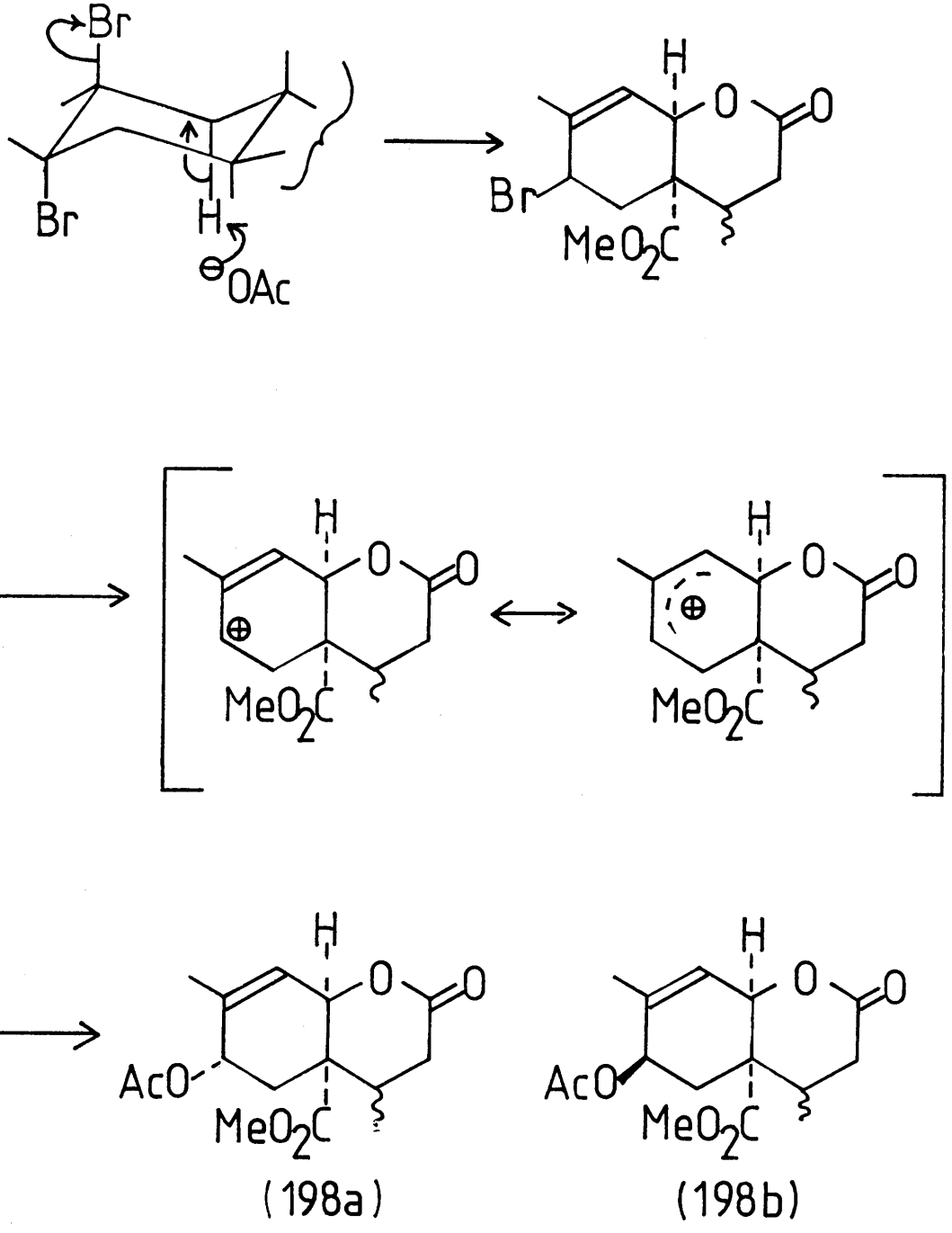


(203) ; 63·8%



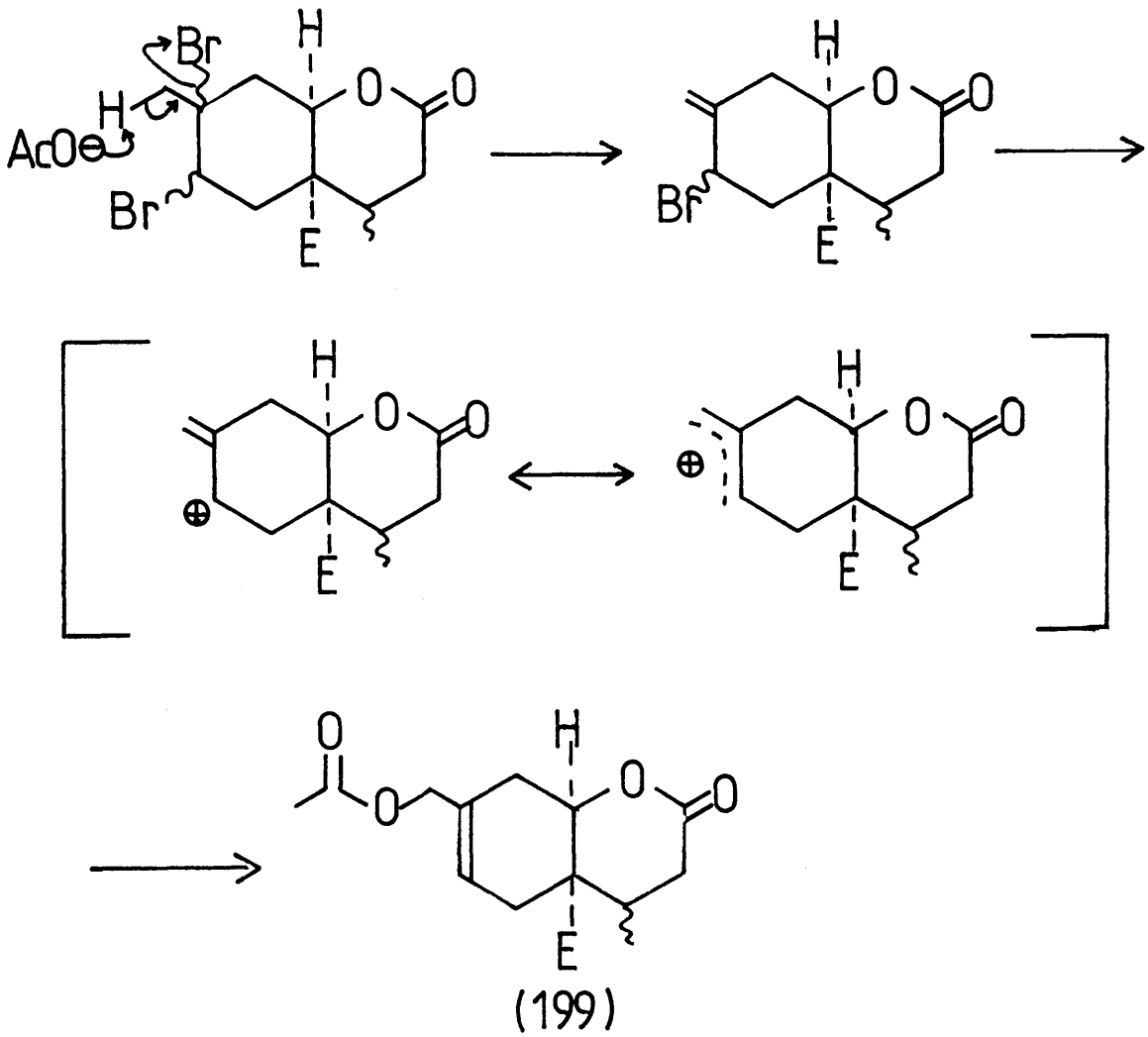
(204)

Scheme 30



(198a) (198b)

Scheme 31



That as much as 41.4% of dibromide was recovered on purification was surprising. At first it was suspected that the acetolysis had not gone to completion, such that when the reaction was later repeated the reflux time was increased to 48 hours. However, upon purification identical results were obtained, with up to 45% of the recovered material being dibromide.

In a final attempt to convert the recovered crystalline dibromide (m.p. 130-132^{o}C) into allylic acetates (198a) and (198b), it was refluxed

The inseparable mixture of acetates (198a) and (198b) was hydrolysed, by stirring with anhydrous potassium carbonate in methanol, to furnish 62.5% of the corresponding α- and β-allylic alcohols (200a) and (200b) respectively. Pyridinium dichromate oxidation of the mixture of allylic alcohols afforded a very respectable 84.7% yield of the enone intermediate (201) as white needles, having a characteristic ultra-violet absorption at 240 nm, and infra-red absorptions at 1755, 1735 and 1695 cm^{-1}. The all-important stereoselective reduction of the α,β-unsaturated ketone (201) to the α-allylic alcohol (200a) was carried out using sodium borohydride in the presence of cerium trichloride[67].

Thin layer chromatography of the crude reaction mixture after work-up indicated that many reaction products had been formed. Furthermore, examination of the ^{1}H-n.m.r. spectrum of the crude mixture revealed that the bridgehead proton (H-8a) was no longer present. It was suspected that the B-ring lactone had undergone reduction and additionally that 1,4-addition to the enone had taken place. Diisobutyl aluminium hydride reduction of the enone intermediate (201) was equally unsuccessful and also suffered from being non-selective.

In conclusion, it would appear that the B-ring lactone of enone derivative (201) is particularly susceptible to reduction.

Careful separation of the mixture of allylic alcohols by column chromatography afforded 31.8% of pure β-allylic alcohol (200b), as a viscous, colourless oil [IR(CCl_4): 3500 (broad), 1760, 1735 cm^{-1}; δ66.71(d,H-C-OH) 119.24(d,C=C-H), 144.67 (s,C=C-CH_3); 4.10(m,H-COH). The more polar α-allylic alcohol (200a) was obtained in 30.5% yield as white crystals [m.p. (decomposition) 142-157°C; IR(CCl_4): 3490 (broad),

1760, 1735 cm^{-1}; δ66.04(d,H-C-OH), 120.00(d,C=CH), 142.03(s,C=C-CH_3), 4.00(m,H-COH)]. Both α- and β-allylic alcohols were observed to have similar infra-red, ^1H- and ^{13}C-n.m.r. spectra; however, in the mass spectrometer, a molecular ion (M^+) was always observed for the β-allylic alcohol, whereas the α-allylic alcohol always showed (M^+-H_2O).

It should be noted that the stereochemical assignments which have been made for each of the allylic alcohols are retrospective of the lactonisation data which now follows.

Basic hydrolysis of the α-hydroxy ester (200a) was a facile process which went to completion in 12 hours, to afford 94.8% of the corresponding α-hydroxy acid (202a). Alternatively, hydrolysis of the β-hydroxy ester (200b) was observed to be incomplete even after stirring in sodium hydroxide for 4 days. It was postulated that the α-hydroxy ester experiences anchimeric acceleration due to the proximity of the 8α-hydroxyl and the carbomethoxy group.

Attempted lactonisation of the β-hydroxy acid (202b), (which was contaminated with some unhydrolysed hydroxy ester), using the Corey-Nicolaou[64] lactonisation method was unsuccessful.

On the other hand, lactonisation of α-hydroxy acid (202a) via the Corey-Nicolaou procedure afforded 63.8% of the expected γ-lactone (203) as white crystals, thereby establishing the α-configuration of the 8-hydroxyl group. The infra-red spectrum of γ-lactone (203) surprisingly showed three carbonyl absorptions at 1790, 1775 and 1755 cm^{-1}; 1790 cm^{-1} being a characteristic value for a five-membered lactone. A similar phenomenon was reported in the preparation of γ-lactone (204) which showed three carbonyl absorptions in the infra-red region, 1800, 1770 and 1735 cm^{-1} [68].

In conclusion, the described bromination sequence resulted in the successful preparation of the potentially useful α-allylic alcohol (200a) and γ-lactone (203) via a sequence of manipulatively simple reactions. Unfortunately this route suffers from an obvious drawback in that it features little stereocontrol, and only half of the total allylic acetate obtained can be taken through the reaction scheme to afford the target α-allylic alcohol.

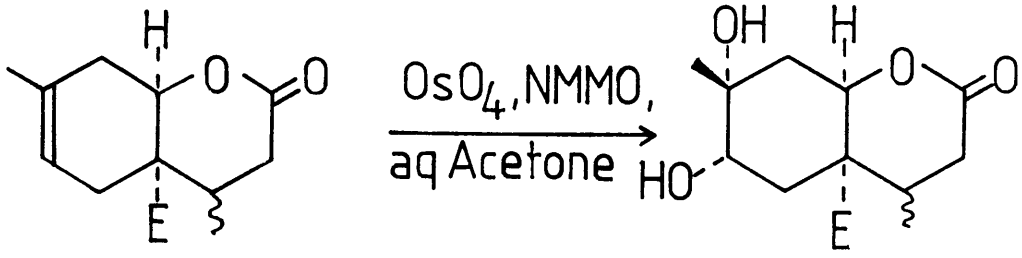
An alternative osmylation-dehydration sequence towards α-allylic alcohol (200a)[1] was devised. As outlined in Scheme 33, catalytic osmylation of the cuprate product (158) in the presence of N-methyl morpholine-N-oxide[69] afforded 81.6% of an inseparable, approximate 6:1 mixture of the α- and β-cis diols (205a) and (205b) respectively. The major diol component was believed to be the α-cis diol on the basis of evidence obtained from molecular model studies, which indicated that osmylation should occur from the less hindered α-face of the molecule to give the corresponding α-osmate ester. This assignment was borne out at a later stage in the synthesis by correlation with α-allylic alcohol (200a), prepared by the aforementioned bromination sequence (Scheme 29).

The mixture of cis diols (205a) and (205b) was selectively protected as the corresponding α- and β-t-butyldimethylsilyloxy alcohols (206a) and (206b)[70], which were easily separated by column chromatography to afford 72.2% of the former and 11.2% of the latter.

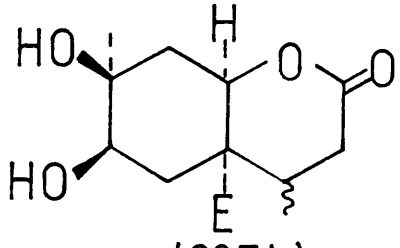
α-Silyloxy alcohol (206a) was believed to be a useful T2 toxin precursor; it possessed a protected 8α-hydroxyl function and the requisite 9,10-double bond could conceivably be introduced regioselectively by a dehydration process to furnish the desired α-allyl silyl ether (207).

Accordingly, α-silyloxy alcohol (206a) was heated with phosphorous oxychloride in the presence of pyridine[31]. Purification of the crude reaction mixture gave 43.7% of elimination product, along with 47.5% of recovered starting material. Full characterisation of the crystalline elimination product unambiguously proved it to be the undesired silyl enol ether (208), [δ107.31(s,C=C-CH_3), 139.58(s,C=C-OSi)], which arises from elimination of the alternative anti-proton at C-8. None of the desired elimination product (207) was detected.

Scheme 33

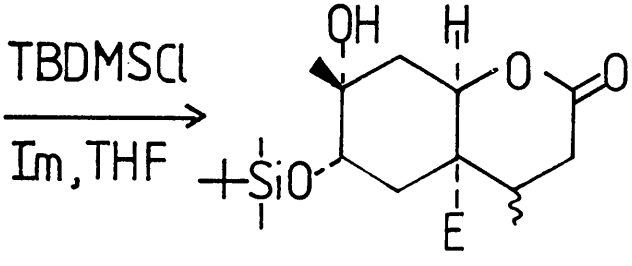


(205a)

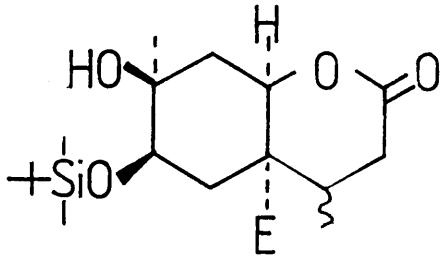


(205b)

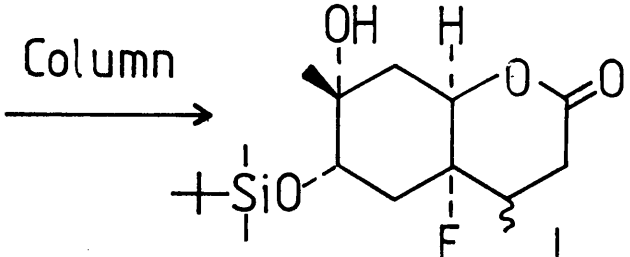
6 : 1 ; 81·6%



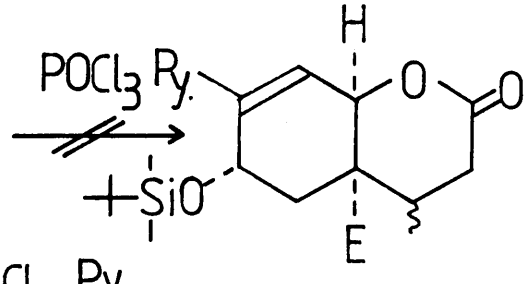
(206a) ; 72·2%



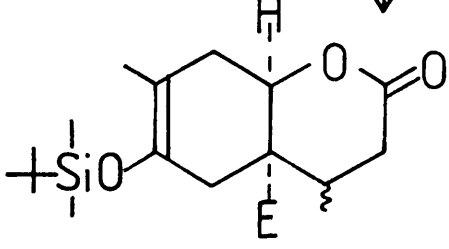
(206b) 11·2%



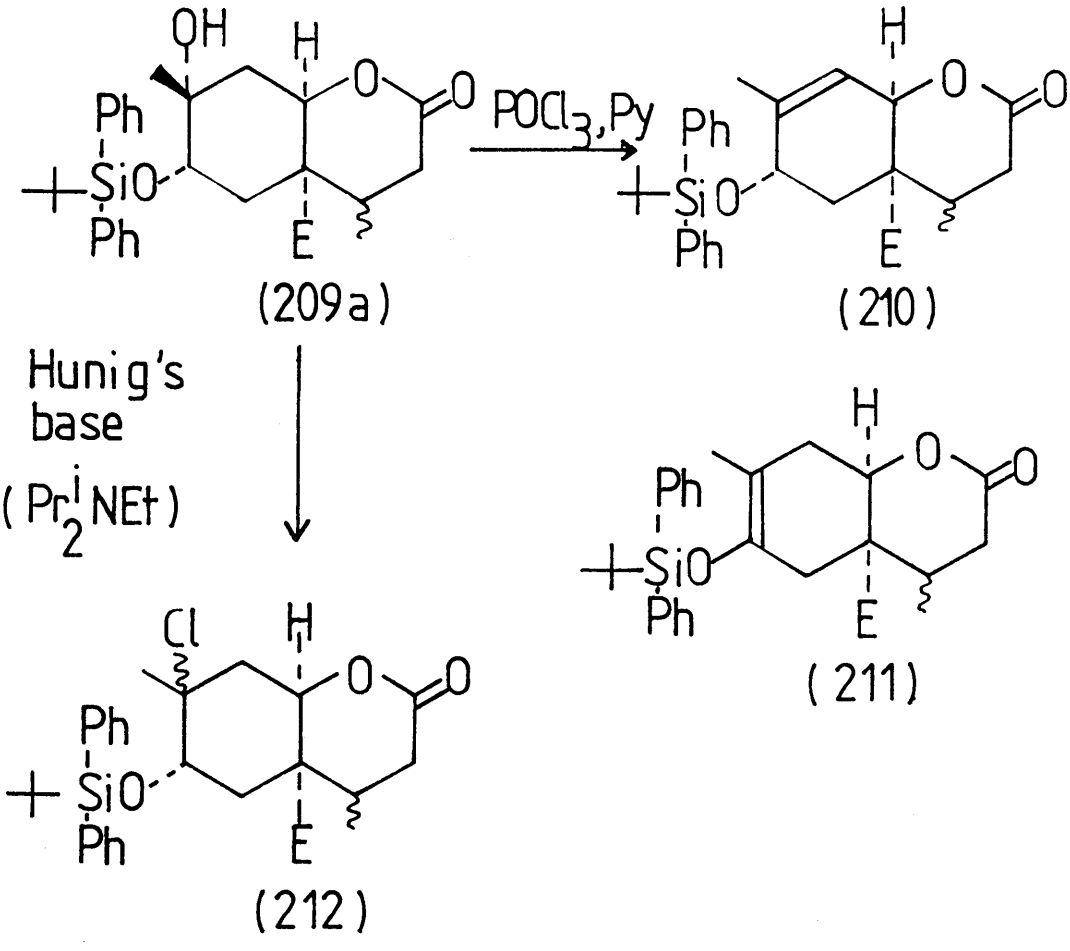
(206a)

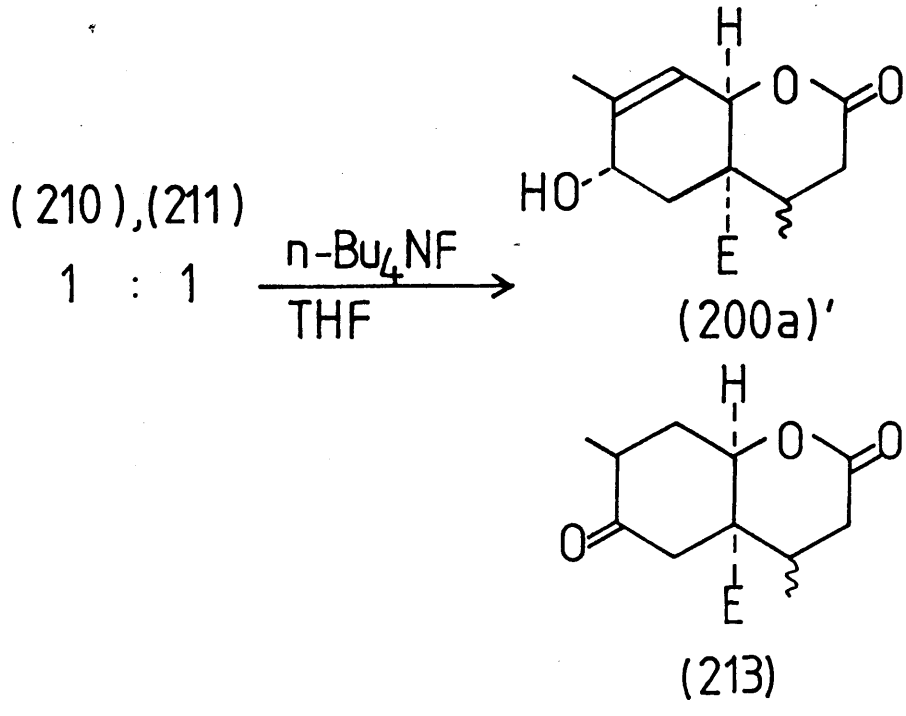


(207)



(208)


OH
H
O
O
Ph
SiO
Ph
E
(209a)
POCl3,Py
(210)
Hunig's
base
(Pr2iNEt)
Cl
(212)
Ph
O
(211)


(210),(211)
1 : 1
n-Bu4NF
THF
HO
(200a)'
(213)

Examination of a molecular model of α-silyloxyalcohol (206a) revealed that both the proton at C-8 and the proton at C-10 were ideally aligned for the E2 elimination process.

In order to obtain the desired α-allyl silyl ether (207) it was necessary to bias proton abstraction in favour of the anti proton at C-10. It was thought that this effect could be achieved in two ways:

(i) use a more hindered base

(ii) use a bulkier protecting group with the aim of making the anti proton at C-8 less accessible to abstraction by base.

The elimination reaction was repeated on the α-t-butyldimethylsilyloxy alcohol (206a) using the more hindered Hunig's base (diisopropyl ethyl amine). Purification of the crude reaction mixture revealed that Hunig's base had induced the desired effect to a limited extent, with a 5:1 mixture of the silyl enol ether (208) and the desired α-allyl silyl ether (207) being obtained in an overall yield of 55%.

In an attempt to enhance this effect and further improve the ratio of the desired product, DBU was employed as base in the elimination reaction. Unfortunately gross decomposition was observed and no characterisable material was recovered.

Due to the limited success achieved on using a hindered base along with the t-butyldimethyl silyloxy protecting group it was decided to study the effect that an even bulkier protecting group would have on the product composition.

The corresponding t-butyldiphenylsilyloxy alcohols (209a) and (209b) were prepared[71] in an overall yield of 69.4%. Subsequent treatment of α-t-butyldiphenylsilyloxy alcohol (209a) with phosphorous oxychloride in the presence of pyridine[31] afforded 40.7% of eliminated product, along with 37.0%

of recovered starting material. Characterisation of the elimination product proved it to be a much improved 1:1 mixture of the desired α-allyl silyl ether (210), [δ68.21(d,C-OSi), 122.62(d,C=C-H), 139.81(s,C=C-CH_3)], and the undesired silyl enol ether (211), [δ106.47(s,C=C-CH_3), 139.47(s,C=C-OSi)].

In an attempt to still further improve the ratio of the α-allyl silyl ether (210), the silyl enol ether (211) and Hunig's base were employed; in this case the only characterisable product obtained appeared to be chloro compound (212). It would appear therefore, that the combination of Hunig's base with the bulky t-butyldiphenylsilyloxy group resulted in a system which was too hindered for the desired proton abstraction to take place. Similar decomposition was observed employing DBU as base. A summary of the results obtained from this study are listed in table 5.

Attempts to separate the α-allyl silyl ether (210) from the silyl enol ether (211) by either chromatographic methods or distillation proved to be unsuccessful. Therefore the 1:1 mixture of compounds (210) and (211) was treated with anhydrous nBu_4NF to afford the desilylated α-allylic alcohol (200a) in 61.6% yield, along with the unsaturated ketone (213).

The crystalline α-allylic alcohol (200a)', [m.p. (decomposition) 142-157°C; IR(CCl_4): 3500 (broad), 1760, 1735 cm^{-1}; δ66.31(d,C-OH), 120.16(d,C=C-H), 142.16(s,C=C-CH_3); 4.00(m,H-COH) m/e, $\overset{+}{M}-H_2O$] was shown to be identical to the α-allylic alcohol (200a) prepared by the earlier bromination scheme in every respect. No depression of the melting point was observed on mixing (200a)' and (200a); furthermore basic hydrolysis of (200a) was observed to be a facile process, which was complete in less than 12 hours.

Table 5

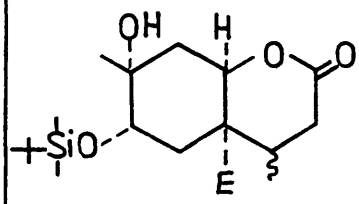
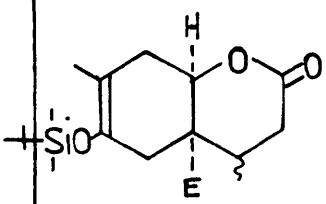
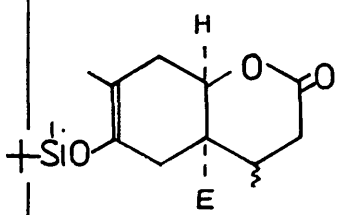
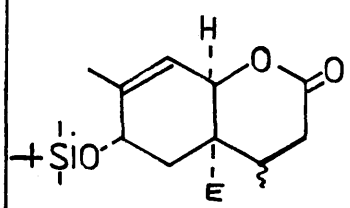
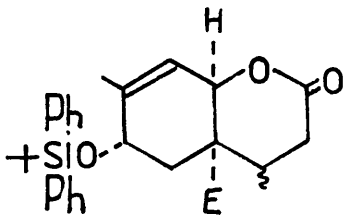
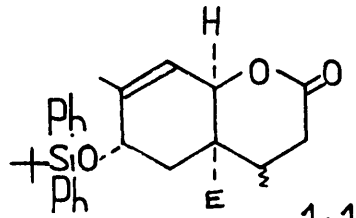
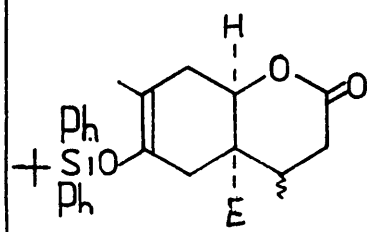
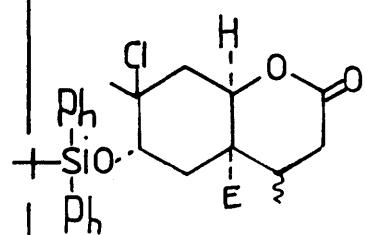
Substrate	Base	Products	Yield
	Pyridine	 Starting material	43·7 % 47·5%
"	Hunig's	 5 : 1 	55%
"	DBU	Decomposition	

Table 5 (contd.)

	Pyridine	 1:1  Starting material	40·7% 37·0%
"	Hunig's	 Decomposition	~10 %
"	DBU	Decomposition	

In conclusion, the osmylation route resulted in the successful preparation of the desired trichothecene precursor (200a)'. Unlike the aforementioned bromination route, the osmylation sequence exhibited a relatively high degree of stereocontrol, with the desired 8α-hydroxyl function being introduced at an early stage in the synthesis with a high degree of stereoselectivity. Furthermore, the osmylation and silylation steps proceeded in fairly respectable yields.

Unfortunately this scheme encountered problems at the elimination step which was necessary for regiospecific introduction of the 9,10-double bond, and under optimised conditions at best a 1:1 mixture of α-allyl silyl ether (210) and silyl enol ether (211) was obtained.

Both the bromination and osmylation routes resulted in the successful preparation of the potentially useful α-allylic alcohol (200a). Furthermore, although the osmylation scheme exhibited a relatively high degree of stereocontrol the bromination route was the manipulatively simpler synthetic strategy, which did not require the use of the potentially hazardous osmium tetroxide.

The development of both of these successful schemes towards α-allylic alcohol (200a) concluded the study of the cycloaddition reaction between isoprene and a coumalic acid derivative.

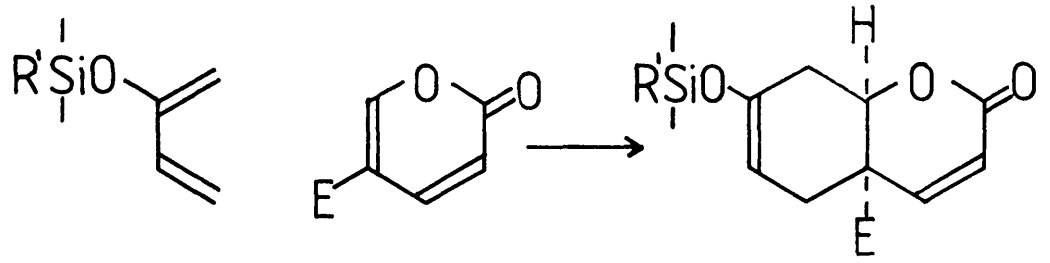
Due to the regioselective problems encountered, coupled with the poor yield of desired adduct obtained from the early Diels-Alder studies involving isoprene and methyl coumalate (Scheme 26), it was decided to try to prepare potential trichothecene precursors by alternative routes.

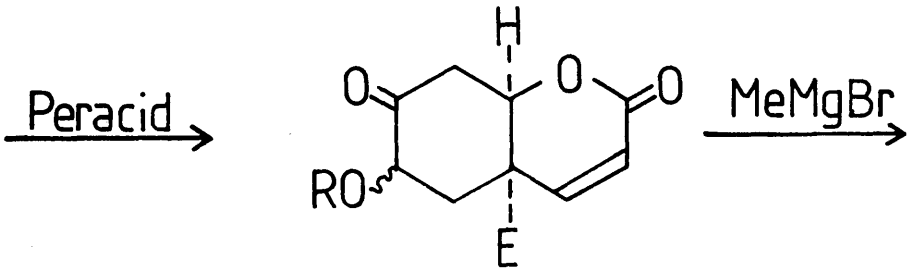
On the basis of frontier molecular orbital theory, it was predicted that cycloaddition between a 2-silyloxy substituted buta-1,3-diene and methyl coumalate would result in a highly regioselective route towards synthetically promising silyl enol ethers. Forseeably, these silyl enol ethers could be further elaborated to afford an intermediate possessing a suitably functionalised A-ring system for T2 toxin by initial transformation into the corresponding α-silyloxy or α-hydroxy ketone by peracid oxidation. Subsequent Grignard treatment of the derived ketone could be expected to furnish a tertiary alcohol, which on selective dehydration should serve to regioselectively introduce the requisite 9,10-double bond.

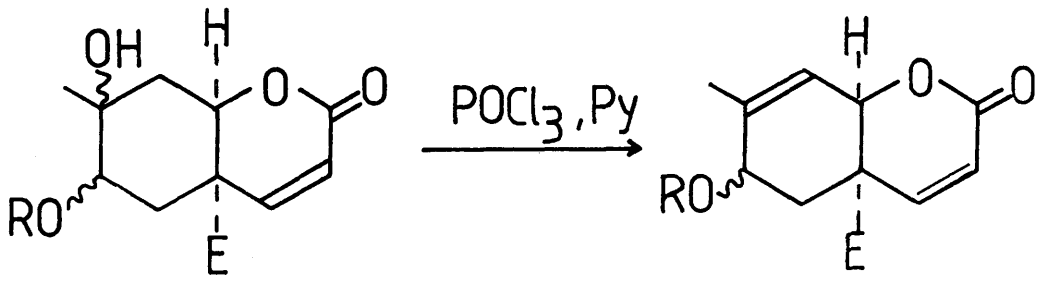
In the light of dehydration studies, carried out at a later stage in this research project (table 5), it was shown that selective dehydration on an intermediate of type (223) was not a facile process and could be expected to furnish a mixture of the desired allylic alcohol and the corresponding enol ether. (This information was not at hand at the time of this study). An idealised route towards α-allylic alcohol (222) is outlined in Scheme 34.

First the Diels-Alder reaction between 2-trimethylsilyloxybutadiene (214) and methyl coumalate was studied. Diene (214) was prepared readily in multigram quatities[72] and subsequently reacted with methyl coumalate (toluene, 110°C, 48h), as shown in Scheme 35.

Scheme 34



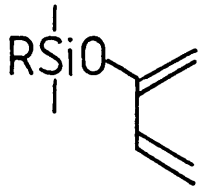




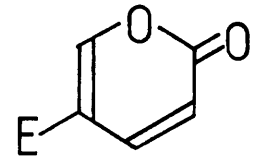
R = H or R = $\overset{|}{\underset{|}{Si}}$R'

R' = Me or t-Butyl

Scheme 35

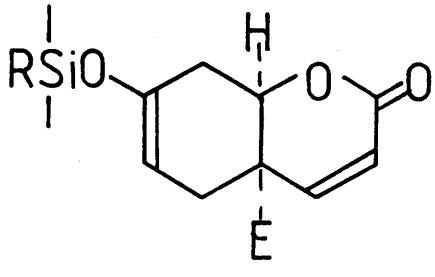


(214) R=Me
(217) R=t-Butyl

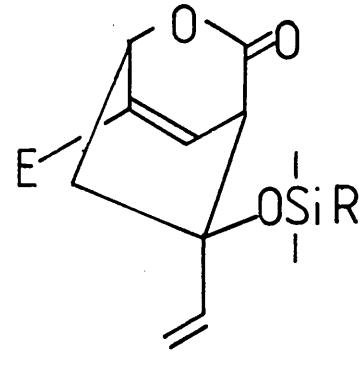


(147)

Toluene
Hydroquinone
110°C, 48h

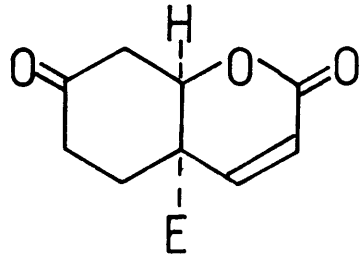


+



(215a) R=Me, 48%
(218a) R=t-Butyl, 74%

(215b) R=Me, 41%
(218b) R=t-Butyl, 21·4%



(216)

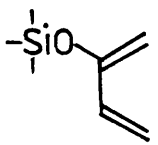
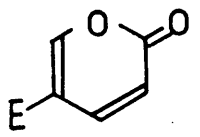
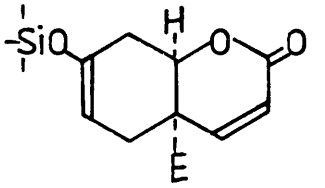
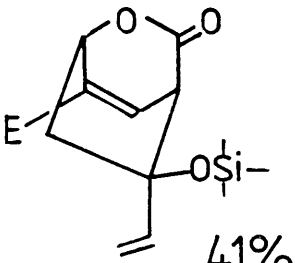
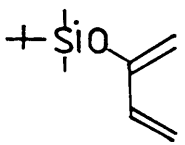
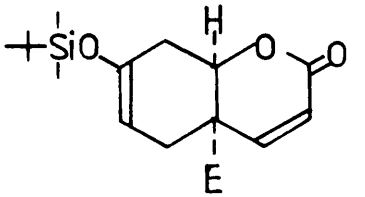
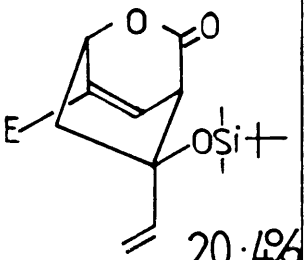
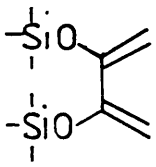
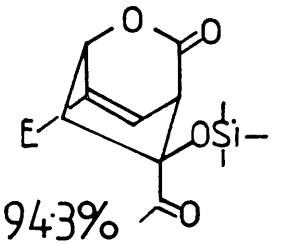
^{1}H-n.m.r. of the crude reaction mixture indicated that the desired silyl enol ether (215a) had been prepared regiospecifically, along with an appreciable amount of the alternative Diels-Alder adduct (215b). Attempts to obtain the trimethylsilyl enol ether pure by Kugelrohr distillation proved to be unsuccessful. The distilled trimethylsilyl enol ether was found to be very labile, undergoing ready desilylation to the corresponding crystalline ketone (216) on exposure to air. Surprisingly and quite uncharacteristically, it was discovered that the trimethylsilyl-enol ether (215a) could be purified by suction dry column chromatography to afford 48.0% of pure crystalline enol ether (215a), along with 41.0% of the undesired alternative adduct (215b).

Similarly, the cycloaddition reaction between 2-t-butyldimethylsilyl-oxybuta-1,3-diene (217) and methyl coumalate was observed to be a regiospecific process. Purification of the crude reaction mixture by column chromatography, gave a very respectable 74.0% yield of the desired t-butyldimethylsilyl enol ether (218a), along with 21.4% of the alternative adduct (218b). These results are summarised in table 6.

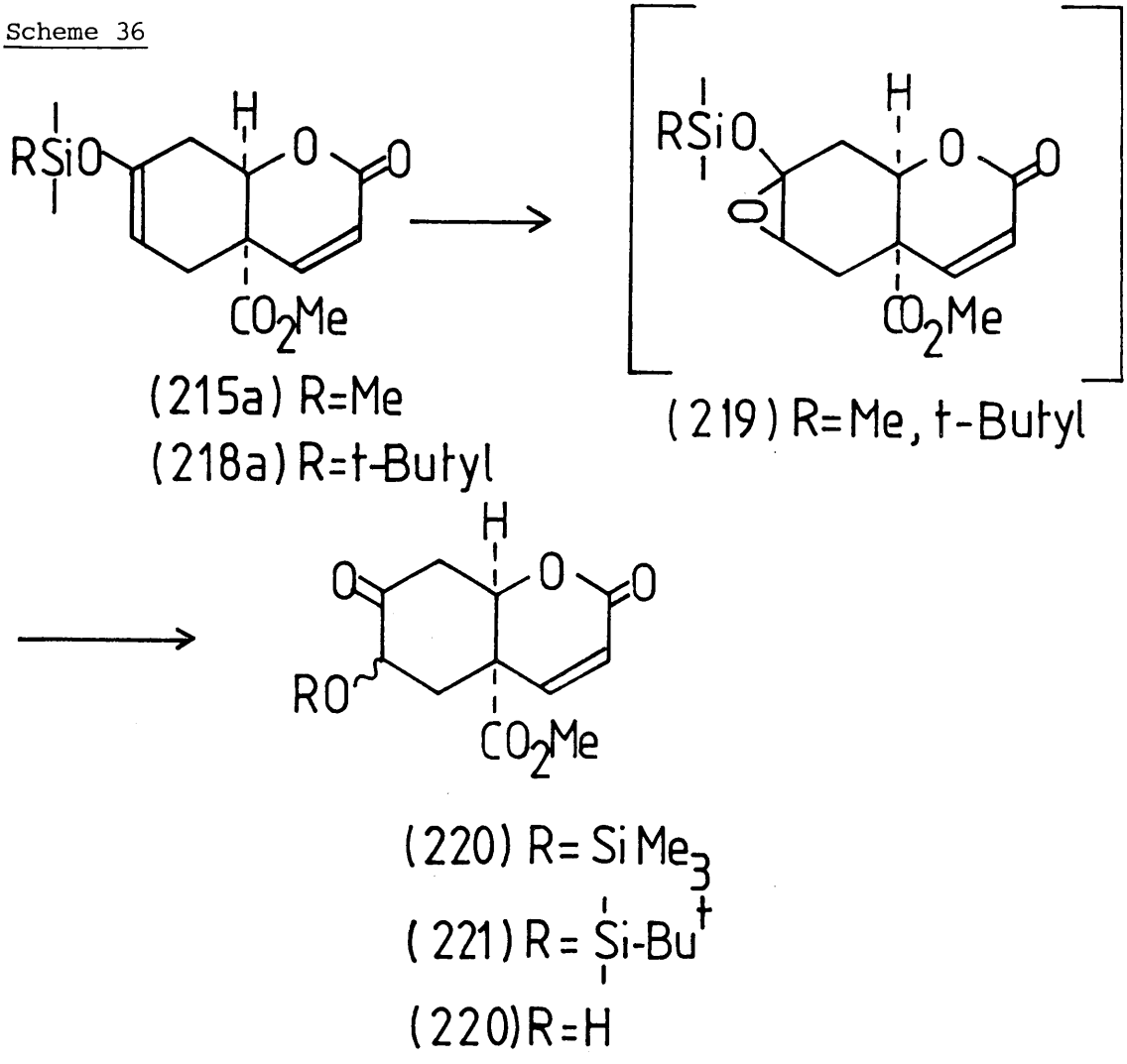
The silyloxybutadienes (214) and (217) were observed to be more efficient 4π components in their cycloaddition reaction with methyl coumalate, than isoprene, and afforded the desired silyl enol ethers (215a) and (218a) regiospecifically and in fairly high yields.

As shown in Scheme 36, peracid oxidation of silyl enol ether (215a) or (218a) was expected to result in regiospecific oxidation of the electron-rich double bond of the silyl enol ether to furnish the corresponding α-silyloxy ketones (220) or (221)[73]. It is believed that the reaction proceeds via the intermediate silyloxy oxirane (219), which subsequently rearranges to the α-silyloxyketone.

Table 6

Diene	Dienophile	Conditions	Desired Adduct	Alternative Adduct	Recovered Diene
		Toluene, hydroquinone, 110°C, 48h	 48%	 41%	—
	〃	〃	 74%	 20·4%	—
	〃	〃	—	 94·3% + regioisomer	✓
〃	〃	BF_3Et_2O, CH_2Cl_2 0°C-RT	—	〃	✓

Scheme 36



Unfortunately however, attempts to epoxidise either the trimethylsilyl enol ether (215a) or the t-butyldimethylsilyl enol ether (218a) proved to be much less straightforward than originally expected. As listed in table 7, various epoxidation procedures were carried out, where none of them provided the desired silyloxy ketone intermediates (220) or (221).

The most interesting result to emerge from these oxidation studies was that treatment of either the trimethylsilyl or t-butyldimethylsilyl enol ethers with m-chloroperbenzoic acid, in methylene chloride, resulted in the formation of the corresponding aryloxy silyloxy acetals (224) and (225), in fairly high yields. These acetals are believed to arise from

Table 7

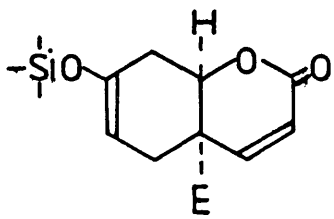
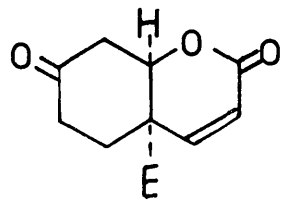
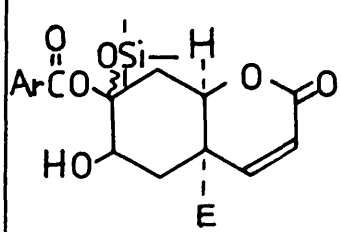
Substrate	Conditions	Product
	[94] CF_3CO_2H, CH_2Cl_2, Na_2HPO_4	
"	Permaleic Acid, CH_2Cl_2	Starting material
"	Bu^tOOH, CH_2Cl_2 Na_2HPO_4, Reflux.	" "
"	[82] Bu^tOOH, CH_2Cl_2 $VO(acac)_2$, Na_2HPO_4, Reflux	" "
"	[84] mCPBA, CH_2Cl_2, Na_2HPO_4	

Table7 (contd.)

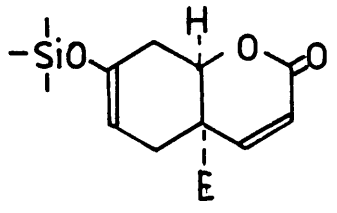
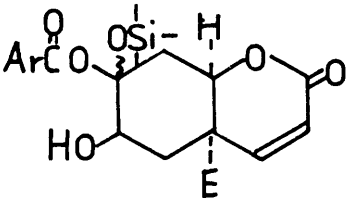
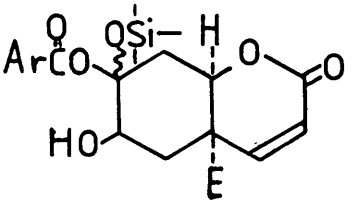
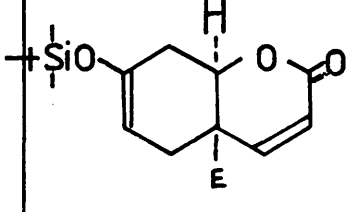
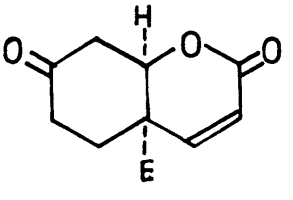
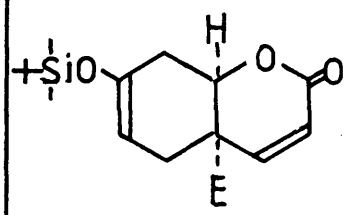
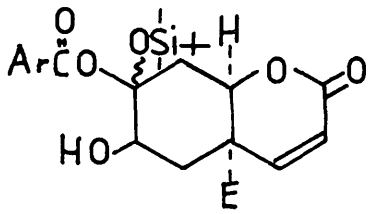
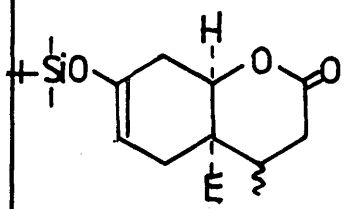
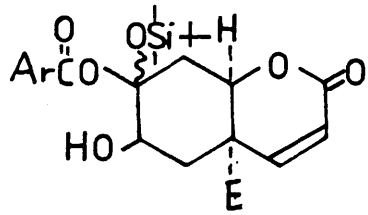
	mCPBA, Hexane, Na_2HPO_4 [85]	
〃	p-NO_2-Perbenzoic Acid, CH_2Cl_2, Na_2HPO_4	
〃	p-NO_2-Perbenzoic Acid, Hexane, Na_2HPO_4	〃
	CF_3CO_3H, Na_2CO_3, CH_2Cl_2 [94]	
〃	Bu^tOOH, Na_2HPO_4, $MO(CO)_6$, CH_2Cl_2, Reflux [82]	Starting material

Table 7 (contd.)

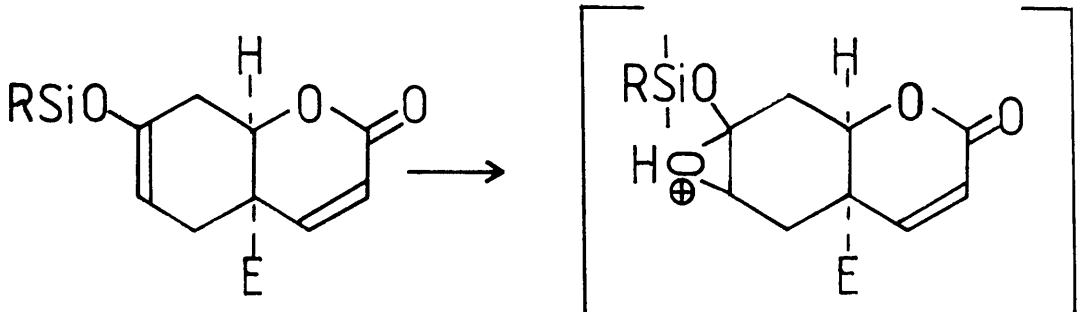
	84 mCPBA, CH_2Cl_2, Na_2HPO_4	
"	p-NO_2-Perbenzoic Acid, CH_2Cl_2 Na_2HPO_4	"
	84 mCPBA, CH_2Cl_2 Na_2HPO_4	
"	p-NO_2Perbenzoic Acid, CH_2Cl_2, Na_2HPO_4	"

m-chlorobenzoic acid opening of the intermediate silyloxy oxiranes, as shown in Scheme 37. Excess buffer added to the reaction mixture in an attempt to prevent acetal formation had little effect. In addition the solvent was changed from methylene chloride to hexane in which m-chlorobenzoic acid has much lower solubility; however this was also observed to be ineffective. Acetal (224), [δ115.56, (ArC(=O)-O-C-OSi), 70.92 (C-OH)] was observed to be stable at room temperature, but readily decomposed on attempted Kugelrohr distillation. On the other hand, acetal (225), [δ103.43 (ArC(=O)-O-C-OSi), 70.62 (C-OH)] was a stable, crystalline solid (m.p. 115-118°C) which allowed full characterisation. Similar results were obtained, on employing p-nitroperbenzoic acid as epoxidising agent.

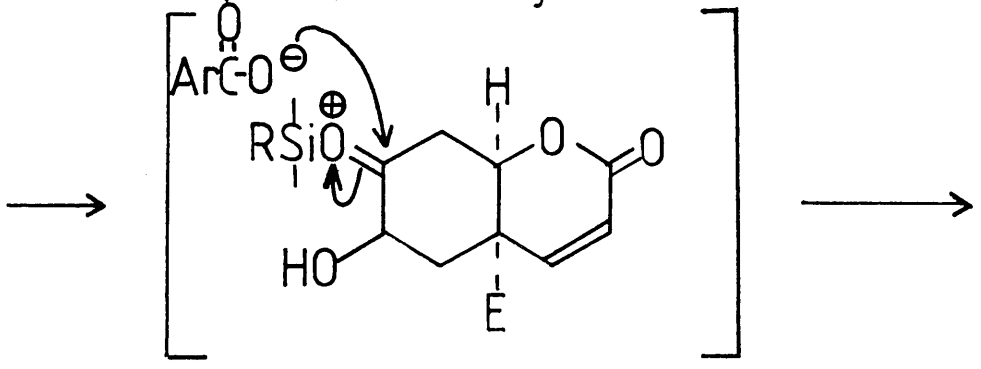
It was anticipated that the obtained acetals could be induced to undergo rearrangement to the desired hydroxy ketone (222). However, as listed in table 8 numerous attempts to bring about this rearrangement were unsuccessful. Treatment of the t-butyldimethylsilyl acetal (225) with HF in acetonitrile appeared encouraging. ^{1}H-n.m.r. of the crude reaction product revealed the expected doublet of doublets at δ 4.30 ppm for H-C-OH and it was suspected that the desired rearrangement to hydroxy ketone (222) and m-chlorobenzoic acid had occurred. Unfortunately, all attempts to purify the crude reaction mixture met with failure.

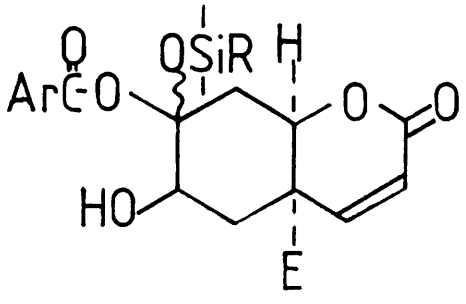
This route did not lead to the successful preparation of trichothecene precursors and was subsequently abandoned.

Scheme 37

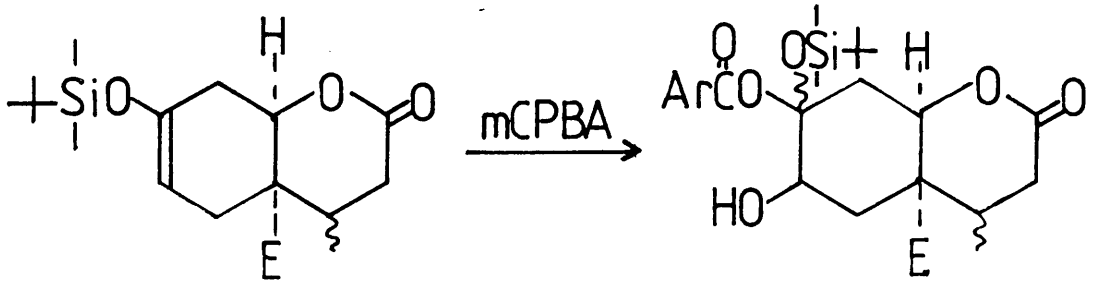


(215a) R = Me
(218a) R = t-Butyl

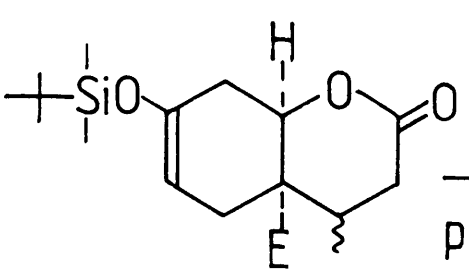




(224) R = Me
(225) R = t-Butyl

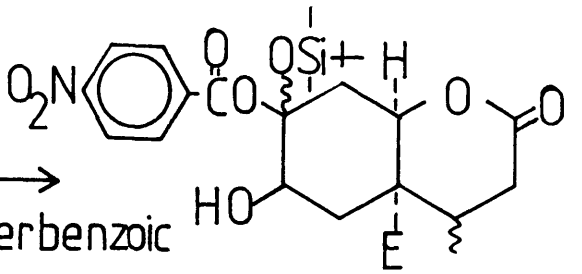


(239) (226a)



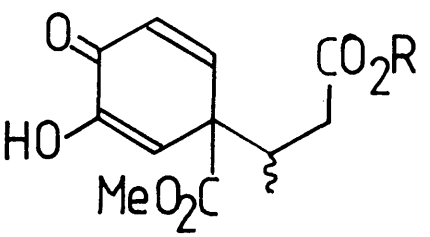
(239)

pNitroperbenzoic Acid



(226b)

K_2CO_3, MeOH
RT, 2h



(227a) R=H
(227b) R=Me

Table 8

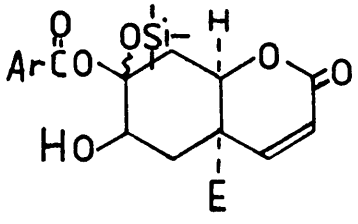
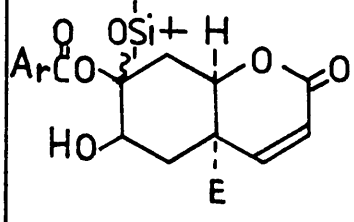
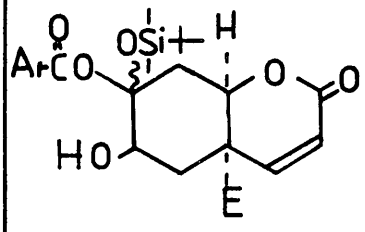
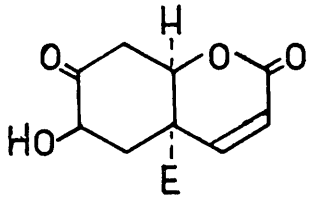
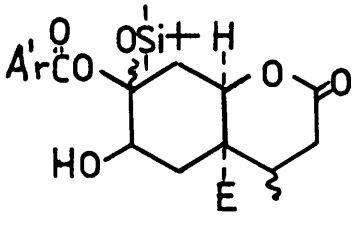
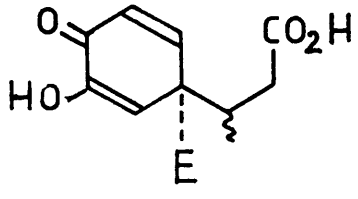
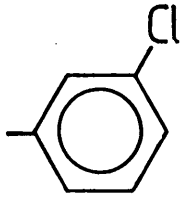
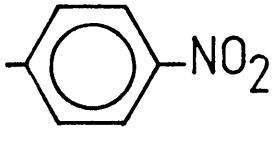
Substrate	Conditions	Product
	NEt_3, HF(catalytic)	Decomposition
"	K_2CO_3, MeOH	"
	NEt_3, MeOH	"
"	Silica, 24h	Starting material
"	catalytic NEt_3, CH_2Cl_2, 24h	"
"	3eq NEt_3HF, CH_2Cl_2	"
"	AcOH, THF, H_2O	Decomposition

Table 8(contd.)

	Excess NaOH	Decomposition
"	HF, CH_3CN, 45min, RT	 + m-Chlorobenzoic acid.
	K_2CO_3, MeOH, RT, 2h	

Ar = 

Ar' = 

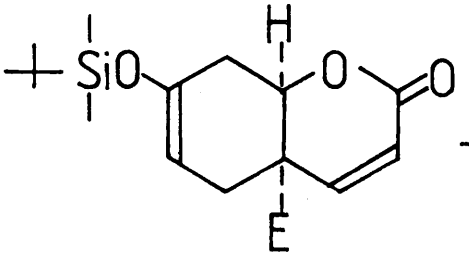
Due to the lack of success observed in attempting to obtain hydroxy ketone (222) by epoxidation methods, it was decided to prepare the alternative α-bromoketone (228) which could conceivably be hydrolysed to the desired hydroxy ketone at a later stage, or even converted into the potentially useful γ-lactone (230) via the corresponding carboxylic acid (229) (Scheme 38).

The desired α-bromoketone (228), should be accessible by bromination of the trimethylsilyl or t-butyldimethylsilyl enol ethers (215a) and (218a), using bromine dioxane[74] complex. Under the reaction conditions employed, bromination of the trimethylsilyl enol ether[48] (215a) furnished the simple desilylated ketone (216) as the sole reaction product.

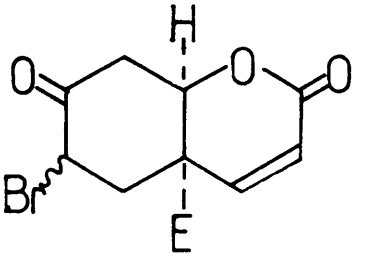
Interestingly, however, it was observed that the nature of the bromo compound obtained from bromination of the corresponding t-butyldimethylsilyl enol ether (218a) depended upon the reaction conditions employed. As shown in Scheme 39, bromination of intermediate (218a) in the absence of base afforded a 3:1 epimeric mixture (as determined by ^{13}C-n.m.r. spectroscopy) of the expected α-bromoketone (228), [δ50.05(d,C-Br), 169.93(s,C=O)], in an overall yield of 67.8%. On the other hand, it was observed that bromination in the presence of pyridine regioselectively furnished bromo silyl enol ether (231), as the major product, in which the t-butyldimethylsilyloxy group remained intact and the double bond had shifted [δ43.66, (d,C-Br), 103.66(d,C=C-H), 151.92(s,C=C-OSi)]. A small amount of the regioisomeric enol ether (232) was observed as a minor by-product.

A short model study was carried out to determine whether this regioselective bromination could be generally extended to other systems.

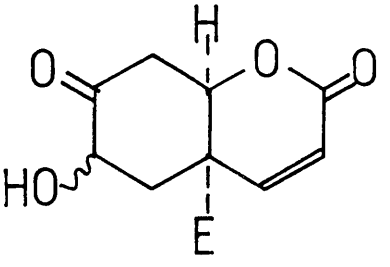
Scheme 38



(218a)

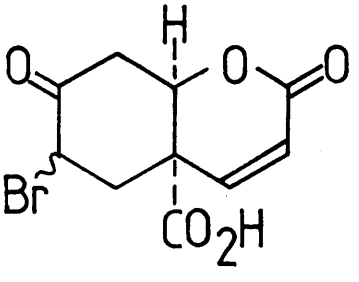


(228)

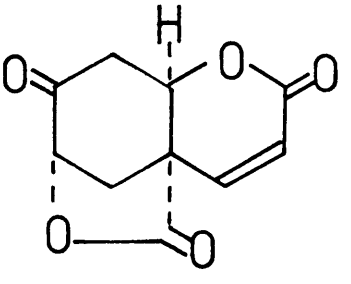


(222)

OR

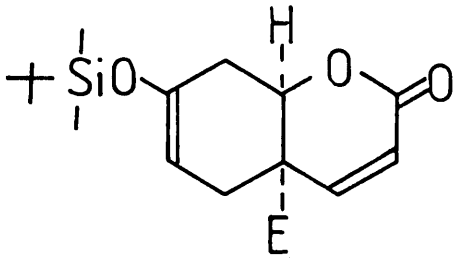


(229)

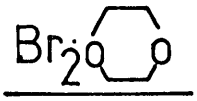


(230)

Scheme 39

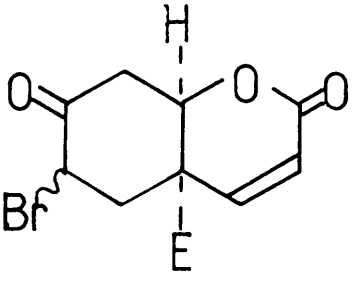


(218a)



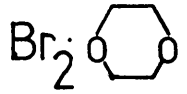
CH_2Cl_2

-78°C

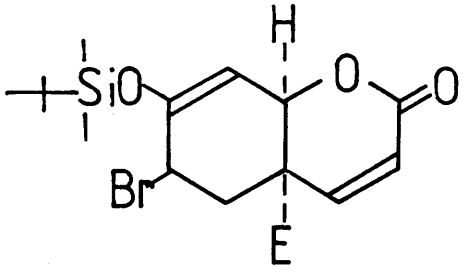


(228), 3 : 1

67·8 %

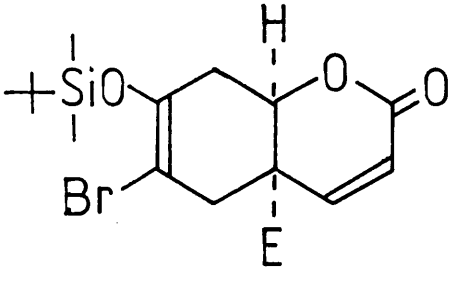


Py, CH_2Cl_2, -78°C



(231) ; 44·2%

major product



(232)

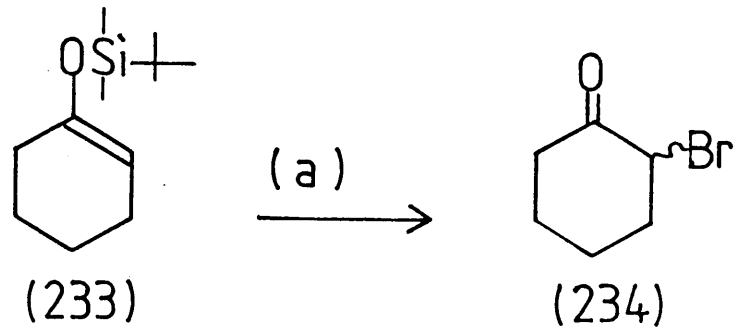
It should be noted that the substrate molecules for this study, namely silyl enol ethers (233) and (237) and their respective bromination products, possess a large number of aliphatic protons, therefore ^{1}H-n.m.r. spectroscopy proved to be of limited utility in determining the relative compositions of reaction mixtures. ^{13}C-n.m.r. spectroscopy proved to be much more useful and was subsequently employed to determine the product composition of resulting reaction mixtures. The results obtained from this study are outlined in Scheme 40 and summarised in table 9.

In conclusion, the model study confirmed that whether the α-bromoketone or the alternative bromo silyl enol ether was obtained depended upon the reaction conditions employed; furthermore in the presence of base, regioselective formation of the α-bromo silyl enol ether was observed. The regioselectivity of the bromination reaction was greatly enhanced by the presence of the t-butyl conformational locking group, whereupon bromo silyl enol ether (238) was obtained as the only bromination product. The bromination reaction is believed to proceed through an intermediate arising from axial attack of bromine on the original silyl enol ether (218a).

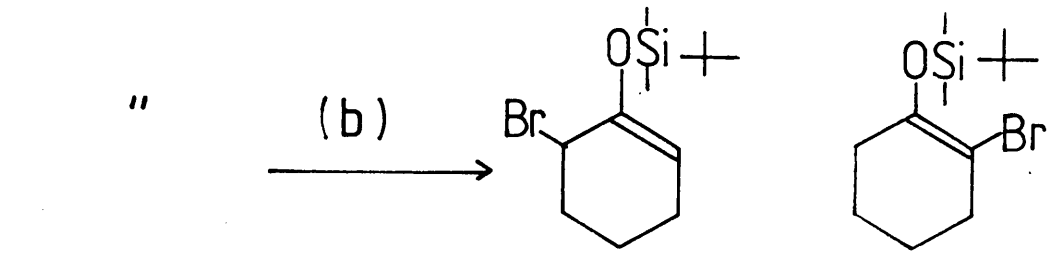
At approximately the same time as this observation was made a related report was published which dealt with the reaction of t-butyldimethylsilyl enol ethers with dimethyl(methylene)ammonium iodide[75]. This group of workers reported survival of the t-butyldimethylsilyl group in the reaction product and observed a regioselective route towards t-butyldimethyl silyl enol ethers, possessing an alternative amino group.

More recently a paper dealing with the reaction of silyl enol ethers with N-halosuccinimide reported survival of the original silyl group which resulted in regioselective formation of the corresponding α-halo silyl enol ethers[76].

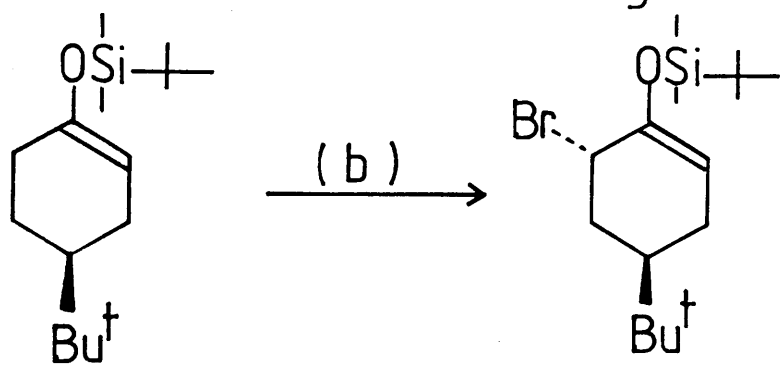
Scheme 40



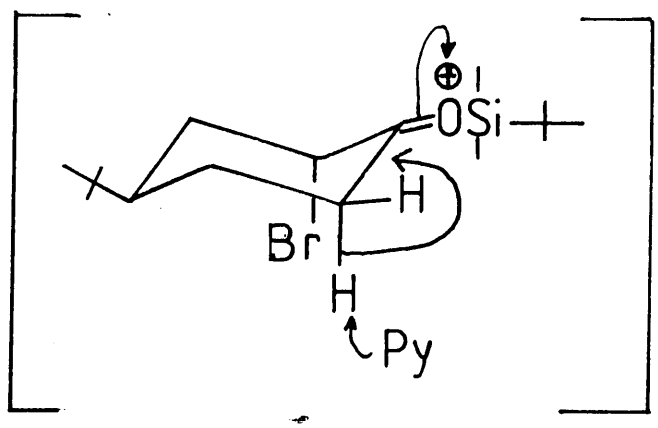
(233) (234)



(235) 3 : (236) 1



(237) (238)



(a) = Bromine dioxane, CH_2Cl_2

(b) = Bromine dioxane, base, CH_2Cl_2

Table 9

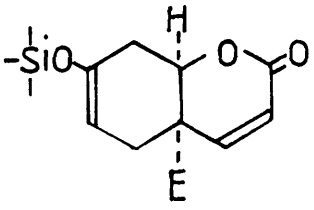
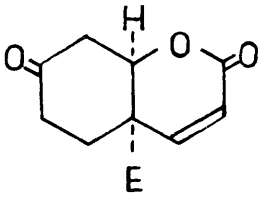
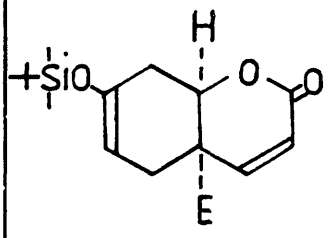
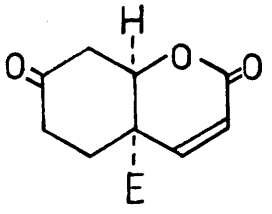
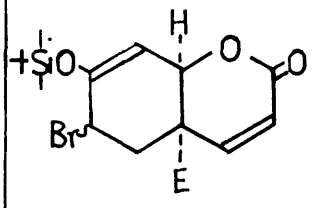
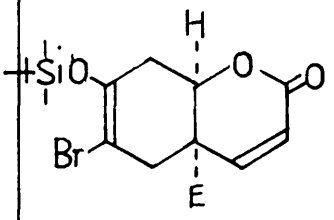
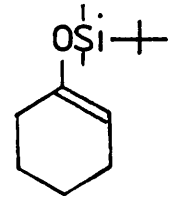
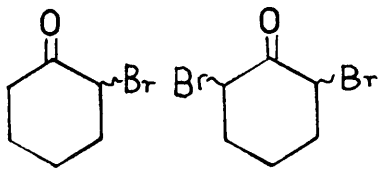
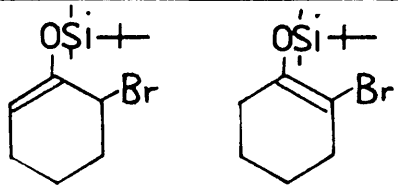
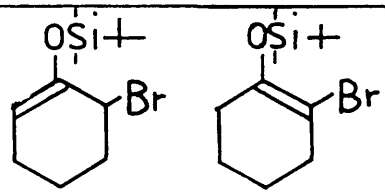
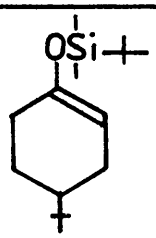
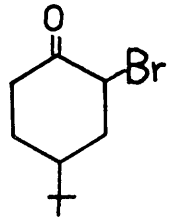
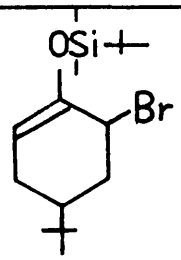
Substrate	Conditions	Product	Yield
	Br_2:Dioxane, CH_2Cl_2, -78°C 20 mins		—
"	Br_2:Dioxane, Py, CH_2Cl_2, -78 °C, 20 mins	"	—
	Br_2:Dioxane, CH_2Cl_2, -78°C, 20 mins		67·8%
"	Br_2:Dioxane, Py, CH_2Cl_2, -78°C, 20mins	 	44·2% 4·1%

Table 9 (contd.)

	Br_2·Dioxane, CH_2Cl_2, -78 °C, 20 mins		58·6%, 22·6%
"	Br_2·Dioxane, Py, CH_2Cl_2, -78° C, 20 mins	 3 : 1	49%
"	Br_2·Dioxane, NEt_3, CH_2Cl_2, -78°C, 30 mins	 3 : 1 Starting material	69·0 % 21·4%
	Br_2·Dioxane, CH_2Cl_2, -78°C, 20 mins		53·1%
"	Br_2·Dioxane, Hunig's base, -78 °C, 30 mins		76·3%
"	Br_2·Dioxane, NEt_3, CH_2Cl_2, -78°C, 30 mins	"	80·2%

Having obtained α-bromoketone (228) in fairly high yield all that remained was to hydrolyse it to the corresponding α-hydroxy ketone (222), or even the alternative bromocarboxylic acid (229).

Unfortunately, all attempts to hydrolyse bromoketone (228) to the corresponding hydroxy ketone proved uniformly unsuccessful. Moreover, attempts to cleave the methyl ester to the free carboxylic acid also met with failure, in spite of employing a wide range of reagents (K_2CO_3, NaOH, Li in DMF, TMS|/NaI/CH_3CN, DBN, DBU and HCl).

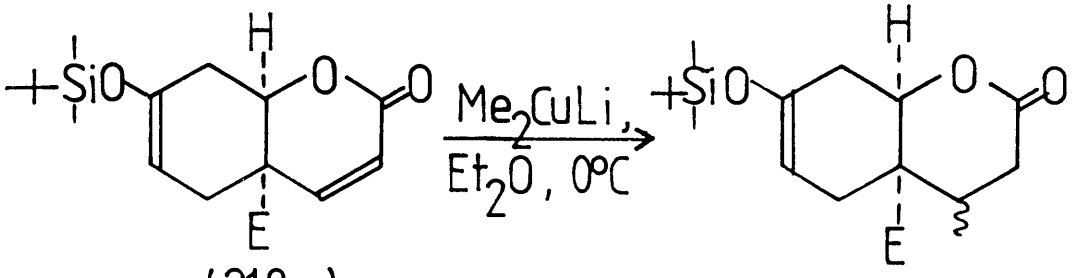
On the basis of these synthetic studies, it was concluded that α-hydroxyketone (222) is not as easy an intermediate to prepare as had first been imagined, with both the epoxidation and bromination routes towards this compound being unfruitful. In a final attempt to prepare this somewhat elusive intermediate, it was anticipated that osmylation of the remaining double bond of silyl enol ether (239) would stereoselectively furnish the desired α-silyloxy protected ketone.

As outlined in Scheme 41, conjugate addition of dimethyl copper lithium to the enone system of silyl enol ether (218a) afforded 75.0% of cuprate product (239), as mainly one epimer. Catalytic osmylation of silyl enol ether (239) in the presence of N-methyl morpholine N-oxide[69] gave 91.4% of a very viscous oil, which was observed to be much more polar on TLC than expected. The ^{1}H-n.m.r. spectrum of the crude osmylation product surprisingly revealed that the B-ring lactone system was no longer intact and on the basis of the evidence obtained it was suspected that the cyclohexenone carboxylic acid intermediate (240) had been formed.

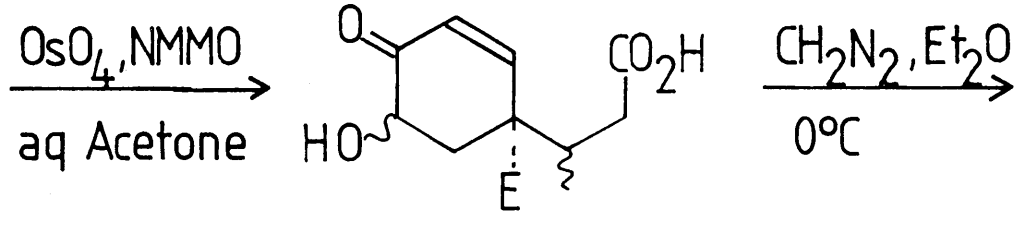
The immediate osmylation product proved to be too polar to allow full characterisation and was subsequently esterified with diazomethane to furnish an approximately 1:1 mixture of the corresponding methyl esters (241). Full characterisation of the methyl esters proved their structures to be the proposed B-ring opened compounds [δ68.97(d,C-OH), 126.88(d,C^{β}=C^{α}-H), 151.22(d,C^{β}=C^{α}-H), 198.24(s,C=O)].

Careful Grignard treatment of the mixture of esters (241) afforded an overall 60% yield of the corresponding diols (242) which were subsequently hydrolysed to give a mixture of diacids (242). Sequential treatment of diacids (243) with acidic methanol and diazomethane afforded γ-lactone (244b) in 35.3% yield (IR(CCl_4) 3590 (sharp), 1795, 1745 cm^{-1}), along with diester (242b).

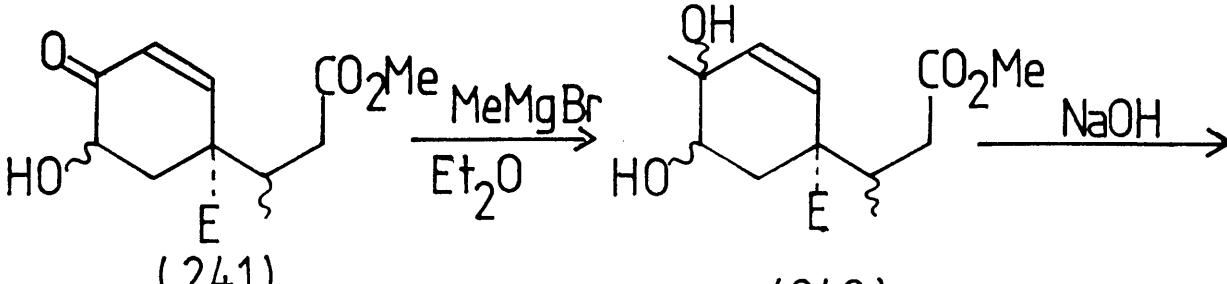
Scheme 41



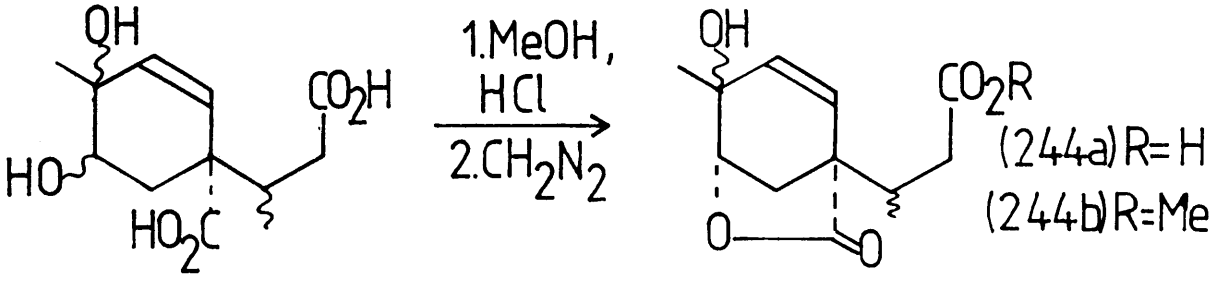
(218a) (239), 75%



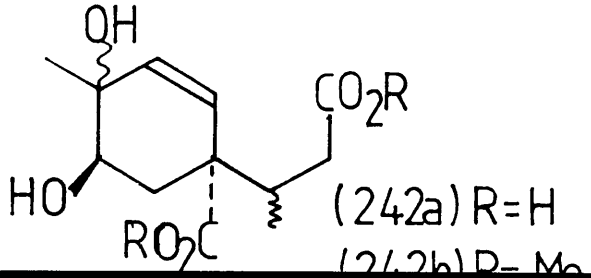
(240) ; 91·4%

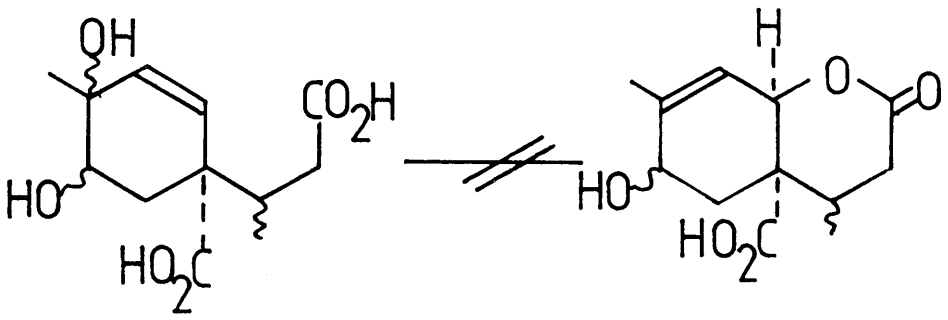


(241) (242)

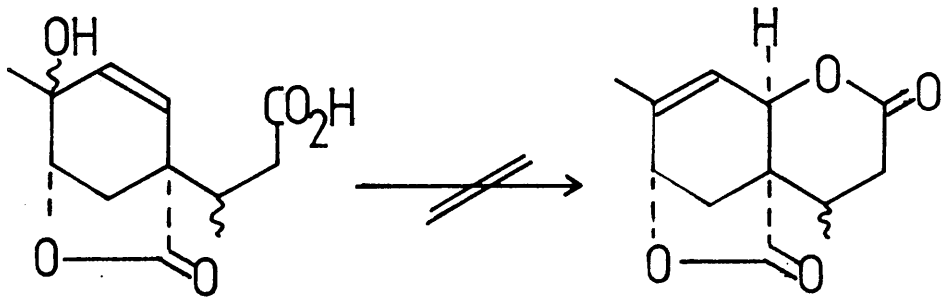


(243)





(243)

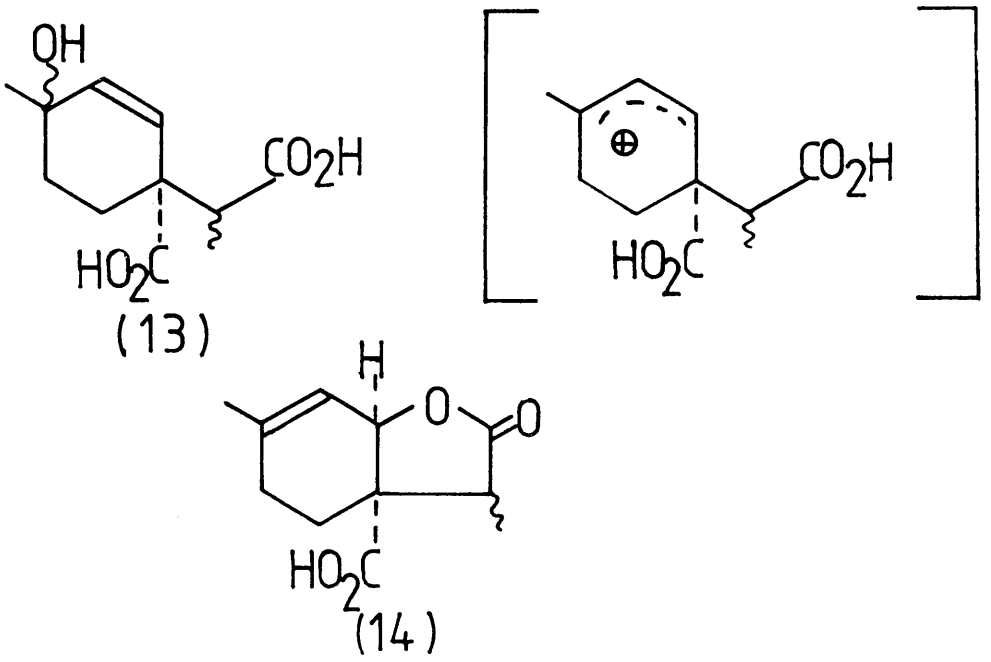


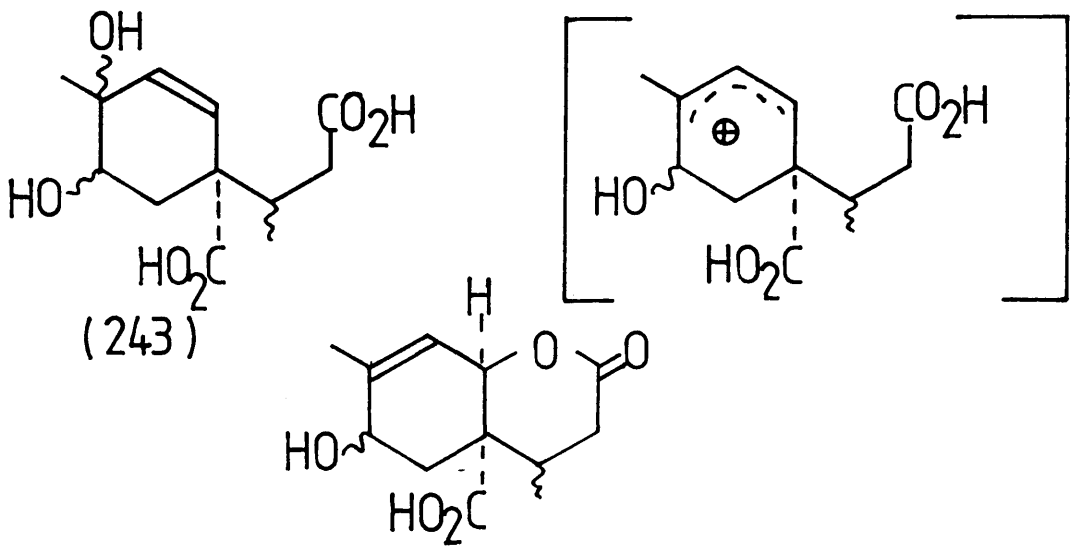
(244a) (203)'

Earlier studies carried out by Colvin et al,[28] reported cyclisation of a carboxylic acid intermediate (13) to afford the thermodynamically favoured cis-fused bicyclic γ-lactone (14) as the sole product, where the reaction was believed to proceed via an intermediate allylic carbonium ion. As shown in Scheme 42, it was hoped that diacid (243) or the alternative γ-lactone (244) could be induced to undergo an analogous cyclisation process, to provide a cis-fused benzopyran intermediate, which possesses ideal functionality for further elaboration to T-2 toxin.

As listed in table 10, all attempts to regenerate the cis-fused B-ring lactone system via a cyclisation reaction were uniformly unsuccessful, and therefore this route also failed to provide the hydroxy ketone.

Scheme 42


OH
CO2H
HO2C
(13)
H
O
O
HO2C
(14)


OH
HO
CO2H
HO2C
(243)
H
O
O
HO
HO2C

OR

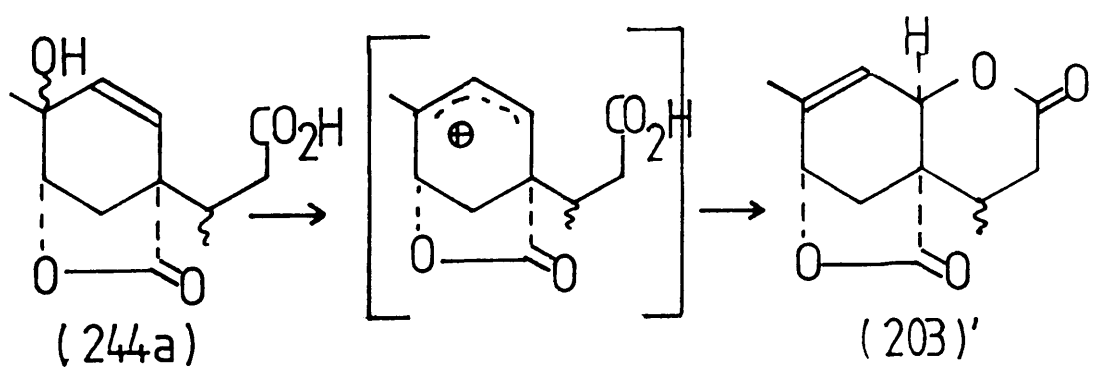

OH
CO2H
O
O
(244a)
CO2H
O
O
H
O
O
O
O
(203)'

Table 10

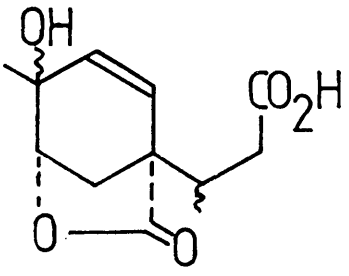
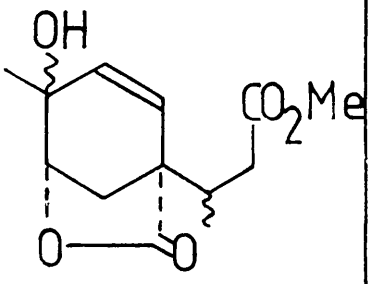
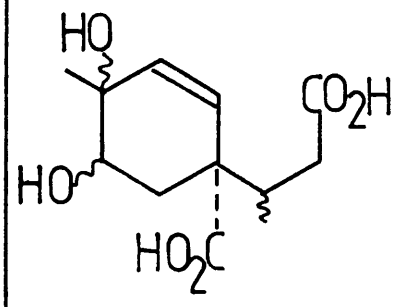
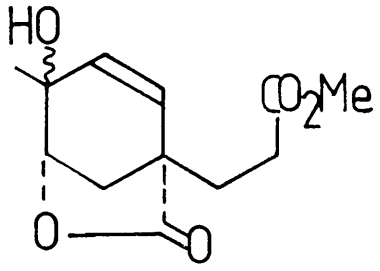
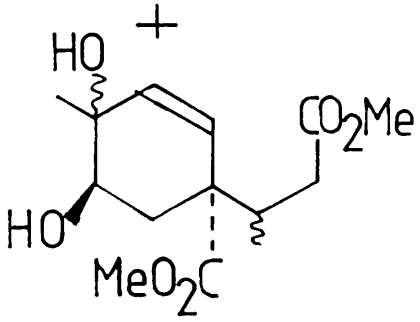
Substrate	Conditions	Product
	1. pTSA (X%), CH_2Cl_2, 4ÅMS 2 CH_2N_2	
"	1. Camphorsulphonic Acid (Y%), CH_2Cl_2, 4ÅMS 2. CH_2N_2	"
"	1. Pyridinium tosylate (Z%), CH_2Cl_2, 4ÅMS 2. CH_2CN_2	"
"	1. Conc H_2SO_4 24h 2 CH_2N_2	"

Table 10 (contd.)

	1.2eq pTSCl, 4eq Py, CH_2Cl_2, 24h 2. CH_2N_2	 + 
	1 4eq 1N HCl, MeOH, 2h 2. CH_2N_2	

X, Y and Z = 5, 10, 20, 25, 30 %

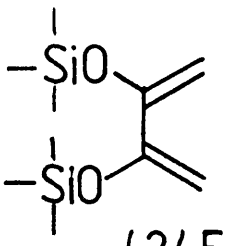
The final route which will be discussed in this report deals with the cycloaddition between 2,3-bistrimethylsilyloxy butadiene (245) and methyl coumalate[77]. Scheme 43 outlines the proposed sequence towards a potential trichothecene precursor (246).

It was envisaged that Diels-Alder reaction between the readily prepared bistrimethylsilyloxy butadiene[78] (245) and methyl coumalate would furnish bicyclic adduct (246). Subsequent treatment of the derived bis-silyl enol ether (246) with methyl lithium could conceivably afford dienolate anion (247)[79], which on exposure to methyl iodide, could be expected to give a mixture of hydroxy ketones (248a) and (248b). Although only intermediate (248a) is useful as a trichothecene precursor this could be endured provided the reaction scheme proceeded as expected, to allow facile and rapid access to this promising compound.

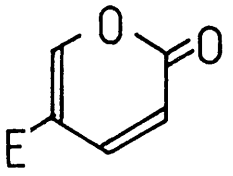
In our hands, cycloaddition between excess bistrimethylsilyloxybutadiene and methyl coumalate (toluene, 110°C, 48h); Scheme 44, afforded a 1:1 regioisomeric mixture of the alternative Diels-Alder adducts (249a) and (249b) as the exclusive products in an overall yield of 94.3%. Varying the temperature at which the reaction was carried out, along with the length of time of the reaction and even employing Lewis acid catalysts did not affect the product composition of the reaction mixture.

This somewhat unexpected result could be explained if bis diene (245) existed predominantly in the trans-conformation, rather than the cis-conformation which was necessary for successful formation of adduct (246). In an attempt to circumvent this unforseen problem it was proposed to effectively "lock" the bis diene into the desired cis-conformation by preparing diene (250). Unfortunately however diene (250) did not

Scheme 43

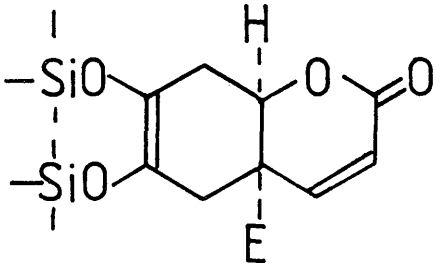


(245)



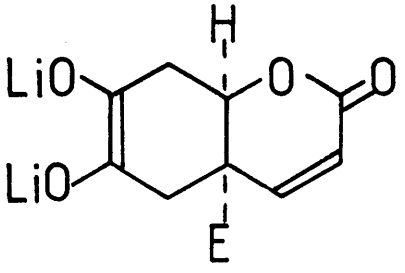
Toluene, 110°C

48h



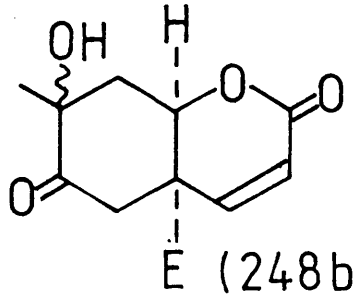
(246)

2eq MeLi

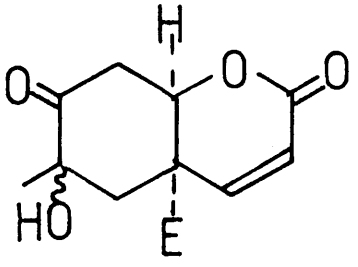


(247)

MeI

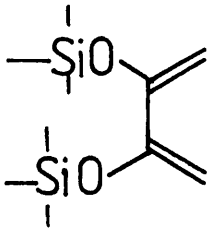


(248b)

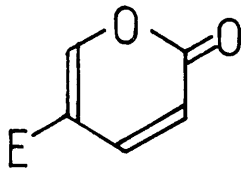


(248a)

Scheme 44

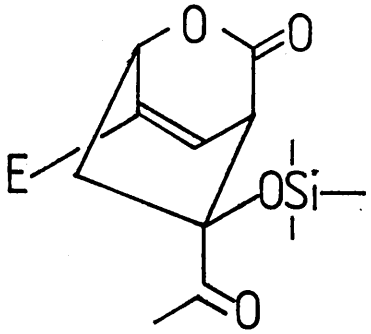


(245)



(147)

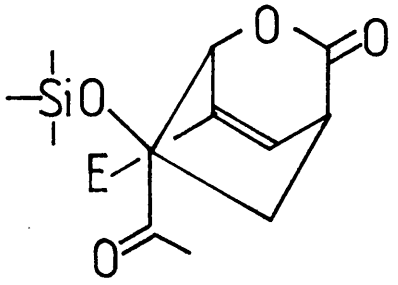
Toluene,
110°C, 48h



(249

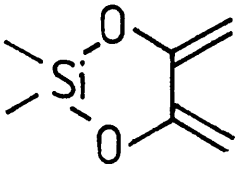
1

:



(249

1, 94·3%



(250)

surrender to our synthetic attempts and this route was subsequently abandoned.

In conclusion, although the Diels-Alder study with silyloxybutadienes did not yield the desired trichothecene precursors, it did provide an interesting, if somewhat unexpected series of results. Furthermore, it is believed that this research has contributed significantly towards a proposed total synthesis of T2 toxin by providing two useful routes towards α-allylic alcohol (200a), which possesses a fully functionalised A-ring and a partially functionalised B-ring for further elaboration to the target molecule.

Experimental Section

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelrohr. Recorded boiling ranges refer to the indicated air-bath temperature. ^{1}H-n.m.r. spectra were recorded on a Perkin-Elmer R32 spectrometer operating at 90 MHz or on a Bruker WP 200 SY spectrometer operating at 200 MHz. ^{13}C-n.m.r. spectra were taken on a Varian XL 100 spectrometer operating at 25 MHz or a Bruker WP 200 SY spectrometer operating at 50 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00 ppm). Data are tabulated or reported using the following convention: chemical shift [multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, integrated intensity]. Infra-red spectra were determined on a Perkin-Elmer 580 spectrometer. Low resolution mass spectra were determined on a VG updated MS 12 instrument and high resolution mass spectra were determined on a MS 902S. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

Reactions were usually carried out under an atmosphere of either nitrogen or argon. Unless otherwise stated anhydrous magnesium sulphate was used to dry reaction mixtures after work-up. Tetrahydrofuran, dimethoxyethane and ether were distilled freshly from sodium/benzophenone. N,N-Dimethylformamide was distilled from silica gel and stored over 4Å molecular sieves. Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves and dichloromethane was filtered through Grade 1 basic alumina and stored over 4Å molecular sieves. Dry column flash chromatography[9] and positive pressure flash chromatography[93] refer to techniques already described.

Numbering System

The numbering system of intermediates, particularly tricyclic, follows the conventional trichothecene numbering system, as indicated in the introduction section. Correspondingly, the direct Diels-Alder adducts described in the discussion section, and bicyclic intermediates resulting from synthetic transformations on these adducts, are numbered as benzopyranone derivatives, as shown in the experimental section.

Coumalyl chloride[60] (191)

Coumalic acid[86] (10.00g, 71.42 mmol) was heated at reflux in thionyl chloride (30 ml, 411.18 mmol), in an oil bath, until all of the coumalic acid had dissolved. Removal of excess thionyl chloride *in vacuo* afforded a solid residue, which was extracted overnight using a Soxhlet extractor with light petroleum. Concentration of the extract under reduced pressure afforded 9.80g (85.8%) of white crystalline acid chloride, m.p. 71-74°C.

(literature[60] m.p. 74-75°C (67% yield)).

(±)-Methyl-(4aα,8aα)-4a,5,8,8a-tetrahydro-7-methyl-2H-1-benzopyran-2-one 4aα-carboxylate (157a) and its 6-methyl-regioisomer (157b)

Method A

A mixture of methyl coumalate[87] (147), (1.90g, 12.33 mmol) in 30 ml of dry toluene, a few crystals of hydroquinone, and freshly distilled isoprene (2-methyl-butadiene; 3.60 ml, 36.00 mmol) was heated at 110°C for 18 hours in a sealed tube. After cooling, removal of solvent *in vacuo* afforded a brown oil, which was purified by dry column flash chromatography to afford 430 mg (15.7%) of an inseparable oily mixture of Diels-Alder adducts (157a) and (157b), in the ratio of 5:2 respectively, as determined by ^{13}C-n.m.r. spectroscopy. The alternative Diels-Alder adduct (157c) was isolated as a white crystalline solid, 1.24g (45.5%); recrystallisation from ether/pentane gave white needles, m.p. 97-99°C.

Diels-Alder adducts (157a) and (157b)

IR(CCl_4): 2980, 1770, 1720, 1640, 1260 cm^{-1}.

MS: 222.0891 (M^+); calc. for $C_{12}H_{14}O_4$: 222.0900

Alternative Diels-Alder adduct (157c)

IR(CCl_4): 1770, 1720, 1640, 1635, 1440, 1260 cm^{-1}.

MS: 222 (M^+)

$C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%.

Found: C, 64.89; H, 6.30%.

Method B

A mixture of coumalyl chloride (191), (9.00g, 57.0 mmol) in 140 ml of dry toluene, a few crystals of hydroquinone, and freshly distilled isoprene (20.0 ml, 200.0 mmol) was heated at 110°C for 18 hours in a sealed tube. The mixture was transferred to a round-bottomed flask and cooled to 0°C in an ice-bath. With stirring, 16 ml (114.87 mmol) of triethylamine was added in one portion, at this temperature, followed by 5 ml (123.28 mmol) of methanol; stirring was continued for 40 mins. The resulting slurry was washed sequentially with 250 ml of saturated aqueous sodium hydrogen carbonate solution, 250 ml of saturated brine and 100 ml of cold water. The organic layer was dried and concentrated under reduced pressure. Purification of the resulting brown oil by dry column flash chromatography afforded 4.95g (39.0%) of Diels-Alder adducts (157a) and (157b), as a solid, in a regioisomeric ratio of 4:1 respectively, as determined by ^{13}C-n.m.r. spectroscopy. Recrystallisation from ether gave white needles, m.p. 44°C.

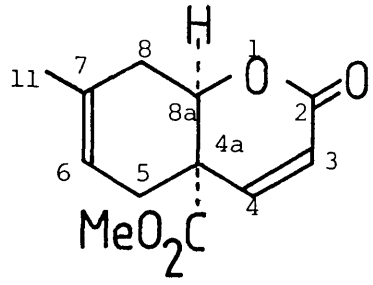
The alternative adduct (157c), (2.66g, 21.0%), was also isolated from the crude reaction mixture.

Diels-Alder adducts (157a) and (157b)

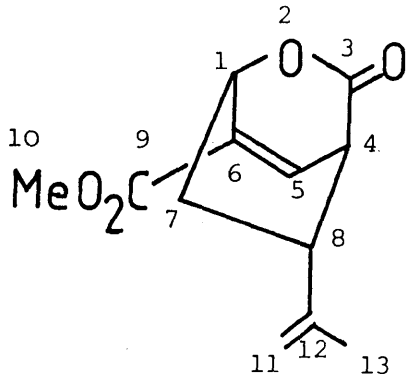
IR, ^{1}H-n.m.r. and ^{13}C-n.m.r. as previously stated.

MS: 222.0878 (M^{+}); calc. for $C_{12}H_{14}O_4$: 222.0900

$C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%. Found: C, 65.02; H, 6.47%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	163.10	-	s	
H-3	6.00	C-3	120.92	d	d	9.10
H-4	6.90	C-4	149.73	d	d	9.10
-	-	C-4a	45.80	-	s	
H-5(2H)	(1.85- ((2.97	C-5	(31.27 ((33.56	(m (	t	
H-8(2H)		C-8			t	
H-6	5.45	C06	117.85	m	d	
-	-	C-7	131.21	-	s	
H-8a	4.95	C-8a	76.09	m	d	
-	-	C-9	171.82	-	s	
H-10(3H)	3.75	C-10	- 52.86	s	q	
H-11(3H)	1.65	C-11	22.71	s	q	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-3	162.6	-	s	
-	-	C-9	172.4	-	S	
H-1	5.70	C-1	73.8	m	d	
H-4	3.78	C-4	46.14	m	d	
H-5	7.25	C-5	139.3	d	d	
-	-	C-6	143.6	-	s	
H-7(2H)	(2.35-((2.95 (	C-7	22.08	m	t	
H-8	(	C-8	38.57	m	d	
H-10(3H)	3.80	C-10	53.70	s	q	
H-11(2H)	4.62, 4.85	C-11	112.31	d	t	20.25
-	-	C-12	135.92	-	s	
H-13(3H)	1.68	C-13	30.91	s	q	

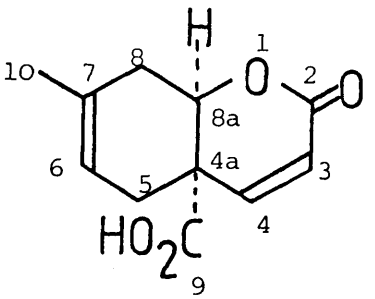
(±)-(4aα,8aα)-4a,5,8,8a-tetrahydro-7-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid (186a) and its 6-methyl regioisomer (186b)

A suspension of the 4:1 mixture of regioisomeric esters (157a) and (157b), (1.00g, 4.50 mmol) was stirred overnight in 2N sodium hydroxide solution (45ml, 90 mmol). The basic solution was acidified to pH1 with 1N HCl, salted out with sodium chloride and extracted thoroughly with ethyl acetate. The combined organic extracts were dried and concentrated under reduced pressure to afford 920 mg (98.3%) of crude acids (186a) and (186b) as a yellow, amorphous solid.

Acids (186a)/(186b)

IR (CCl_4): 3450 (broad), 1725, 1715, 1255 cm^{-1}.

MS: 208.0731 (M^+); calc. for $C_{11}H_{12}O_4$: 208.0743.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	3(Hz) ^1H
-	-	C-2	163.78	-	s	
H-9	8.90	C-9	176.68	-	s	
H-3	6.10	C-3	121.18	d	d	10.0
H-4	6.95	C-4	149.56	d	d	10.0
-	-	C-4a	45.67	-	s	
H-5(2H)	(2.10-	C-5	31.22	m	t	
H-8(2H)	(2.90	C-8	33.70	m	t	
H-6	5.45	C-6	117.59	m	d	
-	-	C-7	131.49	-	s	
H-8a	5.00	C-8a	75.91	m	d	
H-10(3H)	1.68	C-10	22.95	s	q	

(±)-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-6β-phenylseleno-7α-hydroxy-7β-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid δ-lactone (192)[58] and 6α-hydroxy-7α-methyl-7β-phenylseleno-4aα-carboxylic acid γ-lactone (190b)

Method A

With stirring, triethylamine (550 µl, 3.97 mmol) was added dropwise to a mixture of carboxylic acids (186a) and (186b), (824 mg, 3.96 mmol) in 40 ml of dry methylene chloride, at room temperature, and stirring was continued for 40 mins. The mixture was cooled to -78°C and phenylselenenyl chloride (836 mg, 4.36 mmol) was added slowly over a period of 30 mins. After complete addition, the mixture was stirred at -78°C for a further 30 mins, then allowed to warm to room temperature; all of the phenylselenenyl chloride was observed to have disappeared. Evaporation to dryness and purification by dry column flash chromatography gave 755 mg (52.0%) of a mixture of phenylselenolactones (192) and (190b). The mixture of phenylselenolactones proved to be particularly difficult to separate by chromatographic methods. The later fractions collected during column chromatography were found to be highly enriched in the bicyclo [2.2.2] lactone (192), the major product obtained from phenylselenolactonisation, and only the last few fractions were completely free from the bicyclo [3.2.1] lactone (190b) (IR 1790 cm^{-1}).

Bicyclo [2.2.2] phenylselenolactone (192)

IR (CCl_4): 2640, 1765, 1745, 1385 cm^{-1}.

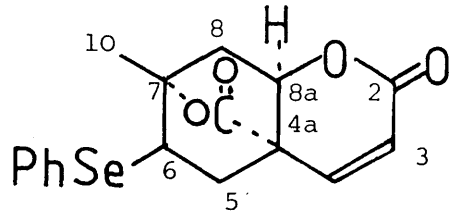
MS:

366.0188 (M^+); calc. for $C_{17}H_{16}O_4$	81.9167 Se :	366.0228.
364.0191 (M^+);	79.9165 Se :	364.0226
362.0189 (M^+);	77.9174 Se :	362.0235
361.0183 (M^+);	76.9199 Se :	361.0260
360.0130 (M^+)	75.9192 Se :	360.0253

$C_{17}H_{14}O_4Se$ requires C, 56.21; H, 4.43%. Found: C, 56.19; H, 4.67%.

Method B

A solution of the mixture of carboxylic acids (186a) and (186b), (1.01g, 4.86 mmol) in 25 ml of dry methylene chloride was cooled to -78°C, then phenylselenenyl chloride (1.04g, 5.43 mmol) was added slowly over a period of 30 minutes and stirring was carried out at this temperature for 4 hours. The solution was allowed to warm to room temperature: all of the phenylselenenyl chloride had disappeared. Concentration in vacuo and purification by dry column flash chromatography afforded 1.18g (67.0%) of phenylselenolactones (192) and (190b). Full characterisation of (192) showed it to be identical to the phenylselenolactone obtained as the major product from Method A.



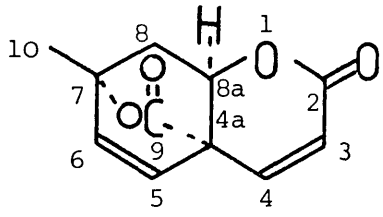
Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	162.10	-	s	
H-3	6.05	C-3	121.62	d	d	9.81
H-4	7.20	C-4	144.39	d	d	9.81
-	-	C-4a	43.1	-	s	
H-5(2H)	2.18 $H_{5(\beta)}$ (2.15-(2.60	C-5	(30.5 ((	m	t	$H_{5(\beta)}H_6$=8.5
H-8(2H)	((2.54 ($H_{8(\beta)}$	C-8	(33.8	m	t	$H_{8(\alpha)}H_{8(\beta)}$= 15.16
H-6	3.5	C-6	43.67	dd	d	H_6H_5=8.5,10.5 $H_6H_{8(\alpha)}$=2.25
-	-	C-7	85.12	-	s	
H-8a	4.65	C-8a	74.20	dd	d	$H_{8a8(\alpha)}$=10.0, $H_{8a}H_{8(\beta)}$=4.98 $H_{8a}H_{5(\alpha)}$=1.60
-	-	C-9	170.00	-	s	
H-10(3H)	1.43	C-10	24.41	s	q	
-	-	ArC	127.91	-	s	
Ar-H(3H)	7.30	2xAr(C-H) 2xAr(C-H)	128.50 129.50	m	d d	
Ar-H(2H)	7.45	1xAr(C-H)	134.72	m	d	

(±)-(4aα,8aα)-4a,7,8,8a-tetrahydro-7α-hydroxy-7β-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid δ-lactone (193)[58]

To a solution of phenylselenolactone (192), (365 mg, 1.00 mmol) in 20 ml of dry methylene chloride under N_2 was added pyridine (235 µl, 2.90 mmol) dropwide at room temperature and stirring carried out for a few minutes. Then 323 µl (2.85 mmol) of 30% H_2O_2 in 245 µl of water was added dropwise, and stirring continued for 90 minutes. The reaction mixture was poured into 50 ml of ether and washed sequentially with 3 x 30 ml of saturated brine solution, and 30 ml of water. The organic layer was dried and concentrated under vacuum to yield a viscous brown oil. Purification by positive pressure chromatography afforded 170 mg (83.0%) of the bicyclo [2.2.2] octene system (193), as a colourless oil, which readily eliminated CO_2 in the mass spectrometer.

IR (CCl_4): 1750, 1735, 1390, 1225 cm^{-1}

MS: 162.0672 ($M-CO_2$); calc. for $C_{10}H_{10}O_2$: 162.0688.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	162.39	-	s	
H-3	6.21	C-3	122.62	d	d	H_3H_4=9.82
H-4	7.56	C-4	144.21	d	d	H_4H_3=9.82
-	-	C-4a	48.58	-	s	
H-5	6.01	C-5	128.96	d	d	H_5H_6=7.37
H-6	6.55	C-6	137.98	d	d	H_6H_5=7.63
-	-	C-7	81.17	-	s	
H-8(2H)	1.88Hα 2.58 β	C-8	39.60	dd	t	$H_{8(\alpha)}H_{8(\beta)}$= 14.24
H-8a	4.74	C-8a	73.98	dd	d	$H_{8a}H_{8\alpha}$=8.59 $H_{8a}H_{8\beta}$=2.99
-	-	C-9	162.39	-	s	
H-10(3H)	1.71	C-10	21.98	s	q	

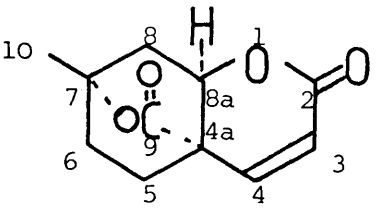
(±)-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-7α-hydroxy-7β-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid δ-lactone (194)[58,61]

To phenylselenolactone (192), (720 mg, 1.98 mmol) in 10 ml of dry toluene was added 1.98 ml (3.96×10^{-2} mmol) of 0.02M solution of azoisobutyronitrile in toluene, followed by tributyl tin hydride (722 µl, 2.86 mmol). The resulting mixture was heated at 110°C for 3 hours in a sealed tube. Concentration of the reaction mixture under reduced pressure and purification by dry column flash chromatography gave 326 mg (79.2%) of the reduced bicyclo [2.2.2] octane system (194). b.p. 120-125°C (Kugelrohr)/0.1 mm Hg.

IR (CCl_4): 2970, 1755, 1745, 1390, 1265, 1255 cm^{-1}.

MS: 208.0736 (M^+); calc. for $C_{11}H_{12}O_4$: 208.0743

$C_{11}H_{12}O_4$ requires C, 63.45; H 5.81%. Found: C, 63.31, H, 5.79%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	162.60	-	s	
H-3	6.05	C-3	121.37	d	d	H_3H_4=9.82
H-4	7.30	C-4	146.08	d	d	H_4H_3=9.82
-	-	C-4a	42.20	-	s	
H-5(2H)	(	C-5	32.29	m	t	
	(					
	(1.2-					
	(					
H-6(2H)	(2.8	C-6	22.19	m	t	
	(					
H-8(2H)	(	C-8	37.47	m	t	
-	-	C-7	81.80	-	s	
H-8a	4.65	C-8a	74.52	dd	d	$H_{8a}H_{8\beta}$=4.51
						$H_{8a}H_{8\alpha}$=10.35
-	-	C-9	170.80	-	s	$H_{8a}H_5$=1.42-w
H-10(3H)	1.48	C-10	24.86	s	q	

(±)-(4aα-8aα)-4a,5,6,7,8,8a-hexahydro-6β-iodo-7α-hydroxy-7β-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid δ-lactone (195) and its 6α-hydroxy-7α-methyl-7β-iodo-4aα-carboxylic acid γ-lactone regioisomer (187b)[57].

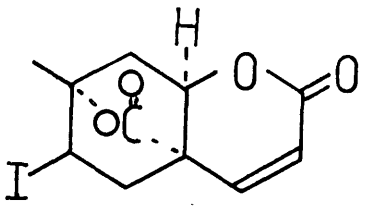
A solution of carboxylic acids (186a) and (186b), (1.13g, 5.43 mmol) in 44 ml of 0.5M aqueous sodium hydrogen carbonate solution was added to a solution containing potassium iodide (3.63g, 21.86 mmol)/iodine (7.23g, 28.49 mmol)/22 ml of water. The resulting mixture was allowed to stand in the dark for 48 hours with occasional shaking. The reaction mixture was then extracted thoroughly with methylene chloride, and the combined organic extracts washed sequentially with 2 x 40 ml of 50% aqueous sodium thiosulphate solution and 40 ml of brine. The organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford 1.01g of crude product as a yellow solid. Purification by dry column flash chromatography gave 0.845g (46.6%) of a mixture of iodolactones (195) and (187b). The later chromatographic fractions yielded pure iodolactone (195). Recrystallisation from ethyl acetate afforded white crystals, m.p. (decomposition) 175-178°C.

Bicyclo [2.2.2] lactone (195)

IR (CCl_4): 1760, 1740, 1245 cm^{-1}.

MS: 333.9705 (M^+); calc. for $C_{11}H_{11}O_4I$: 333.9709; base peak at 207.0658 (M^+-I), calc. for $C_{11}H_{11}O_4$: 207.0665.

$C_{11}H_{11}O_4I$ requires C, 39.54; H, 3.29%. Found: C, 39.54; H, 2.96%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	161.82	-	s	
H-3	6.05	C-3	122.00	d	d	H_3H_4=11.0
H-4	7.15	C-4	143.70	d	d	H_4H_3=11.2
-	-	C-4a	43.39	-	s	
H-5(2H)	(2.5-	C-5	(33.82,	m	t	
	(		(			
	(		(35.81			
H-8(2H)	(2.8	C-8		m	t	
H-6	4.20	C-6	22.29	dd	d	H_6H_5=9.0
-	-	C-7	84.31	-	s	
H-8a	4.65	C-8a	74.35	dd	d	$H_{8a}H_{8\beta}$=7.0, 10.1
H-9	-	C-9	169.52	-	s	
H-10(3H)	1.62	C-10	26.31	s	q	

(±)-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-7α-hydroxy-7β-methyl-2H-1-benzopyran-2-one-4aα-carboxylic acid δ-lactone (194)'[58,61]

To iodolactone (195), (145 mg, 0.43 mmol) in 2.5 ml of toluene was added 430 µl (8.6×10^{-3} mmol) of a 0.02 M solution of azoisobutyronitrile in toluene, followed by tributyl tin hydride (168 µl, 0.62 mmol). The resulting mixture was heated at 110°C for 3 hours in a sealed tube. Concentration under reduced pressure and purification by positive pressure flash column chromatography gave 60 mg (67.1%) of the reduced bicyclo [2.2.2] octane system (194)', which was identical to the compound (194) obtained from reduction of the corresponding phenylselenolactone (192).

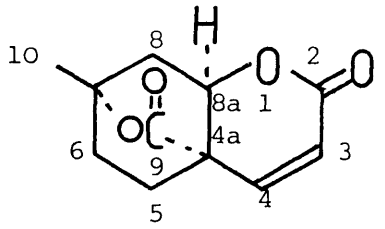
δ-lactone (194)'

IR (CCl_4): 2970, 1765, 1755, 1745, 1390, 1240 cm^{-1}

MS: 208 (M^+).

$C_{11}H_{12}O_4$ requires: C, 63.45; H, 5.81%.

Found: C, 63.35; H, 5.75%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-		C-2	162.58	-	s	
H-3	6.04	C-3	121.33	d	d	H_3H_4=9.83 H_4H_3=9.82
H-4	7.30	C-4	146.04	d	d	
-	-	C-4a	42.19	-	s	
H-5(2H)	(((1.87-	C-5	32.26	m	t	
H-6(2H)	(2.45	C-6	22.17	m	t	
H-8(2H)	((	C-8	37.44	m	t	
-	-	C-7	81.77	-	s	
H-8a	4.65	C-8a	74.48	dd	d	$H_{8a}H_{8\beta}$=4.51 $H_{8a}H_{8\alpha}$=10.35
-	-	C-9	170.89	-	s	$H_{8a}H_5$=1.42
H-10(3H)	1.47	C-10	24.83	s	q	

(±)-Methyl-(4aα,8aα)-3,4,4a,5,8,8a-hexahydro-4,7-dimethyl-2H-1-benzopyran-2-one 4aα-carboxylate[50] (158)

Methyl lithium-lithium bromide complex (1.2M in ether) was added slowly to a suspension of cuprous iodide (1.90g, 9.97 mmol) in 45 ml of dry ether at 0°C until the initially formed yellow precipitate had just disappeared. The resulting clear solution was stirred at 0°C for 5 minutes, then the 4:1 mixture of Diels-Alder adducts (157a) and (157b), (1.80g, 8.10 mmol) in 10 ml of ether was added dropwise. The mixture was stirred at 0°C for 45 minutes, then poured into 50 ml of ice-cold saturated ammonium chloride solution and filtered through Celite. The separated aqueous layer was extracted three times with ether and the combined organic extracts were dried and concentrated *in vacuo*. Purification by dry column flash chromatography yielded 1.51g (78.0%) of the conjugate addition product (158), (as a mixture of regioisomers, with mainly one methyl epimer being obtained), as white needles which were recrystallised from ether,

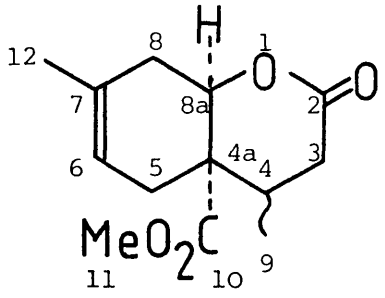
m.p. 79-81°C.

IR(CCl_4): 2950, 1755, 1735, 1445, 1200 cm^{-1}.

MS: 238.1209 (M^+); calc. for $C_{13}H_{18}O_4$: 238.1213.

$C_{13}H_{18}O_4$ requires C, 65.52; H, 7.61%.

Found: C, 65.45; H, 7.60%.



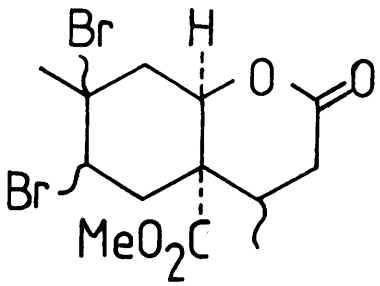
Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	171.30	-	s	
H-3(2H)	(	C-3	(30.04	(broad	t	
	(		(	(		
	(1.95		(	(		
	(		(	(		
H-5(2H)	(	C-5	(34.08	(multi-	t	
	(		(	plet		
	(-2.70		(35.89			
	(					
H-8(2H)	(	C-8			t	
	(					
H-4	(	C-4	33.03		d	
-	-	C-4a	47.74	-	s	
H-6	5.15	C-6	118.47	broad m	d	
-	-	C-7	130.84	-	s	
H-8a	4.80	C-8a	74.20	dd	d	
H-9(3H)	0.95	C-9	17.93	d	q	$9H_2$
-	-	C-10	173.31	-	s	
H-11(3H)	3.60	C-11	51.89	s	q	
H-12(3H)	1.55	C-12	22.92	s	q	

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-4,7-dimethyl-6,7-dibromo-2H-1-benzopyran-2-(4H)-one-4aα-carboxylate (197)[65]

Bromine was added dropwise to a stirred solution of a mixture of cuprate products (158a) and (158b), (2.01g, 8.44 mmol) in 65 ml of ether at $0^{o}C$, until a permanent brown colouration was observed. The reaction mixture was poured into 100 ml of ethyl acetate and washed with saturated sodium thiosulphate solution to remove excess bromine. The organic layer was dried and concentrated under reduced pressure to yield 3.17g (94.3%) of a 1:1 mixture of the two possible trans-1,2-dibromides (197a) and (197b) as a yellow oily solid.

IR (CCl_4): 1765, 1755 cm^{-1}.

MS: 319 (M^+-Br); 317 (M^+-Br).



Br-C-6(α), Br-C-7(β)

Br-C-6(β), Br-C-7(α)

Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	(172.37 (171.57 (170.72	-	s	
—	—	C-10	(168.23	-	**S**	
H-3(2H) H-5(2H) H-8(2H)	(2.10- (2.98 (	C-3 C-5 C-8	(34.24 (35.61 (35.64 (38.45 (44.29	m	t t t	
H-4		C-4	35.64	m	d	
-	-	C-4a	42.04 56.50	-	s	
H-6(Br-α)	4.46	C-6	58.6	dd	d	H_5H_6=3.9, 12.1
H-6(Br-β	4.58			dd	d	H_5H_6=4.6,8.10
-	-	C-7	61.73 64.62	-	s	
H-8a(7Br-β)	4.85	C-8a	73.36	dd	d	$H_{8a}H_{8\beta}$=6.1 $H_{8a}H_{8\alpha}$=2.7
H-8a(7Br-α)	4.98		74.90	dd	d	$H_{8a}H_{8\beta}$=4.5 $H_{8a}H_{8\alpha}$=7.3

H-9(3H)	0.95, 1.05	C-9	15.83, 16.42	d	q	7.0
H-11(3H)	3.74 3.81	C-11	52.60 52.72	s	q	
H-12(3H)	1.93, 2.00	C-12	28.53 29.80	s	q	

(±)-Methyl-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6-acetoxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (198)[65]

A mixture of dibromides (197a) and (197b), (1.67g, 4.20 mmol) was headed at 110°C for 48 hours in a stirred solution of glacial acetic acid (19 ml, 332.50 mmol), acetic anhydride (3.5 ml. 37.05 mmol) and anhydrous sodium acetate (5.80g, 70.70 mmol). The reaction mixture was cooled, evaporated to dryness and the solid residue dissolved in 40 ml of water. This aqueous solution was extracted thoroughly with 3 x 50 ml of ethyl acetate and the combined organic extracts were washed sequentially with 2 x 20 ml of water, and 2 x 40 ml of aqueous sodium hydrogen carbonate solution. Drying and subsequent evaporation afforded a brown oil. Purification of the residue by dry column flash chromatography yielded 574 mg (46.2%) of the desired acetates as an inseparable 1:1 mixture of α-acetoxy compound (198a) and β-acetoxy compound (198b); b.p. 170-200°C (Kugelrohr)/0.015 mm Hg. The desired acetates were preceded from the column by 690 mg (41.4%) of some crystalline dibromide (197c), which was recrystallised from ethyl acetate/pentane; m.p. 130-132°C. Attempts to convert this recovered dibromide into the desired acetates (198a) and (198b) by repeating the acetolysis procedure proved to be unsuccessful with starting material being recovered.

A more polar, rearranged isomeric product (199), (106 mg, 8.5%), was also isolated, bp 170-200°C (Kugelrohr)/0.015 mm Hg.

1:1 mixture of acetates (198a) and (198b)

IR (CCl_4): 2950, 1750, 1740, 1230 cm^{-1}.

MS: 254.1160 ($M-CH_2=C=O$); calc. for $C_{13}H_{18}O_5$. 254.1162.

$C_{15}H_{20}O_6$ requires C, 60.80; H, 6.82%.

Found: C, 60.85; H, 6.81%.

Acetate (199).

IR (CCl_4): 2950, 1745 (broad), 1235 (broad) cm^{-1}.

MS: 296.1247 (M^+); calc. for $C_{15}H_{20}O_6$: 296.1269.

$C_{15}H_{20}O_6$ requires C, 60.80: H, 6.82%.

Found: C, 60.57; H, 6.88%.

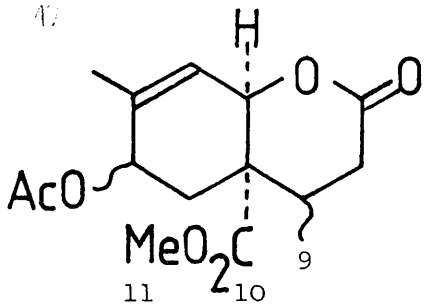
Dibromide (197c)

IR (CCl_4): 2950, 1765, 1755 cm^{-1}.

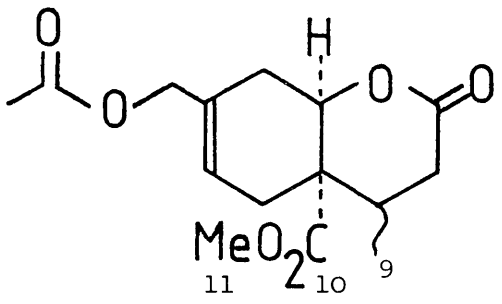
MS: 319 (M^+-Br)

$C_{13}H_{18}O_4Br_2$ requires C, 39.20; H, 4.56; Br, 40.16%.

Found: C, 39.12; H, 4.59; Br, 40.34%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
-	-	C-2	(170.17	-	s
-	-	C-10	(170.23	-	s
-	-	C=O,Ac	(171.52	-	s
H-3(2H)	(2.20-	C-3	(31.72	m	t
H-5(2H)	(2.70	C-5	(32.43	m	t
H-4	(	C-4	34.54	m	d
-	-	C-4a	47.36	-	s
H-6	5.15, 5.35	C-6	68.52	broad m	d
-	-	C-7	139.81	-	s
H-8	5.64	C-8	123.11	m	d
H-8a	4.97	C-8a	78.85	dd	d
H-9(3H)	0.95	C-9	16.62	d	q
H-11(3H)	3.68	C-11	51.86	s	q
H-12(3H)	1.66	C-12	20.62	s	q
CH_3,Ac (3H)	2.05	CH_3,Ac	19.14	s	q



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
-	-	C-2	170.66	-	s
-	-	C-10	171.21	-	s
-	-	C-13	172.84	-	s
H-3(2H)	(2.20	C-3	35.69	m	t
H-5(2H)	(2.80	C-5	(30.07	m	t
H-8(2H)	(	C-8	(29.62	m	t
H-4	(	C-4	33.11	m	d
-	-	C-4a	47.70	-	s
H-6	5.58	C-6	122.95	m	d
-	-	C-7	129.82	-	s
H-8a	4.90	C-8a	73.39	dd	d
H-9(3H)	1.00	C-9	17.90	d	q
H-11(3H)	3.70	C-11	52.01	s	q
H-12(2H)	4.45	C-12	67.19	s	t
H-14(3H)	2.05	C-14	20.85	s	q

(±)-Methyl-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6α-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (200a) and its 6β-hydroxy-epimers (200b).

A 1:1 mixture of acetates (198a) and (198b), (830 mg, 2.80 mmol) in 20 ml of dry methanol, was stirred with anhydrous potassium carbonate (1.34g, 9.71 mmol) at room temperature, for 1.5 hours. The reaction mixture was then cooled to $0^{\circ}C$, acidified with 1N HCl and salted out with sodium chloride. The resulting aqueous layer was extracted with 3 x 40 ml of ether and the combined ethereal extracts were dried and concentrated in vacuo to afford an oily residue. Purification by dry column flash chromatography gave 226 mg (31.8%) of the less-polar, β-allylic alcohol (200b) as a colourless oil. The more polar α-allylic alcohol (200a) was obtained as a white solid (217 mg; 30.5%), which recrystallised from ethyl acetate as white crystals, m.p. (decomposition) 142-157$^{\circ}C$.

β-allylic alcohol (200b)

IR (CCl_4): 3500 (broad), 2925, 1760, 1735 cm^{-1}.

MS: 254.1146 (M^+); calc. for $C_{13}H_{18}O_5$: 254.1162.

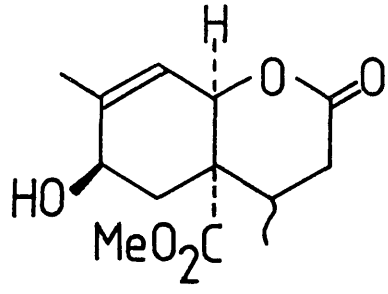
α-allylic alcohol (200a)

IR (CCl_4): 3490 (broad), 2925, 1760, 1735, 1435 cm^{-1}.

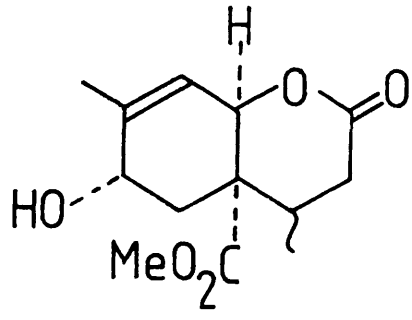
MS: 236.1058 ($M-H_2O$); calc. for $C_{13}H_{16}O_4$: 236.1057.

$C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%.

Found: C, 61.26; H, 7.09%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	(172.05	-	s	
-	-	C-10	(172.33	-	s	
H-3(2H)	(1.90-	C-3	(34.61	m	t	
H-5(2H)	(2.70	C-5	35.57	m	t	
H-4	(	C-4	35.50	m	d	
-	-	C-4a	47.72	-	s	
H-6	4.10	C-6	66.71	broad m	d	
-	-	C-7	144.67	-	s	
H-8	5.53	C-8	119.24	dd	d	
H-8a	4.98	C-8a	73.99	d	d	
H-9(3H)	0.96	C-9	15.86	d	q	9.0
H-11(3H)	3.67	C-11	52.03	s	q	
H-12(3H)	1.80	C-12	19.00	s	q	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
-	-	C-2	(171.52	-	s
-	-	C-10	(174.22	-	s
H-3(2H)	(	C-3	(34.96	m	t
H-5(2H)	(1.80-2.60	C-5	(35.03	m	t
H-4	(	C-4	33.53	m	d
-		C-4a	47.04	-	s
H-6	4.00	C-6	66.04	broad d	d
-	-	C-7	142.03	-	s
H-8	5.56	C-8	120.00	dd	d
H-8a	5.10	C-8a	75.02	d	d
H-9(3H)	1.03	C-9	15.73	d	q
H-11(3H)	3.72	C-11	52.04	s	q
H-12(3H)	1.85	C-12	20.02	s	q

(±)-Methyl-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6-keto-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (201)[88]

A 1:1 mixture of allylic alcohols (200a) and (200b), (230 mg, 0.90 mmol) in 22 ml of dry methylene chloride was stirred under N_2 with pyridinium dichromate (574 mg, 1.53 mmol) for 24 hours at room temperature. The reaction mixture was filtered through Celite and then evaporated to dryness. The resulting residue was dissolved in ether, re-filtered through Celite, and then concentrated in vacuo. Dry column flash chromatography afforded 192 mg (84.7%) of crystalline enone (201), which was observed to be u.v. active. Recrystallisation from ether gave white needles, m.p. 84°C.

Enone (201)

u.v. λ max at 240 nm in EtOH.

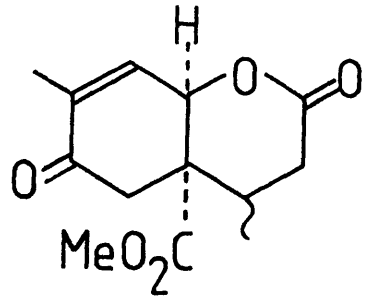
IR (CCl_4): 2950, 1755, 1735, 1695 (sharp,strong) cm^{-1}.

MS: 252.1001 (M^+); calc. for $C_{13}H_{16}O_5$: 252.1005.

$C_{13}H_{16}O_5$ requires C, 61.90; H, 6.40%.

Found: C, 62.09; H, 6.44%.

Enone (201) could not be stereoselectively reduced to give α-allylic alcohol (200a) as the exclusive product. Using sodium borohydride, in the presence of cerium trichloride[67] afforded a number of products, none of which was the desired α-allylic alcohol. It was suspected that enone (201) underwent non-selective hydride reduction.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-		C-2	(170.53	-	s	
-		C-10	(171.63	-	s	
H-3(2H)	(2.50-	C-3	34.83	m	t	
H-5(2H)	(3.00	C-5	41.62	m	t	
H-4	(	C-4	33.62	m	d	
-	-	C-4a	49.95	-	s	
-	-	C-6	195.00	-	s	
-	-	C-7	138.70	-	s	
H-8	6.57	C-8	136.67	dd	d	
H-8a	5.31	C-8a	74.37	broad d	d	4.20
H-9(3H)	1.10	C-9	15.37	d	q	6.95
H-11(3H)	3.60	C-11	52.65	s	q	
H-12	1.78	C-12	15.67	s	q	

(±)-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6α-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylic acid (202).

α-Hydroxyester (200a), (130 mg, 0.51 mmol) was stirred overnight in sodium hydroxide solution (10 ml, 2N, 20 mmol). The basic solution was acidified with 1N HCl, salted out with sodium chloride and extracted with ethyl acetate. The organic extracts were dried out and concentrated *in vacuo* to afford 116 mg (94.8%) of α-hydroxy acid (202) as an oil.

(±)-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6α-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylic acid γ-lactone (203)[64]

A solution of unpurified α-hydroxy acid (202), (116 mg, 0.48 mmol) in 40 ml of dry THF was stirred overnight at room temperature with triphenylphosphine (188 mg, 0.72 mmol) and dipyridyl disulphide (160 mg, 0.73 mmol). Removal of the solvent in vacuo and purification of the residue by positive pressure chromatography afforded 68 mg (63.8%) of lactone (203) as a white crystalline solid. Recrystallisation from chloroform and a drop of pentane gave white needles, mp 118°C.

Bicyclo [3.2.1] lactone (203).

IR (CCl_4): 2970, 1790, 1775, 1755, 1685 cm^{-1}.

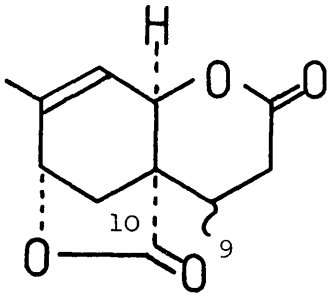
MS: 222.0870 (M^+); calc. for $C_{12}H_{14}O_4$: 222.0892.

$C_{12}H_{14}O_4$ requires C, 64.84; H, 6.35%.

Found: C, 64.66, H, 6.22%.

That hydroxy acid (202) undergoes lactonisation to afford bicyclo [3.2.1] lactone (203) proves that the 6-hydroxyl is the α-configuration.

That lactone (203) apparently shows three carbonyl absorptions in the infra-red region is not uncommon[68]. γ-lactone (204) reportedly showed three infra-red absorptions at 1800 (shoulder), 1770 and 1735 (shoulder).



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	170.59	-	s	-
-	-	C-10	175.45	-	s	-
H-3(2H)	(2.30-	C-3	35.67	m	t	
H-5(2H)	(2.70	C-5	36.68	m	t	
H-4	(	C-4	31.49	m	d	
-	-	C-4a	46.11	-	s	-
H-6	4.61	C-6	72.44	dd	d	H_6H_5=3.30, 5.20 H_6H_8=1.60-w
-	-	C-7	143.04	-	s	-
H-8	5.62	C-8	121.09	dd	d	3.70, H_8H_6=1.70-w
H-8a	4.82	C-8a	73.36	dd	d	$H_{8a}H_8$=3.65 $H_{8a}H_{5\alpha}$=1.70-w
H-9(3H)	1.40	C-9	14.70	d	q	7.50
H-11(3H)	1.95	C-11	21.19	s	q	

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-6α,7α-hydroxy-4,7β-dimethyl-2H-1-benzopyran-2-(4-H)-one-4aα carboxylate (205)[69]

A solution of N-methylmorpholine-N-oxide (596 mg, 5.09 mmol) in 28 ml of acetone and 14 ml of water was cooled to 0°C, and 2.47 ml (0.097 mmol) of a 0.039M solution of osmium tetroxide in t-butanol was added. A solution of the mixture of cuprate products (158a) and (158b), (1.01g, 4.24 mmol) in 10 ml of acetone was rapidly added dropwise and stirring continued at 0°C for 8 hours. The reaction mixture was then allowed to warm to room temperature and stirred overnight. A slurry of sodium dithionite (845 mg) and fluorosil (3.60g) was added and stirring continued for 30 mins. The mixture was filtered through Celite, acidified to pH 7 with 1N HCl and concentrated in vacuo to remove acetone. The aqueous solution was re-acidified to pH2, salted out with sodium chloride and extracted thoroughly with ethyl acetate. Drying of the combined organic extracts and concentration under reduced pressure afforded 941 mg (81.6%) of white solid, which was recrystallised from methanol, m.p. (decomposition) 188-201°C.

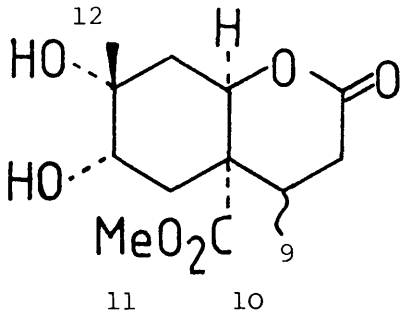
Mixture of diols (205a) and (205b)

IR (nujol mull): 3450 (broad), 2940 (strong), 2550, 1710, 1510 cm^{-1}.

MS: 254 ($M-H_2O$); 236 ($M-2H_2O$).

$C_{13}H_{20}O_6$ requires C, 57.34; H, 7.40%.

Found: C, 57.31; H, 7.24%.



(^{1}H and ^{13}C-nmr in CD_3OD.)

Proton No.	δppm ^{1}H	Carbon No.	δppm ^{13}C	Multiplicity ^{1}H	Multiplicity ^{13}C	J(Hz) ^{1}H
-	-	C-2	172.69	-	s	
H-4	(	C-4	26.53	m	d	
H-3(2H)	((1.80-	C-3	33.27	m	t	
H-5(2H)	((2.70	C-5	(36.10	m	t	
H-8(2H)	((	C-8	(41.57	m	t	
-	-	C-4a	46.45	-	s	
H-6(βH)	3.34	C-6	73.39	dd	d	
H-6(OH)	(((4.75					
H-7(OH)	((	C-7	72.22	s	s	
H-8a	4.95	C-8a	79.37	dd	d	8.5,12.3
H-9(3H)	1.05	C-9	15.18	d	q	6.8
-	-	C-10	174.59	-	s	
H-11(3H)	3.75	C-11	52.48	s	q	
H-12(3H)	1.25	C-12	27.89	s	q	

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-6α-t-butyldimethylsilyloxy-4-7β-dimethyl-7α-hydroxy-2H-1-benzopyran-2-(4H)-one-4aα-carboxylate (206a)[70]

A solution of imidazole (632 mg, 9.28 mmol) in 3 ml of dry DMF was added dropwise to crude diols (205a) and (205b), (626 mg, 2.30 mmol) in 10 ml of DMF under Ar. Stirring was continued for 5 mins, then a solution of t-butyldimethylsilyl chloride (695 mg, 4.60 mmol) in 3 ml of DMF was added dropwise at room temperature and stirring continued overnight. The reaction mixture was then poured into 120 ml of ethyl acetate, washed with 2 x 40 ml of water and dried. Concentration under reduced pressure and purification by dry column flash chromatography gave 641 mg (72.2%) of the cis-6α-t-butyldimethylsilyloxy-7α-hydroxy compound (206a) as a viscous oil; b.p. 210-220°C (Kugelrohr)/0.2 mm Hg; along with 100 mg (11.2%) of the cis-6β-t-butyldimethylsilyloxy-7β-hydroxy compound (206b). The approximately 6:1 ratio of silyloxy alcohols obtained reflects the ratio of the corresponding cis-diols (205a) and (205b) obtained from osmylation.

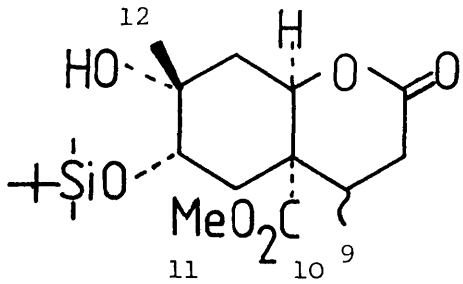
α-Silyloxy alcohol (206a)

IR (CCl_4): 3580 (weak, 3° alcohol), 2950, 1735 (broad), 1240 cm^{-1}.

MS: 329.1425 (M-t-butyl); calc. for $C_{15}H_{25}O_6Si$: 329.1418.

$C_{19}H_{34}O_6Si$ requires C, 59.03; H, 8.87%.

Found: C, 58.81; H, 8.92%.



Proton No.	ppm ^1H	Carbon No.	ppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
-	-	C-2	169.60	-	s
H-3(2H)	1.90-	C-3	40.01	m	t
H-4		C-4	27.41	m	d
H-5(2H)		C-5	35.33	m	t
H-8(2H)		C-8	32.53	m	t
-	-	C-4a	47.60	-	s
H-6(βH)	3.75	C-6	71.19	dd	d
-	-	C-7	71.65	-	s
H-8a	4.85	C-8a	77.21	dd	d
H-9(3H)	1.05	C-9	15.40	d	q
-	-	C-10	172.68	-	s
H-11(3H)	3.70	C-11	52.21	s	q
H-12(3H)	1.20	C-12	26.31	s	q
t-butyl (9H)	0.90	CH_3-+	17.94	s	q
-		qC-+	25.73	-	s

(±)-Methyl-(4aα,8aα)-3,4,4a,5,8,8a-hexahydro-6-t-butyldimethylsilyloxy-4,7-dimethyl-2H-benzopyran-2-one-4aα-carboxylate (208)[31]

A solution of silyl ether (206a), (375 mg, 0.97 mmol) in dry pyridine (8.6 ml, 106.50 mmol) was heated under N_2 in an oil-bath at 72°C. Phosphorous oxychloride (72µl, 0.77 mmol) was added and stirring continued at this temperature for 14 hours. The reaction mixture was cooled, poured into 100 ml of ethyl acetate and washed sequentially with 2 x 40 ml of water and 2 x 25 ml of saturated aqueous $CuSO_4$ solution. After drying, concentration in vacuo afforded an oily residue. Purification by dry column flash chromatography yielded 156 mg (43.7%) of silyl enol ether (208), as the exclusive product of elimination, together with 178 mg (47.5%) of starting material (206a).

Silyl enol ether (208) was recrystallised from ether, to give white needles, m.p. 104-105°C.

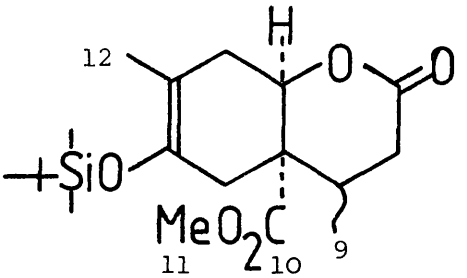
Silyl enol ether (208)

IR (CCl_4): 2950, 2930, 1750, 1735, 1690 cm^{-1}.

MS: 368.2025 (M^+); calc. for $C_{19}H_{32}O_5Si$: 368.2019; base peak at 311.1322 (M-t-butyl): Calc. for $C_{15}H_{23}O_5Si$: 311.1313.

$C_{19}H_{32}O_5Si$ requires C, 61.92; H, 8.76%.

Found: C, 61.71; H, 8.73%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	171.28	-	s	
H-4	(	C-4	32.99	m	d	
H-3(2H)	(2.00-	C-3	(33.67	m	t	
H-5(2H)	(2.80	C-5	(34.48	m	t	
H-8(2H)	(	C-8	(35.68	m	t	
-	-	C-4a	49.32	-	s	
-	-	C-6	139.58	-	s	
-	-	C-7	107.31	-	s	
H-8a	4.80	C-8a	73.55	t	d	
H-9(3H)	1.00	C-9	15.58	d	q	8.0
-	-	C-10	172.63	-	s	
H-11(3H)	3.70	C-11	51.84	s	q	
H-12(3H)	1.52	C-12	17.76	s	q	
+,9H	0.90	CH_3-+	25.65	s	q	
-	-	qC-+	18.00	-	s	

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-6α-t-butyldiphenylsilyloxy-7α-hydroxy-4,7β-dimethyl-2H-1-benzopyran-2-(4H)-one-4aα-carboxylate (209)[71]

To a solution of crude diol (205), (2.00g, 7.35 mmol) in 30 ml of dry DMF under Ar, was added dropwise a solution of imidazole (3.00g, 44.00 mmol) in 5 ml of DMF, at room temperature. Stirring was continued for 5 mins, then t-butyldiphenylsilyl chloride (6.0 ml, 23.13 mmol) was added slowly and the reaction mixture was stirred overnight. It was then poured into 200 ml of ethyl acetate, washed with 3 x 45 ml of water and the organic layer dried. Concentration and purification by dry column flash chromatography afforded 2.24g (60.0%) of (209a) as a white solid, which was recrystallised from diethyl ether to give white plates, m.p. 156-158°C: 352 mg (9.4%) of isomer (209b) was also isolated.

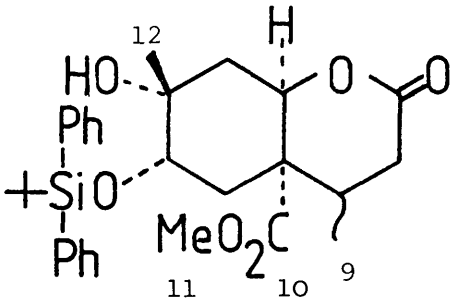
α-silyloxy alcohol (209a)

IR (CCl_4); 3580 (weak), 2960, 2930, 1740, 1240 cm^{-1}.

MS: 453.1742 (M-t-butyl); calc. for $C_{25}H_{29}O_6Si$: 453.1740.

$C_{29}H_{38}O_6Si$ requires C, 68.20; H, 7.50%.

Found C, 68.18; H, 7.48%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	169.60	-	s	
H-3(2H)	(	C-3	40.03	m	t	
H-4	(1.80-	C-4	27.71	m	d	
H-5(2H)	(2.50	C-5	35.19	m	t	
H-8(2H)	(	C-8	32.20	m	t	
-	-	C-4a	47.87	-	s	
H-6(β)	3.72	C-6	72.53	dd	d	
-	-	C-7	72.08	-	s	
H-8a	4.90	C-8a	77.10	dd	d	
H-9(3H)	1.10	C-9	14.73	d	q	7.8
-	-	C-10	172.49	-	s	
H-11(3H)	3.65	C-11	52.00	s	q	
H-12(3H)	1.18	C-12	26.01	s	q	
+,9H	1.10	CH_3,+	27.02	s	q	
-	-	9C+	19.56	-	s	
Ar(4H)	7.70	ArC	127.81, 127.91,	m	d,s	
Ar(6H)	7.45		130.00, 135.91	m	d	

(±)-Methyl-(4aα,8aα)-3,4,4a,5,6,8a-6α-t-butyldiphenylsilyloxy-4,7β-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (210) and (±)-Methyl-(4aα,8aα)-3,4,4a,5,8,8a-6-t-butyldiphenylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (211)[31]

A solution of silyl alcohol (209a), (2.21g, 4.34 mmol) was placed in an oil-bath at 82°C under Ar, and phosphorous oxychloride (350 µl, 3,74 mmol) was added dropwise, and the mixture stirred at this temperature overnight. After cooling, it was poured into 400 ml of ethyl acetate, and washed sequentially with 2 x 150 ml of water and 2 x 100 ml of saturated aqueous $CuSO_4$ solution. Drying of the organic layer and concentration in vacuo yielded an oily brown residue. Purification by dry column flash chromatography afforded 8.70 mg (40.7%) of an inseparable 1:1 mixture of allyl silyl ether (210) and silyl enol ether (211), as a very viscous oil; 830 mg (37.0%) of starting silyl alcohol (209a) was also recovered.

Attempts to separate compounds (210) and (211) by column chromatography were unsuccessful.

Distillation of the 1:1 isomeric mixture of allylsilyl ether (210) and silyl enol ether (211) also failed to separate both compounds. Distillation at 235-240°C at 0.3 mm Hg; glass-like solid.

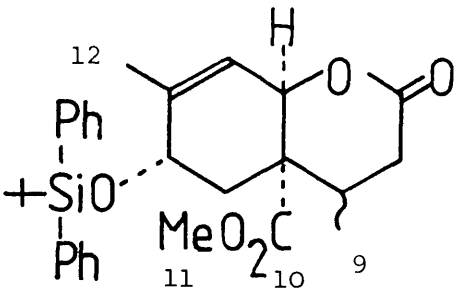
Allyl silyl ether (210) and Silyl enol ether (211)

IR (CCl_4): 2950, 2930, 1750, 1735, 1690 cm^{-1}.

MS: 492.2335 (M^+); calc. for $C_{29}H_{36}O_5Si$: 492.2341; base peak at 435.1645 (M-t-butyl); calc. for $C_{25}H_{27}O_5Si$: 435.1635.

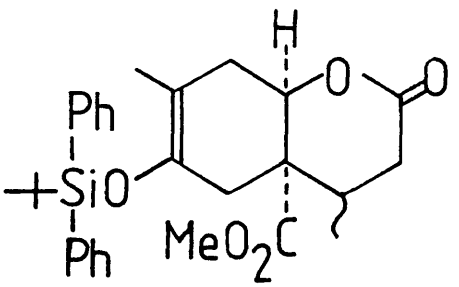
$C_{29}H_{36}O_5Si$ requires C, 70.71; H, 7.37%.

Found: C, 70.66; H, 7.42%.



NMR data for (163)

Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	169.32	-	s	
H-4	(1.10	C-4	27.49	m	d	
H-3(2H)	(2.50	C-3	(35.19	m	t	
H-5(2H)	(	C-5	(35.65	m	t	
-	-	C-4a	47.36	-	s	
H-6(β)	4.09	C-6	68.21	m	d	
-	-	C-7	139.81	-	s	
H-8	5.50	C-8	122.62	d	d	
H-8a	5.25	C-8a	78.12	d	d	3.0
H-9(3H)	0.75	C-9	15.60	d	q	7.0
-	-	C-10	172.23	-	s	
H-11(3H)	3.63	C-11	51.68	s	q	
H-12(3H)	1.75	C-12	19.75	s	q	
+,9H	1.15	+,CH_3	26.90	s	q	
		qC,+	19.36	-	s	
ArH	7.70,	(ArC	127.66,	m	s,d	
	7.34		129.80			
			132.83			
			135.11			



NMR data for

Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1J
-	-	C-2	170.74		s	
H-4	(1.10-	H-4	(32.22		d	
H-3(2H)	(2.50	C-3	(33.70		t	
H-5(2H)	(	C-5	(33.89		t	
H-8(2H)	(	C-8	(34.98		t	
-	-	C-4a	48.70		s	
-	-	C-6	139.47		s	
-	-	C-7	106.47		s	
H-8a	4.67	C-8a	73.42	dd	d	c,4
H-9(3H)	0.54	C-9	14.76	d	q	6.5Hz
-	-	C-10	172.44	-	s	
H-11(3H)	3.50	C-11	53.69	s	q	
H-12(3H)	1.65	C-12	17.49	s	q	
+,9H	1,15	CH_3,+	26.42	s	q	
-		qC,+	19.29	-	s	
	7.34	Arc	128.90	m	s	
ArH(10H)	7.70					

Although the ^{1}H- and ^{13}C-n.m.r. data is for a 1:1 mixture of compounds (210) and (211), the signals from the mixture have been assigned individually to allyl silyl alcohol (210) and silyl enol ether (211) by comparing with the respective ^{1}H- and ^{13}C-n.m.r. spectra for allyl alcohol (200a) and silyl enol ether (208), which were determined on pure single compounds.

(±)-Methyl-(4aα,8aα)-3,4,4a,5,6,8a-hexahydro-6α-hydroxy-4,7-dimethyl-2H-1-benzopyran-2-one-4aα-carboxylate (200a)'[89]

A solution of a 1:1 mixture of allyl silyl ether (210) and silyl enol ether (211), (634 mg, 1.29 mmol) in 10 ml of dry THF was treated under Ar with anhydrous Bu^n_4NF* (2.60 ml, 2.60 mmol) as a 1M solution in THF, and stirring continued overnight at room temperature. The reaction mixture was poured into 100 ml of diethyl ether, washed with 2 x 20 ml of brine, dried and concentrated in vacuo. Positive pressure flash chromatography gave 101 mg (61.6%), (based on starting material) of allylic alcohol (200a)' as a white solid. Recrystallisation from ethyl acetate gave white crystals of allylic alcohol (200a)', m.p. (decomposition) 142-157°C.

α-Allylic alcohol (200a)'

IR (CCl_4): 3500 (broad), 2925, 1760, 1735, 1435 cm^{-1}.

MS: 236.1053 (M-H_2O); Calc. for $C_{13}H_{16}O_4$: 236.1057.

$C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%.

Found: C, 61.42; H, 7.03%.

The α-allylic alcohol (200a), prepared by the aforementioned bromination scheme, was observed to be identical to allylic alcohol (200a)', in every respect.

m.p. (decomposition) of alcohol (200a); 142-157°C.

m.p. (decomposition) of alcohol (200a)'; 142-157°C.

Mixed melting point, (200a) + (200a)'; 142-157°C.

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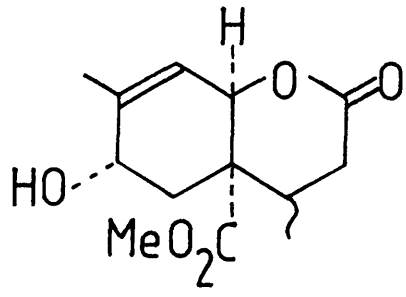
* Anhydrous Bu^n_4NF was prepared by Kugelrohr treating of $Bu^n_4NF.3H_2O$ at 95°C/0.1 mmHg for 2.5 hours.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	(171.23	-	S	
-	-	C-10	(174.39	-	s	
H-3(2H)	(	C-3	(35.15	m	t	
	(		(			
	(1.80-		(			
H-5(2H)	(2.60	C-5	(35.56	m	t	H_5H_6=5.0
H-4	(	C-4	33.56	m	d	
-	-	C-4a	47.19	-	s	
H-6	4.00	C-6	66.31	d	d	H_6H_5=5.0
H-6(OH)	2.45	-	-	s	-	w to H_8=1.6
-	-	C-7	142.16	-	s	
H-8	5.56	C-8	120.16	d	d	
H-8a	5.10	C-8a	75.15	dd	d	$H_{8a}H_8$=5.0
H-9(3H)	1.00	C-9	15.84	d	q	7.0
H-11(3H)	3.72	C-11	52.54	s	q	
H-12(3H)	1.81	C-12	20.10	s	q	

2-Trimethylsilyloxy-buta-1,3-diene (214)[72]

A solution of triethylamine (55.5 ml, 0.40 mol) in 200 ml of dry DMF was stirred under N_2 at 80-90°C. To this was added, dropwise and simultaneously from two pressure-equilibrated dropping funnels, a solution of freshly distilled methyl vinyl ketone (25.30g, 0.36 mol) in 25 ml of DMF, and a solution of trimethylsilyl chloride (51.5 ml, 0.40 mol) in 25 ml of DMF and the resulting mixture was stirred overnight at this temperature. The brown reaction mixture, which supported a precipitate, was twice filtered through Celite and then poured into 300 ml of n-pentane. The organic solution was washed with 1:1 of 5% aqueous sodium hydrogen carbonate solution and the aqueous layer was extracted with 2 x 300 ml of pentane. The combined organic extracts were dried and the pentane removed by fractional distillation, at atmospheric pressure. The remaining brown residue was distilled (33-37°C/water pressure) to afford 17.96g (35.0%) of pure diene (214), whose IR and ^{1}H-n.m.r. spectra were identical with those reported[72].

2-t-Butyldimethylsilyloxy-buta-1,3-diene (217)[90]

A solution of lithium diisopropylamide was prepared *in situ*[91] by dropwise addition of diisopropylamine (8.5 ml , 60.64 mmol) to butyl-lithiu (40 ml of 1.5M solution in hexane, 60.00 mmol), at 0°C under Ar; the resulting gel was stirred at this temperature for 30 mins. The hexane was removed *in vacuo* and 100 ml of dry THF was added to the solid white lithium diisopropylamide. The solution was cooled to -78°C and freshly distilled methyl vinyl ketone (4.20g, 60.00 mmol) was added dropwise and stirring continued for 30 mins. HMPA (10.5 ml, 60.35 mmol) was added to the reaction mixture, at -78°C, followed by a solution of t-butyldimethylsilyl chloride (9.51g, 63.10 mmol) in 60 ml of pentane and the mixture was allowed to warm to room temperature and stirring continued overnight. The mixture was poured into 400 ml of n-pentane and washed sequentially with 2 x 200 ml of water, and 2 x 200 ml of brine. The organic extract was dried over anhydrous sodium sulphate and concentrated under vacuum, without heating, to yield an oily residue. Distillation (66-72°C/water pressure) afforded 7.06g (64.0%) of diene (217), as a colourless liquid; whose I.R. and ^{1}H-n.m.r. spectra were identical with those reported.

(±)-Methyl-(4aα,8aα)-4a,5,8,8a-tetrahydro-7-trimethylsilyloxy-2H-1-benzopyran-2-one-4aα-carboxylate (215a)

A mixture of methyl coumalate (147), (3.60g, 23.38 mmol) in 60 ml of dry toluene, a few crystals of hydroquinone and diene (214), (8.30g, 58.44 mmol) was heated at 110°C for 48 hours in a sealed tube. The reaction mixture was cooled and concentrated under reduced pressure to afford a viscous oil. Attempts to purify the crude Diels-Alder mixture by distillation were unsuccessful; b.p. 150°C (Kugelrohr)/ 0.03 mm Hg; afforded a colourless oil, which readily underwent desilylation on opening to air, to afford the crystalline ketone (216) as the exclusive product. Recrystallisation from chloroform gave the pure ketone as white needles.

Ketone (216)

IR (CCl_4): 2960, 1775 (shoulder), 1740 (broad) cm^{-1}.

MS: 224 (M^+).

$C_{11}H_{12}O_5$ requires C, 58.72; H, 5.35%.

Found: C, 58.86; H, 5.32%.

The Diels-Alder reaction was repeated on the same scale and under identical experimental conditions. Purification of the crude reaction mixture by dry column flash chromatography afforded 3.32g (48.0%) of the desired adduct (215a), as a single crystalline regioisomer. Recrystallisation from ether/pentane gave white crystals, mp. 51-52°C.

The alternative Diels-Alder adduct (215b) (2.90g, 41.9%) was also isolated as a crystalline compound. Recrystallisation from ether gave white needles, m.p. 51-52°C.

Diels-Alder adduct (215a)

IR (CCl_4): 2950, 1735 (broad), 1670 cm^{-1}.

MS: 296.1077 M^+, calc. for $C_{14}H_{20}O_5Si$ 296.1078;

base peak at 281.0841 ($M^+ - CH_3$), calc. for $C_{13}H_{17}O_5Si$ 281.0843.

$C_{14}H_{20}O_5Si$ requires C, 56.75; H, 6.75%.

Found: C, 56.58; H, 6.84%.

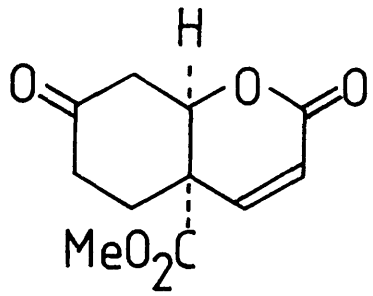
Alternative Diels-Alder adduct (215b)

IR (CCl_4): 2950, 1755, 1725, 1640 cm^{-1}.

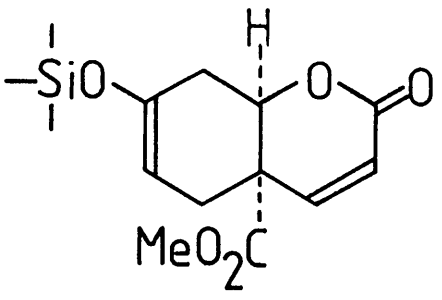
MS: 281.0865 ($M-CH_3$); calc. for $C_{13}H_{17}O_5Si$: 281.0843.

$C_{14}H_{20}O_5Si$ requires C, 56.75; H, 6.75%.

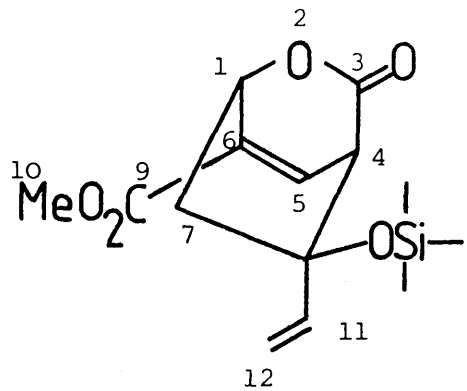
Found: C, 56.57; H, 6.73%.



Proton No.	δppm ^1H	Carbon no.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	161.91	-	s	-
-	-	C-7	205.01	-	s	-
-	-	C-9	170.99	-	s	-
H-3	6.08	C-3	121.08	d	d	9
H-4	7.05	C-4	147.95	d	d	9
-	-	C-4a	46.71	-	s	
H-5(2H)	(2.00-	C-5	29.42	m	t	
H-6(2H)	(3.00	C-6	37.23	m	t	
H-8(2H)	(	C-8	43.57	m	t	
H-8a	5.30	C-8a	78.61	dd	d	
H-10(3H)	3.90	C-10	53.52	s	q	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	163.04	-	s	
-	-	C-9	171.47	-	s	
H-3	5.98	C-3	120.91	d	d	9
H-4	6.87	C-4	149.15	d	d	9
-	-	C-4a	45.95	-	s	
H-5(2H)	2.30	C-5	29.80	m	t	
H-8(2H)	2.65	C-8	33.5	m	t	
H-6	4.95	C-6	100.29	dd	d	
-	-	C-7	147.75	-	s	
H-8a	4.75	C-8a	76.38	dd	d	
H-10(2H)	3.70	C-10	52.89	s	q	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-3	162.48	-	s	-
-	-	C-9	170.04	-	s	-
H-1	5.65	C-1	73.02	dd	d	3.7, 1.8
H-4	3.75	C-4	56.01	d	d	H_4H_5=6.34
H-5	7.30	C-5	141.37	d	d	H_1H_5=2.16 H_5H_4=6.34
-	-	C-6	135.05	-	s	-
H-7(2H)	1.85, 2.65	C-7	40.65	dd	t	14.4 H_7H_1 3.7, 1.8
-	-	C-8	75.48	-	s	
H.10(3H)	3.75	C-10	51.95	s	q	-
H-11	5.92	C-11	140.37	d	d	cis.17.18 trans-10.60
H-12(2H)	5.20, 5.30	C-12	115.36	d	t	

(±)-Methyl-(4aα,8aα)-4,5,8,8a-7-t-butyldimethylsilyloxy-2H-1-benzopyran-2-one-4aα-carboxylate (218a)

A mixture of methyl coumalate (147), (2.52g, 16.36 mmol) in 40 ml of dry toluene, a few crystals of hydroquinone and diene (217) (7.52g, 40.90 mmol) was heated at 110°C for 48 hours in a sealed tube. The reaction mixture was cooled and concentrated under reduced pressure. Purification of the resulting viscous oil by dry column flash chromatography afforded 4.0g (74.0%) of the desired adduct (218a), as a single crystalline regioisomer. Recrystallisation from ether gave white crystals, m.p. 70-72°C.

The alternative Diels-Alder adduct (218b), (1.13g, 20.40%) was also isolated as a crystalline compound. Recrystallisation from ether gave white crystals, m.p. 76-79°C.

Diels-Alder adduct (218a)

IR (CCl_4): 2950, 1735 (broad), 1670 cm^{-1}.

MS: 338 (M^+); 281 (M-t-butyl).

$C_{17}H_{26}O_5Si$ requires C, 60.35; H, 7.69%.

Found: C, 60.12; H, 7.57%.

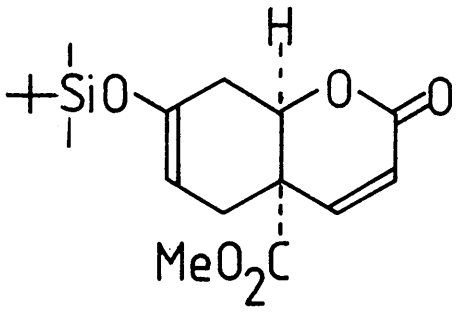
Alternative Diels-Alder adduct (218b)

IR (CCl_4): 2950, 1775, 1725, 1640 cm^{-1}.

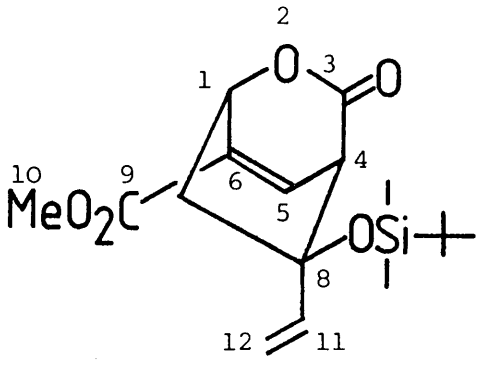
MS: 338.1538 (M^+); calc. for $C_{17}H_{26}O_5Si$: 338.1549.

$C_{17}H_{26}O_5Si$ requires C, 60.35; H, 7.69%.

Found: C, 60.36; H, 7.73%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	163.04	-	s	
-	-	C-9	171.58	-	s	
H-3	5.90	C-3	120.99	d	d	9
H-4	6.80	C-4	149.17	d	d	9
-	-	C-4a	45.99	-	s	
H-5(2H)	(2.00	C-5	29.85	m	t	
H-8(2H)	(-2.80	C-8	33.57	m	t	
H-6	4.90	C-6	100.21	broad m	d	
-	-	C-7	147.94	-	s	
H-8a	4.75	C-8a	76.48	broad m	d	
H-10(3H)	3.65	C-10	52.91	s	q	
-	-	qC,t-butyl	17.89	-	s	
t-butyl, 9H	0.75	CH_3,t-butyl	25.51	s	q	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
—	—	C-3	162.69	-	s	
-	-	C-9	170.19	-	s	
H-1	5.67	C-1	73.70		d	3.72,1.72
H-4	3.77	C-4	56.24		d	$J_{H4}H_5$=6.40
H-5	7.30	C-5	141.22	dd	d	H_1H_5=2.10 H_4H_5=6.35
-	-	C-6	135.22	-	s	-
H-7(2H)	1.85, 2.64	C-7	40.62	dd	t	14.41 H_7H_1=3.72
-		C-8	75.69	-	s	1.72
H-10(3H)	3.80	C-10	52.19	s	q	-
H-11	5.95	C-11	140.54	dd	d	10.80, 17.40
H-12(2H)	5.34, 5.25	C-12	115.99	dd	t	trans 17.40 cis,10.80
-	-	qC,t-butyl	17.95	-	s	-
t-butyl, 9H	0.75	CH_3,t-butyl	25.42	s	q	-

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-6-hydroxy-7,7-aryloxy, trimethylsilyloxy-2H-1-benzopyran-2-one-4aα-carboxylate (224)[84].

A slurry of disodium hydrogen orthophosphate (2.70g) and m-chloroperbenzoic acid (758 mg, 85% pure, 3.87 mmol) in 9 ml of dry methylene chloride was stirred under N_2, in an ice-methanol bath at $-15^{o}C$. To this was added a solution of silyl enol ether (215a), (1.00g, 3.38 mmol) in 2 ml of methylene chloride and stirring was continued at $-15^{o}C$ for 20 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour. The reaction mixture was then diluted with methylene chloride and washed sequentially with 15 ml of water, 15 ml of dilute aqueous sodium hydrogen carbonate solution. Drying and concentration under vacuum afforded 1.53g (96.6%) of acetal (224). Purification of the crude acetal by dry column flash chromatography gave 1.33 (84.0%) of acetal (224) as a colourless foam. Attempted Kugelrohr distillation resulted in decomposition of acetal (224).

Acetal (224)

IR (CCl_4): 3600 (weak), 2970 (weak), 1740, 1705, 1260 cm^{-1}.

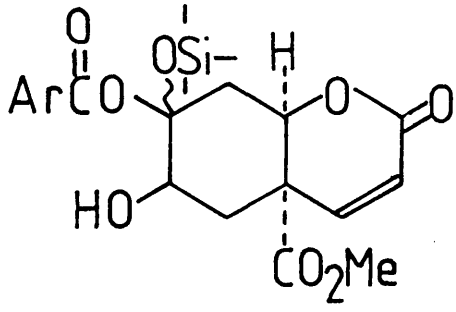
MS: 312 ($M-Cl-C_6H_4-CO_2H$); 297 ($M-ClC_7H_5O_2CH_3$).

Method B[85]

A solution of m-chloroperbenzoic acid (266 mg, 1.36 mmol) in 5 ml of hexane was stirred under N_2 at $-15^{o}C$. To this was added dropwise, a solution of silyl enol ether (215a), (408 mg, 1.36 mmol) in 20 ml of hexane and after stirring for a few minutes a white precipitate was observed. The reaction mixture was stirred at $-15^{o}C$ for 1 hour and

15 minutes, then warmed to room temperature and stirring continued for a further 15 minutes. The reaction mixture was filtered through Celite and concentrated in vacuo. Purification by dry column chromatography afforded 500 mg (78.6%) of acetal (224).

IR and MS as stated



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	170.56	-	s	
-	-	C-11	173.49	-	s	
-	-	C-9	174.41	-	s	
H-3	6.00	C-3	122.41	d	d	8
H-4	6.75	C-4	145.30	d	d	8
-	-	C-4a	45.67	-	s	
H-5(2H)	(2.05	C-5	(37.72	m	t	
H-8(2H)	(3.05	C-8	(41.48	m	t	
H-6	4.10	C-6	70.92	dd	d	
-	-	C-7	115.56	-	s	
H-8a	5.00	C-8a	77.54	dd	d	
H-10(3H)	3.75	C-10	53.66	s	q	
ArH(2H)	7.40,	-	-	m		
-	7.85	ArC	128.26	m	d	
			129.81		d	
			130.18		d	
			130.95		s	
			133.82		d	
			134.64		s	

(±)-Methyl-(4aα,8a)-4a,5,6,7,8,8a-hexahydro-6-hydroxy-7,7-aryloxy, t-butyldimethylsilyloxy-2H-benzopyran-2-one-4aα-carboxylate (225)[84]

A slurry of disodium hydrogen orthophosphate (4.51g) and m-chloroperbenzoic acid (1.23g, 85% pure, 6.09 mmol) in 15 ml of dry methylene chloride was stirred under N_2, in an ice-methanol bath at -15°C. To this was added a solution of silyl enol ether (218a), (1.71g, 5.07 mmol) in 2 ml of methylene chloride and stirring was continued at -15°C for 20 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour. The reaction mixture was then diluted with 15 ml of methylene chloride and washed with 20 ml of water, followed by 20 ml of dilute aqueous sodium hydrogen carbonate solution. Drying and concentration under vacuum afforded a white solid which was purified by dry column flash chromatography to accord 2.02g (78.4%) of crystalline acetal (225). Recrystallisation from ether afforded white crystals, m.p. 115-118°C.

Acetal (225)

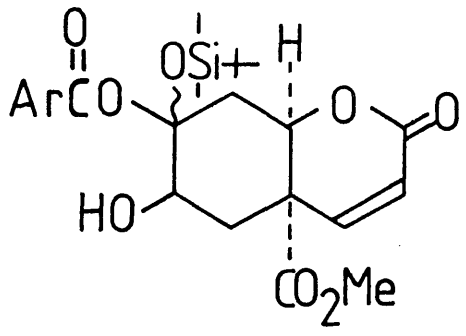
IR (CCl_4): 3610 (weak), 2970, 1745 (strong), 1710 (shoulder) cm^{-1}.

MS: 297.0819 (M-CO_2-(C_6H_4)-Cl-t-butyl); Calc. for $C_{13}H_{18}O_8Si$ 297.0870.

$C_{24}H_{31}O_8SiCl$ requires C, 56.42; h,6.07%.

Found: C, 56.31; H, 5.92%.

Acetal (225) could not be cleanly converted to the desired α-hydroxy ketone (222)



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	160.71	-	s	
-	-	C-11	169.32	-	s	
-	-	C-9	170.46	-	s	
H-3	6.00	C-3	122.64	d	d	8
H-4	6.75	C-4	145.75	d	d	8
-	-	C-4a	45.77	-	s	
H-5(2H)	(2.10	C-5	32.13	m	t	
H-8(2H)	(3.10	C-8	35.05	m	t	
H-6	4.15	C-6	70.62	dd	d	
-	-	C-7	103.43	-	s	
H-8a	5.05	C-8a	75.62	dd	d	
H-10(3H)	3.75	C-10	53.58	s	q	
ArH(2H)	7,40,	-		m	-	
ArH(2H)	7.85					
		ArC	129.55,q,	-	s	
			128.00		d	
			133.81	d	d	
			130.39	d	d	
			134.77,q		s	

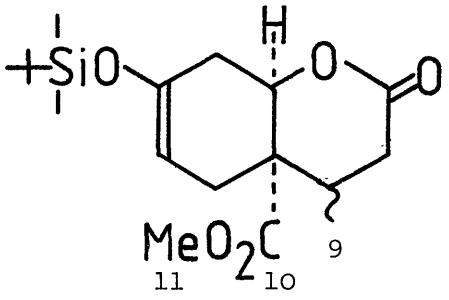
(±)-Methyl-(4aα,8aα)-3,4,4a,5,8,8a-hexahydro-4-Methyl-7-t-butyldimethyl-silyloxy-2H-1-benzopyran-2-one-4aα-carboxylate (239)[50]

Methyl lithium-bromide complex (1.5M in ether) was added slowly to a suspension of cuprous iodide (1.47g, 7.71 mmol) in 40 ml of dry ether at 0°C until the initially formed yellow precipitate had just disappeared. The resulting clear solution was stirred at 0°C for 5 minutes, then a solution of silyl enol ether (218a), (2.05g, 6.06 mmol) in 10 ml of ether was added dropwise. After complete addition, the mixture was stirred at 0°C for 40 minutes, then poured into 40 ml of ice-cold saturated ammonium chloride solution and filtered through Celite. The separated aqueous layer was extracted three times with 3 x 30 ml of ether and the combined organic extracts were dried and concentrated in vacuo. Purification by dry column flash chromatography afforded 1.61g (75.0%) of pure conjugate addition product (239), as a yellow oil, with mainly one methyl epimer being obtained.

Cuprate product (239)

IR (CCl_4): 2950, 1755, 1735 (broad), 1670 cm^{-1}.

MS; 354.1877 (M^+); calc. for $C_{18}H_{30}O_5Si$: 354/1862; base peak at 297.1167 (M-t-butyl); calc. for $C_{14}H_{21}O_5Si$: 297.1156.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	H(Hz) ^1H
-	-	C-2	166.70	-	s	
-	-	C-10	173.11	-	s	
H-3(2H)	(	C-3	(31.62	m	t	
	(		(			
	(2.00-		(			
	(		(			
H-5(2H)	(	C-5	(33.79	m	t	
	(		(			
	(2.60		(			
	(		(			
H-8(2H)	(	C-8	(36.05	m	t	
	(					
H-4	(	C-4	32.90	m	d	
-	-	C-4a	48.00	-	s	
H-6	4.95	C-6	101.08	m	d	
-	-	C-7	147.56	-	s	
H-8a	4.80	C-8a	74.25	m	d	
H-9(3H)	1.0	C-9	18.00	d	q	7.8Hz
H-10(3H)	3.71	C-11	51.91	s	q	
-	-	qC,+	17.47	-	s	
+,9H	0.90	CH_3,+	25.43	s	q	

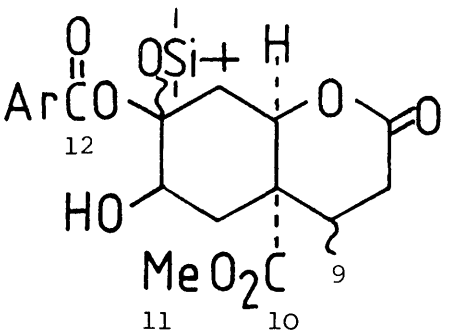
(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-4-methyl-6-hydroxy-7,7-aryloxy, t-butyldimethylsilyloxy-2H-1-benzopyran-2-(4H)-one-4aα-carboxylate (226a)[84]

A slurry of disodium hydrogen orthophosphate (3.17g) and m-chloroperbenzoic acid (1.05g, 85% pure, 5.18 mmol) in 15 ml of dry methylene chloride was stirred under N_2, in an ice-bath at 0°C for 20 minutes. To this was added a solution of cuprate product (239), (1.61g, 4.54 mmol) in 5 ml of methylene chloride and stirring continued at 0°C for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour and 15 minutes. The reaction mixture was then diluted with 40 ml of ether, cooled to -78°C and quickly filtered through a pad of Celite. The organic layer was washed sequentially with 2 x 30 ml of sodium hydrogen carbonate solution and 40 ml of water. Drying and concentration under vacuum afforded 2.15g of acetal (226a). The crude product was purified by dry column flash chromatography to afford 1.87g (78.3%) of acetal (226a) as a colourless foam. Acetal (226a) decomposed on Kugelrohr distillation.

Acetal (226a)

IR (CCl_4): 2950, 1740 (broad) cm^{-1}

MS: 313 (M-(Cl-C_6H_4-CO_2H)-t-butyl).



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
-	-	C-2	163.61	-	s
-	-	C-10	169.75	-	s
-	-	C-12	173.59	-	s
H-3(2H)	(2.10-	C-3	(33.22	m	t
H-5(2H)	(	C-5	(34.34	m	t
H-8(2H)	(2.90 (	C-8	(35.69	m	t
H-4	(	C-4	(32.83	m	s
-	-	C-4a	43.95	-	s
H-6	4.50	C-6	70.53	dd	d
-	-	C-7	104.44	-	s
H-8a	5.05	C-8a	75.67	dd	d
H-9(3H)	1.00	C-9	16.41	d	q
H-11(3H)	3.65	C-11	52.39	5	q
-	-	qC,+	17.47	-	s
+,9H	0.80	CH_3,+	25.55	s	q
ArH,2H	7.40	ArC,	133.18, 129.76	m	d
ArH,2H	7.58		129.56, 128.03	m	d
		q,ArC	132.48, 133.18		s

(±)-Methyl-(4aα,8aα)-4a,5,6,7,8,8a-hexahydro-4-methyl-6-hydroxy-7,7-aryloxy, t-butyldimethylsilyloxy-2H-1-benzopyran-2-(4H)-one-4aα-carboxylate (226b)[84]

A slurry of disodium hydrogen orthophosphate (3.50g) and p-nitroperbenzoic acid (680 mg, 85% pure, 3.15 mmol) in 10 ml of dry methylene chloride was stirred at -15°C, under N_2 for 15 mins. To this was added a solution of cuprate product (239), (950 mg, 2.68 mmol) in 5 ml of methylene chloride and stirring was continued at -15°C for 20 mins. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour. The reaction mixture was then diluted with 20 ml of ether, cooled to -78°C and quickly filtered through a pad of Celite. The organic layer was washed sequentially with 2 x 20 ml of saturated sodium hydrogen carbonate solution and 20 ml of water. Drying and concentration in vacuo, followed by purification by dry column chromatography afforded 1.26g (87.6%) of acetal (226b) as a colourless foam. Attempts to Kugelrohr distill acetal (226b) resulted in its decomposition.

Acetal (226b)

IR (CCl_4): 3610 (weak), 2950, 1740 (broad), 1540 cm^{-1}.

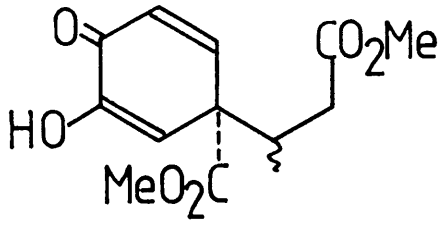
MS* 313 (M-(NO_2-(C_6H_4)-CO_2H)-t-butyl).

In an attempt to convert acetal (226b) to the desired α-hydroxy ketone (222), it was stirred with potassium carbonate in methanol, as described.

A solution of acetal (226b), (700 mg, 1.30 mmol) in 7 ml of methanol, with potassium carbonate added (746 mg, 5.40 mmol) was stirred

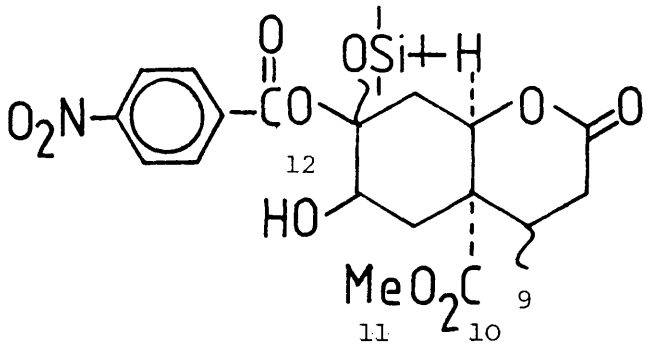
under N_2 for 2 hours at room temperature. The solution was acidified with 1N HCl, and concentrated under vacuum to remove methanol. The resulting aqueous solution was salted out with sodium chloride, extracted with 3 x 40 ml of ether and dried. Concentration in vacuo afforded a viscous oil, which from TLC appeared to be very polar and it was suspected that the B-ring opened carboxylic acid had been formed. The crude oil was treated with an ethereal solution of diazomethane and was subsequently columned to afford 291 mg (87.2%) of compound (227a). Full characterisation of (227b) proved that it was the ring-opened product indicated.

Compound (227b)

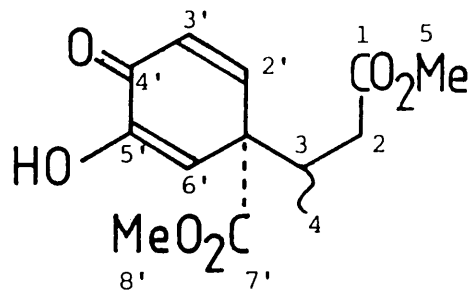


IR (CCl_4): 3450 (strong), 2960, 1740 (strong), 1665 (strong) cm^{-1}.

MS: 237.0741 ($M-OCH_3$); calc. for $C_{12}H_{13}O_5$: 237.0771.



Proton no.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	161.84		s	
-	-	C-10	162.77		s	
-	-	C-12	171.38		s	
H-3(2H)	(((2.20 (	C-3	31.70		t	
H-5(2H)	(((3.10 (	C-5	(((35.12 (		t	
H-8(2H)	(((	C-8	(			
H-4	(	C-4	32.85		d	
H-6	4.35	C-6	70.10	broad m	d	
-	-	C-7	104.36		s	
H-8a	5.10	C-8a	75.10		d	
H-9(3H)	1.00	C-9	18.10		q	7.80
H-11(3H)	3.74	C-11	52.63		q	
-	-	qC,+	17.78		s	
+,9H	0.80	CH_3,+	25.32		q	
-	-	qC,Ar	135.98, 150.32		s	
Ar,4H	8.20	CH,Ar	123.34, 130.57		d	



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-4'	180.70	-	s	-
-	-	C-7'	172.24	-	s	-
-	-	C-1	170.49	-	s	-
OH	6.44	C-5'	148.41	s	-	-
H-6'	6.13	C-6'	115.09	s	d	2.80
H-2'	7.16	C-2'	149.13	d	d	10.40, 2.80
H-3'	6.52	C-3'	128.51	d	d	
-	-	C-1'	56.30	-	s	-
H-8'(3H)	3.77	C-8'	(51.82	s	q	
H-5(3H)	3.63	C-5	(53.12	s	q	
H-3	2.85	C-3	38.04	dd	d	H_9H_{11} 4.14,9.93
H-2(2H)	1.95,2.30	C-2	36.45	2xdd	t	15.71,4.14 9.93
H-4(3H)	1.01	C-4	15.89	d	q	6.78

(±)-Methyl-(4aα,8aα)-4,5,6,7,8,8a-hexahydro-6-bromo-7-keto-2H-1-benzopyran-2-one-4aα-carboxylate (228)[48]

A solution of silyl enol ether (218a), (1.00g, 2.98 mmol) in 9 ml of dry methylene chloride was stirred under Ar, at -78°C. To this was added dropwise, with stirring, a 1M solution of bromine-dioxane[74] complex in methylene chloride (3.27 ml, 3.27 mmol); initial rapid decolourisation of the bromine solution was observed which tailed off to give a permanent brown colouration of the reaction mixture. The reaction mixture was stirred at -78°C for a further 20 mins. Concentration of the reaction mixture under reduced pressure and purification of the oily residue by dry column flash chromatography yielded 612 mg (67.8%) of α-bromoketone (228), b.p. 230°C (Kugelrohr)/ 0.15 mm Hg.

Examination of molecular models and ^{13}C-n.m.r. spectroscopy showed this to be a 3:1 epimeric mixture of the α- and β-α-bromoketones.

Bromoketones (228)

IR (CCl_4): 2960, 2940, 1740 (broad), 1670 cm^{-1}.

MS: 303.9781 (M^+): calc. for $C_{11}H_{11}O_5$ 80.9163. Br

: 303.9777; 301.9824 (M^+); calc. for $C_{11}H_{11}O_5$ 78.9184. Br.

$C_{11}H_{11}O_5Br$ requires C, 43.57; H, 3.66%.

Found: C, 43.95; H, 3.87%.

(±)-Methyl-(4aα,8aα)-4,5,6,8a-tetrahydro-6-bromo-7-t-butyldimethyl-silyloxy-2H-1-benzopyran-2-one-4aα-carboxylate (231)[48]

A mixture of silyl enol ether (218a), (1.03g, 3.05 mmol), pyridine (490 µl, 6.07 mmol) in 10 ml of dry methylene chloride was stirred at -78°C under Ar. To this was added dropwise, with stirring a 1M solution of bromine-dioxane complex in methylene chloride (3.34 ml, 3.34 mmol); initial rapid decolourisation of the bromine solution was observed which tailed off to give a permanent brown colouration. The reaction mixture was stirred at -78°C for a further 20 mins; after which time it was concentrated in vacuo, without heating, to afford an orange oil. Purification of the residue by dry column flash chromatography afforded 564 mg (44.2%) of bromo-silylenolether (231).

Bromo-silylenol ether (231)

IR (CCl_4): 2950 , 2930, 1740 (broad), 1665 cm^{-1}.

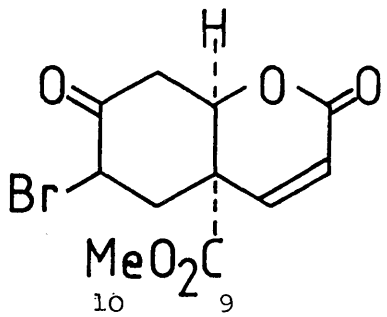
MS* 418.0612 (M^+); calc. for $C_{17}H_{25}O_5Si$ 80.9163.

Br: 418.0634, 416.0624 (M^+); calc. for $C_{17}H_{25}O_5Si$ 78.9184.

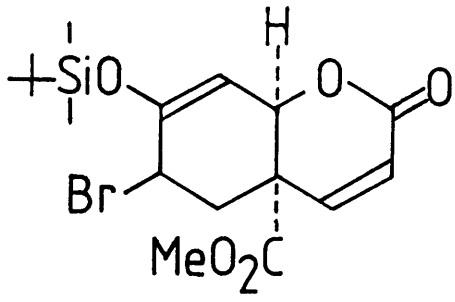
Br: 416.0655, 360.9874 (M-t-butyl); calc. for $C_{13}H_{16}O_5Si$ 80.9163.

Br: 360.9928, 358.9889 (M-t-butyl); calc. for $C_{13}H_{16}O_5Si$ 78.9184.

Br: 358.9949.

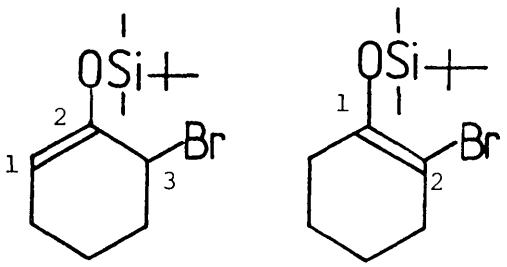


Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	161.12	-	s	-
-	-	C-9	169.93	-	s	-
-	-	C-7	195.93	-	s	-
H-5(2H)	(3.05(3H) ((2.40(1H)	C-5	39.80	m	t	
H-8(2H)		C-8	42.49	m	t	
H-3	6.10	C-3	120.81	d	d	11.2
H-4	6.95	C-4	146.42	d	d	11.2
-	-	C-4a	48.41	-	s	-
H-6	4.79	C-6	50.05	dd	d	5.6,14.6
H-8a	5.20	C-8a	77.82	dd	d	
H-10(3H)	3.90	C-10	53.73	s	q	-



10 9

Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-2	162.03	-	s	-
-	-	C-9	170.19	-	s	-
H-5(2H)	2.65	C-5	37.56	m	t	14.96,4.37 5.38
H-3	6.05	C-3	121.63	d	d	10.00
H-4	6.85	C-4	146.32	d	d	9.90
-	-	C-4a	44.41	-	s	-
H-6	4.55	C-6	43.66	dd	d	H_5H_6=4.37, 5.38
-	-	C-7	151.92	-	s	-
H-8	5.45	C-8	103.66	d	d	4.80
H-8a	5.20	C-8a	74.76	d	d	4.40
H-10,3H	3.80	C-10	53.11			
-	-	qC,+	18.09	-	s	-
t-butyl, 9H	0.90	CH_3,+	25.50	s	q	-

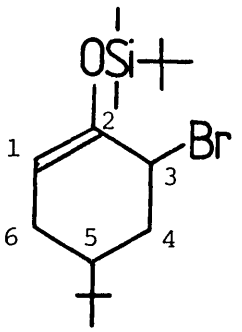


NMR Data for

Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
H-1	4.95	C-1	107.51	dd	d
-	-	C-2	149.30	-	s
H-3	4.55	C-3	51.59	m	d
H-4(2H)	(1.80-	C-4	(23.81	m	+
H-5(2H)	(	C-5	(33.27	m	t
	(2.30		(		
H-6(2H)	(	C-6	(34.58	m	t
-	-	+,qC	17.90	-	s
+,9H	0.95	+,CH_3	25.55	s	q

NMR data for (193)

-	-	C-1	145.70	-	s
-	-	C-2	108.23	-	s
H-3(2H)	(alpha-	C-3	23.81	m	t
H-4(2H)	(tic region	C-4	31.97	"	t
H-5(2H)	(	C-5	33.27	"	t
H-6(2H)	(	C-6	34.58	"	t
-	-	+,qC	17.86	-	s
+,9H	0.95	+,CH_3	25.43	s	q



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C
H-1	4.95	C-1	107.46	dd	d
-	-	C-2	149.27	-	s
H-3	4.55	C-3	52.81	m	d
H-5	(1.70-	C-5	38.39	m	d
H-4(2H)	(	C-4	25.27	m	t
H-6(2H)	(2.26	C-6	34.38	m	t
-	-	OSi+,qC	18.02	-	s
+,9H	0.95	OSi+,CH_3	25.58	s	q
-	-	+,qC	31.52	-	s
+,9H	0.85	+,CH_3	27.23	s	q

t-Butyldimethylsilyl enol ethers (233) and (237) were prepared from cyclohexanone and 4-t-butyl-cyclohexan-1-one respectively, via the method previously described.[90] Silyl enol ether (233) was obtained in 72.5% yield, and silyl enol ether (237) was prepared in 54.0% yield.

(±)-3-(1-Carbomethoxy-5-hydroxy-4-keto-cyclohex-2-enyl)-butanoic acid (240)[69]

A solution of N-methylmorpholine-N-oxide (1.73g, 14.77 mmol) in 53 ml of acetone and 24 ml of water was cooled to 0°C and 6.16 ml (0.24 mmol) of a 0.039M solution of osmium tetroxide in t-butanol was added. A solution of cuprate product (239), (4.50g, 12.71 mmol) in 20 ml of acetone was rapidly added dropwise and stirring continued at 0°C for 8 hours. The reaction mixture was then allowed to warm to room temperature and stirred overnight. A slurry of sodium dithionite (2.1g) and fluorosil (8.0g) was added and stirring continued for 30 mins. The mixture was filtered through Celite, acidified to pH7 with 1N HCl and concentrated in vacuo to remove the acetone. The aqueous solution was re-acidified to pH2, salted out with NaCl and extracted thoroughly with ethyl acetate. Drying of the combined organic extracts and concentration under reduced pressure afforded 2.97g (91.4%) of cyclohexenone (240) as a very viscous oil. Compound (240) was observed to be very polar and remained at the origin in a thin layer chromatography system of 60% ethyl acetate: 40% light petroleum; purification of compound (240) as its free acid was not attempted.

^{1}H-n.m.r. (90 MH_3, $CD_3\overset{O}{\overset{\|}{C}}CD_3$): δ 0.95, 1.15 (2xd, 3H), 2.00-2.70 (m, 5H), 3.75 (s, 3H, $CO_2\underline{Me}$), 4.35 (dd, H), 6.05 (d, 1H), 6.90, 7.15 (2xd, in ratio of approx. 1:1.4 respectively, 1H), 7.25 (broad s, 1H, $CO_2\underline{H}$).

(±)-Methyl-3-(1-carbomethoxy-5-hydroxy-4-keto-cyclohex-2-enyl)-butanoate (241).

A solution of crude acid (240), (2.97g, 11.60 mmol) in 50 ml of dry ether at 0°C, was treated with an ethereal solution of diazomethane until a permanent yellow colouration of the reaction mixture was observed and effervescence had ceased. The excess diazomethane was removed by gentle heating and the ethereal solution was concentrated in vacuo. Purification of the resulting oily residue by dry flash chromatography afforded 778 mg (24.8%) of less polar diester (241a) and 1.12g (35.8%) of a slightly more polar diester (241b), both as viscous oils; b.p. 210-220°C (Kugelrohr)/0.1 mmHg.

1:1 mixture of (241a) and (241b)

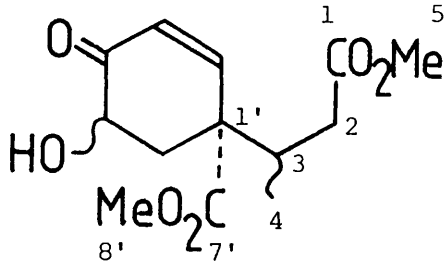
Strong u.v. adsorption at 220 nm.

IR (CCl_4): 3510, 2970, 1745 (very strong), 1690 cm^{-1}.

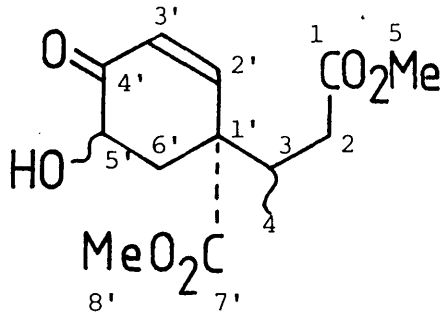
MS: 240 ($M-CH_2O$); 222 ($M-CH_2O-H_2O$).

$C_{13}H_{18}O_6$ requires C, 57.77; H, 6.67%.

Found: C, 57.69; H, 6.75%.



Proton No.	δppm ^{1}H	Carbon No.	δppm ^{13}C	Multiplicity ^{1}H	Multiplicity ^{13}C	J(Hz) ^{1}H
-	-	C-4'	198.24	-	s	
-	-	C-7'	(	-	s	
			(			
			(172.3			
			(			
-	-	C-1	(	-	s	
H-3	(2.10	C-3	37.15	m	d	
	(					
H-6'(2H)	(2.75	C-6'	(37.46	m	t	
			(			
H-2(2H)		C-2	(36.61	m	t	
H-2'	6.15	C-2'	126.88	d	d	12.30
H-3'	7.15	C-3'	151.22	d	d	12.30
-	-	C-1'	37.15	-	s	-
H-5'	4.40	C-5'	68.97	dd	d	11.70
H-8'(3H)	3.68	C-8'	(51.73	s	q	
			(			
H-5(3H)	3.78	C-5	(52.49	s	q	
H-4(3H)	1.10	C-4	16.49	d	q	7.80



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-4'	199.21	-	s	
-	-	C-7'	(172.20	-	s	
-	-	C-1	(	-	s	
H-3	(2.00	C-3	37.10	m	d	
H-6'(2H)	(2.80	C-6'	(36.42	m	t	
H-2(2H)	(	C-2	(33.71	m	t	
H-2'	6.10	C-2'	126.88	d	d	12.30
H-3'	6.85	C-3'	150.95	d	d	12.30
-	-	C-1'	37.20	-	s	-
H-5'	4.35	C-5'	69.93	dd	d	6.75, 11.70
H-8'(3H)	(3.69	C-8'	(51.70	s	q	
H-5(3H)	(3.78	C-5	(52.70	s	q	
H-4(3H)	1.10	C-4	15.00	d	q	7.80

(±)-Methyl-3-(1-carbomethoxy-4,5-dihydroxy-4-methyl-cyclohex-2-enyl)-butanoate (242)[37]

A solution of methyl magnesium bromide (3.5 ml of a 3M solution in ether, 10.50 mmol) in 22 ml of dry THF was stirred under Ar at -25°C in a Drikold-carbon tetrachloride bath. To this was added dropwise a solution of the mixture of diesters (241), (1.06g, 3.92 mmol) in 10 ml of THF and stirring was continued at -25°C for 2 hours. The reaction mixture was allowed to warm to room temperature and 10 ml of a saturated aqueous solution of sodium sulphate was added. The reaction mixture was filtered through Celite and the residual granular precipitate was washed with ether. The resulting organic layer was dried and concentrated under reduced pressure to afford 1.15g of a viscous oil, which was observed as two close-running spots in a number of different thin layer chromatography systems. Purification of the oily residue by dry column flash chromatography afforded 274 mg (24.4%) of the less polar diol, along with 398 mg (35.5%) of a more polar diol; b.p. (mixture of diols) 220°C (Kugelrohr)/0.1 mm Hg.

Additionally, it was suspected that some 1,4-addition product had also been formed but this was not characterised.

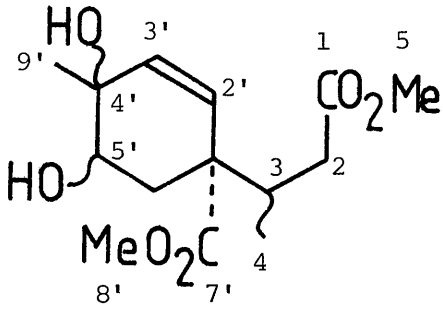
Mixture of Diols (242)

IR (CCl_4): 3630 (weak), 3570 (broad), 1740, 1720, 1435 cm^{-1}.

MS: 269 (M-17)

$C_{14}H_{22}O_6$ requires C, 58.76; H, 7.75%.

Found: C, 58.47; H, 7.59%.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
H-2'		C-2'	127.89		d	
	5.70		128.98	broad m		
H-3'		C-3'	134.24		d	
			136.15			
-	-	C-4'	73.48	-	s	
			69.92			
H-5'	3.75	C-5'	72.69	dd	d	
2xOH	3.24		69.92	broad s		
H-6'(2H)	(	C-6'	30.21	m	t	
	(1.70					
H-2(2H)	(	C-2	31.09	m	t	
	(2.10					
H-3	(	C-3	37.32	m	d	
-	-	C-1'	36.95	-	s	
H-9'(3H)	1.25	C-9'	24.17	s	q	
			21.19			
H-4(3H)	0.90	C-4	14.86	d	q	
			15.49			
-	-	C-7'	172.84	-	s	
			173.11			
-	-	C-1	174.62	-	s	
			176.09			

H-8'	3.66	C-8'	50.13 51.61	s	q	8.50
H-5(3H)	3.70	C-5	52.39 53.43	s	q	

(±)-Methyl-3-(1-carboxy-4,5-dihydroxy-4-Methylcyclohex-2-enyl)-butanoate γ-lactone (244b)

A solution of the mixture of diols (242), (590 mg, 2.06 mmol) in 9 ml of methanol and 20 ml of 1N sodium hydroxide solution (20.0 mmol) was stirred overnight at room temperature. The resulting basic solution was acidified with 1N HCl, salted out with sodium chloride and extracted thoroughly with ethyl acetate. The organic solution was dried and concentrated *in vacuo* to afford 486 mg (91.4%) of diacids (243) (Treatment of a small portion of the unpurified diacids (243) with an ethereal solution of diazomethane regenerated the starting diesters (242)).

A mixture of unpurified diacids (243), (272 mg, 1.06 mmol) in 5.4 ml of methanol and 11 ml of 1N HCl (11.0 mmol) was stirred at room temperature for 2 hours. The aqueous solution was extracted thoroughly with ethyl acetate and the organic extracts were dried. Concentration under reduced pressure afforded an oily residue (244a), which was dissolved in ether and subsequently treated with an ethereal solution of diazomethane. Concentration *in vacuo* afforded an oily residue which was purified by positive pressure flash chromatography to afford 95 mg (35.3%) of five-membered lactone (244b) as a white solid. Recrystallisation from diethyl ether afforded white needles, mp 120°C. 77 mg (25.4%) of diester (242b) was also obtained - (suspect that this is 4β-hydroxy compound).

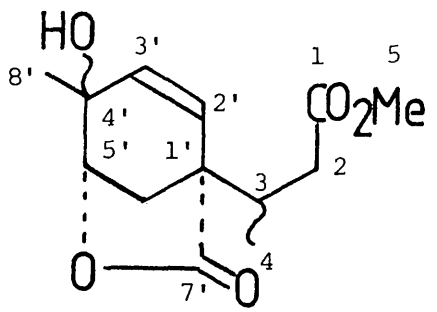
γ-lactone (244b)

IR (CCl_4): 3590 (sharp), 2970, 1795, 1745, 1260 cm^{-1}.

MS: 223.0972 ($M-OCH_3$); calc. for $C_{12}H_{15}O_4$: 223.0978.

$C_{13}H_{18}O_5$ requires C, 61.39; H, 7.14%.

Found: C, 61.32; H, 7.18%



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
H-2'	6.72	C-2'	131.94	d	d	9.5
H-3'	6.90	C-3'	135.73	d	d	9.5
OH	4.45	C-4'	66.43	-	-	-
H-5'	4.35	C-5'	81.54	dd	d	5.64
H-6'(2H)	(2.10	C-6'	37.17	m	t	5.64
H-2(2H)	(2.50	C-2	31.67	m	t	
H-3		C-3	30.57	m	d	
H-8'(3H)	1.27	C-8'	24.08	s	q	
H-4(3H)	1.00	C-4	15.36	d	q	6.72
-	-	C-7'	117.04	-	s	-
-	-	C-1	173.04	-	s	-
H-5(3H)	3.62	C-5	51.66	s	q	
-	-	C-1'	49.97	-	s	-

(±)-Methyl-3-(1-carbomethoxy-5-hydroxy-4-keto-cyclohexa-2,5-dienyl)-butanoate (227b)'

A solution of the mixture of diesters (241), (380 mg, 1.33 mmol) in 9 ml of methanol was stirred with anhydrous potassium carbonate (680 mg, 4.90 mmol) under N_2 for 1 hour. The reaction mixture was acidified with 1N HCl, salted out with sodium chloride and extracted thoroughly with diethyl ether. The ethereal extracts were dried and concentrated in vacuo. Purification of the resulting oily residue by dry column flash chromatography afforded 302 mg (84.7%) of dienol (227b)'.

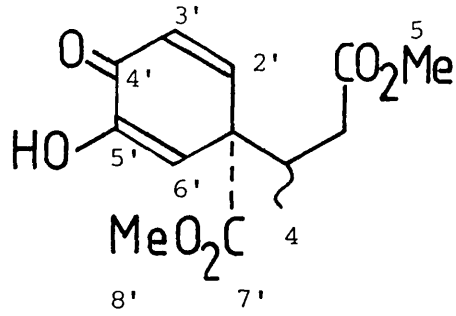
Characterisation of compound (227b)' showed that it was identical to compound (227b) obtained from (i) potassium carbonate, followed by (ii) diazomethane treatment of acetal (226b).

Dienol (227b)'

IR (CCl_4): 3450 (strong), 2960, 1740, 1665 (strong) cm^{-1}.

MS: 268.0952 (M^+); calc. for $C_{13}H_{16}O_6$: 268.0955.

237.0752 (m-OCH_3); calc. for $C_{12}H_{13}O_5$: 237.0771.



Proton No.	δppm ^1H	Carbon No.	δppm ^{13}C	Multiplicity ^1H	Multiplicity ^{13}C	J(Hz) ^1H
-	-	C-4'	180.66	-	s	
-	-	C-7'	(170.45	-	s	
-	-	C-1	((172.19	-	s	
-	-	C-5'	148.41	-	s	
H-6'	6.11	C-6'	115.09	s with w	d	2.80
-	-	C-1'	56.24	-	s	
H-2'	7.14	C-2'	149.02	d	d	2.80, 9.80
H-3'	6.50	C-3'	128.49	d	d	9.80
H-8'(3H)	3.70	C-8'	53.05	s	q	
H-5(3H)	3.61	C-5	51.74	s	q	
H-3	2.85	C-3	37.98	dd	d	4.13, 9.91
H-2(2H)	1.95, 2.27	C-2	36.38	2xd	t	15.63
H-4(3H)	0.99	C-4	15.81	d	q	9.00

2,3-Bistrimethylsilyloxy-buta-1,3-diene (245)[78]

To a mixture of trimethylsilyl chloride (54.3g, 0.50 mol) and triethylamine (83 ml, 0.60 mol) in 75 ml of dry DMF was added dropwise, over a period of 30 mins, a solution of biacetyl (17.2g, 0.20 mol) in 25 ml of DMF. The resulting mixture was stirred under reflux for 5 hours and then cooled. The reaction mixture was diluted with 600 ml of pentane, filtered through Celite and quickly washed with 1ℓ of 5% aqueous sodium hydrogen carbonate solution. The organic layer was dried and the pentane removed at atmospheric pressure. The residue was distilled (b.p. 125-130°C/80 mm Hg) to afford 27.6 (60%) of pure bisdiene (245), whose ^{1}H-n.m.r. spectrum was identical with that previously reported.

^{1}H-n.m.r. for diene (245) δ 0.1 (s, 18H); 4.3 (s, 2H), 4.8 (s, 2H).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-6,7-bistrimethylsilyloxy-2H-1-benzopyran-2-one (246)[77]

A mixture of methyl coumalate (147), (480 mg, 3.11 mmol) in 10 ml of dry toluene, a few crystals of hydroquinone and diene (245), (1.79g, 7.78 mmol) was heated in a sealed tube at 110°C for 48 hours. The reaction mixture was cooled and solvent was removed in vacuo; ^{1}H-n.m.r. of the crude reaction mixture indicated that some of the starting diene (245) still remained. Purification of the oily residue by dry column flash chromatography afforded 915 mg (94.3%) of a solid 1:1 mixture of the alternative Diels-Alder adducts (249a) and (249b) as the exclusive cycloaddition products. Recrystallisation from acetone gave white needles, m.p. 110-114°C.

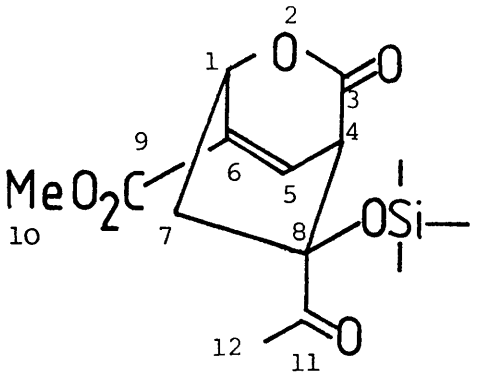
Alternative adducts (249a)/(249b)

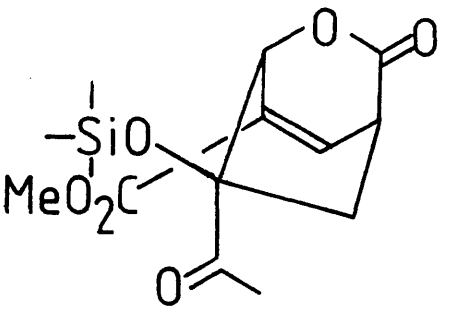
IR (CCl_4): 2960, 1775, 1730, 1640, 1255 cm^{-1}.

MS: 312 (M^+); 269 ($M-CH_3-C=O$).

$C_{14}H_{20}O_6Si$ requires C, 53.84; H, 6.46%.

Found: C, 54.03; H, 6.40%.





Proton No. (209a)	δppm (209a)	Proton No. (209b)	δppm (209b)	Multiplicity 209a	209b
11-5	7.22	H-5	7.08	dd	dd
H-1	5.50	H-1	5.50	broad m	broad m
H-4	3.75	H-4	3.68	d	d
H-10(3H)	3.60	H-10(3H)	3.58	s	s
H-12(3H)	2.15	H-12(3H)	2.08	s	s
H-7(2H)	2.30, 2.85	H-7(2H)	1.70, 2.55	d	d

Attempted preparation of Diene (250)

Methyl lithium (5.27 ml of a 1.45M solution in ether, 7.64 mmol) was added dropwise at room temperature to a solution of diene (245), (800 mg, 3.48 mmol) in 4 ml of dry dimethoxy ethane under Ar. The resulting mixture was stirred vigorously for 30 mins, after which time the dimethoxy ethane was replaced by 5 ml of THF and the solution cooled to $0^{\circ}C$. A solution of dimethyldichloro silane (424 µl, 3.48 mmol) in 2 ml of THF was added dropwise at $0^{\circ}C$, and the reaction mixture was allowed to warm to room temperature and stirring continued overnight. The reaction mixture was poured into 50 ml of pentane and washed twice with 10 ml of 1N HCl. Drying of the organic layer and concentration under reduced pressure afforded only polymeric material.

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