SYNTHETIC APPROACHES TO THE TRICHOTHECENE, T-2 TETRAOL.

by

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SUMMARY

The trichothecenes are a group of 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. This research project has concentrated on the synthesis of T-2 tetraol, one of the most highly oxygenated trichothecenes.

Diels-Alder reaction between isoprene and coumalyl chloride (260, R=Cl) followed by *in situ* conversion to methyl ester (266) established the *cis*-fused AB ring system of T-2 tetraol. Dimethyl lithium cuprate addition to (266) gave the 1,4-addition product (259) as a single methyl epimer. Stereoselective epoxidation produced (280) in good yield. Epoxide rearrangement using $BF_3.Et_2O$ gave ketone (283) which was converted into ketal (258). Alternatively, a one pot epoxide-ketal conversion could be used to transform (280) into (258). Oxidation of (258) was accomplished using the MoOPH reagent of Vedejs. Corey oxidation of the epimeric mixture of α-hydroxy lactones gave enol lactone (288). Allylation of (288) furnished enol ether lactone (289), a two step reduction of which using the method of Kraus gave pyran (291). $LiAlH_4$ reduction of (291) gave the unstable neopentyl alcohol (292), Claisen rearrangement of which produced allyl ketone (294) as a 3.2:1 mixture of α-allyl:β-allyl epimers as determined by G.L.C. and n.O.e. experiments. Protection of the free alcohol (294) as the silyl ether (302) followed by catalytic osmylation gave diol (320), which was cleaved with ethereal

periodic acid to yield nor-aldehyde (303). Aldol cyclisation then gave the tricyclic ketol (306) which was protected as its tetrahydropyranyl ether (333). Installation of the 12,13-alkene was achieved by means of a Wittig reaction. Selective removal of the THP ether gave olefin-alcohol (332) and thence ketone (336). Alpha oxygenation, followed by hydride reduction, generated (346), possessing the required ring C trans-3α,4β-diol system.

Deketalisation, epoxidation, dehydrogenation, reduction and finally deprotection are the operations necessary to complete the synthesis of T-2 tetraol in racemic form.

ABBREVIATIONS

Ac	Acetate
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHP	Dihydropyran
DIBAH	Diisobutylaluminium hydride
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
HMPT	Hexamethylphosphorous triamide
Im	Imidazole
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
m-CPBA	*m*-Chloroperoxybenzoic acid
Ms	Methanesulphonyl
NBS	*N*-Bromosuccinimide
NMMO	*N*-Methylmorpholine-*N*-oxide
PCC	Pyridinium chlorochromate
PPTS	Pyridinium *p*-toluenesulphonate
p-TSA	*p*-Toluenesulphonic acid
Py	Pyridine
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl

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HISTORICAL INTRODUCTION

The trichothecene mycotoxins constitute the most numerous group of fungal sesquiterpenes known to mankind.[1] Collectively, they exhibit a broad spectrum of biological activities amongst which are antibacterial, antifungal, insecticidal and cytostatic properties.[2] In addition, they have been implicated in a number of human and economically important animal mycotoxicoses arising from the ingestion of mouldy grain.[3] One of the worst examples of trichothecene poisoning was an outbreak of alimentary toxic aleukia which occurred in the Soviet Union during World War II.[4] Overwintered grain infected with a *Fusarium* fungus together with the prevailing conditions of alternate thawing and freezing produced high toxin concentrations. Many people died after repeated ingestion over several weeks. Subsequently Soviet scientists described the poisoning which occurs as a four stage process. In the first stage the victim feels a burning sensation in the mouth, oesophagus and stomach. The victim may experience vomiting, diarrhoea, weakness, fever and sleep disturbances. If recovery does not occur, the patient enters the second stage during which a marked decrease in white blood cells, granulocytes and lymphocytes occurs. In the third phase, a petechial rash develops on the skin, spreading over the body; necrotic lesions in the mouth may cause death by strangulation in the most severe cases. In the fourth or recovery stage, the patient is subject to secondary infections. Convalescence is long, lasting up to several months.

The trichothecenes have also been implicated[5] in the controversial 'Yellow Rain' scandal, involving the purported use of toxin-based weapons. In 1981, the U.S. government accused the Soviet Union and its allies of using chemical weapons in Southeast Asia and Afghanistan.

Five trichothecenes were reported to have been used: T-2 toxin, HT-2, nivalenol (NIV), diacetoxyscirpenol (DAS) and deoxynivalenol (DON). The U.S. government based its evidence on the fact that it found abnormally high levels of these potent mycotoxins which were not indigenous to the region. However, some scientists are sceptical of the evidence, preferring to believe that the 'Yellow Rain' was, in fact, bee excrement; photomicrographs of 'Yellow Rain' and locally collected bee excrement were very similar in appearance even down to the presence of bee hairs and a high pollen count.

The first compounds of the trichothecene class were discovered in 1946 by P.W. Brian at Imperial Chemical Industries laboratories during an extensive search for new antibiotics. The original stimulus for the research arose from the observation of their antifungal and phytotoxic effects. It was the efforts to obtain these active ingredients in pure form that led Freeman and Morrison[6] to the first isolation and purification of a trichothecene, *trichothecin*, in 1949. In 1961, Brian isolated another member of this class, *anguidine*, and in his publication,[7] he commented on its phytotoxic effects. Soon after, a series of papers appeared[8,9] disclosing the isolation of a number of structurally related cytotoxic macrocyclic esters of the trichothecene, *verrucarol*. The isolation of *trichodermin* by Godtfredsen and Vangedal[10] and subsequent structural determination by Abrahamsson and Nilsson[11,12] using X-ray diffraction analysis, together with the earlier chemical work, led to the realisation that all of the compounds discovered to that date were structurally related.

Subsequent to these initial discoveries, the implication of various trichothecene-producing fungi in a number of animal and human toxicoses resulting from the ingestion of mouldy cereal grains has led

to the isolation and characterisation of over 148 trichothecenes and nine genera of trichothecene-bearing fungi[1,2,13]: *Fusarium, Myrothecium, Trichothecium, Trichoderma, Cephalosporium, Cyclindrocarpen, Stachybotrys, Verticimonosporium* and *Calonectria.* Trichothecenes have been shown to be the causative agents in fescue foot disease[14], mouldy corn toxicoses[15], stachybotrytoxicoses[16], food-refusal phenomena[17] and human alimentary toxic aleukia.[18]

An extensively studied and potentially important property of the trichothecenes is their cytostatic activity. In 1962 Harri[8] found that *verrucarin A*, a macrocyclic trichothecene, caused substantial growth inhibition of the mouse tumour cell P-815 at very low concentrations, making it one of the most active cytostatic agents known at that time. This activity does not seem to be limited to macrocycles; the majority of the simple trichothecenes have also been shown to possess significant *in vitro* cytostatic activity. Indeed, *anguidine*, has undergone Phase II clinical trials[19,20] by the National Cancer Institute against cancer of the colon and breast. However, despite this multiplicity of activity, no trichothecene or related synthetic analogue has so far been put to therapeutic use.

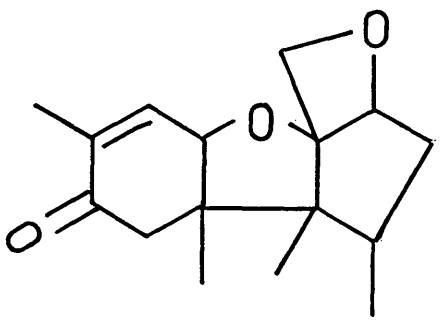
Biochemically the trichothecenes are highly toxic to eukaryotic cells: this cytotoxicity depends on biological features characterised by a potent inhibitory effect on DNA and protein synthesis.[21] Studies have demonstrated that crude toxins cause inhibition in the uptake of labelled amino acids into protein in rabbit reticulocytes. Although the molecular basis of their action is still unclear, Ueno has presented evidence[22] that the trichothecenes react with thiol residues in the enzyme peptidyl transferase. The 12,13-epoxide in the trichothecanoid framework is thought to be the electrophilic site responsible for this

reactivity, as removal of this epoxide nullifies the cytostatic behaviour.[23]

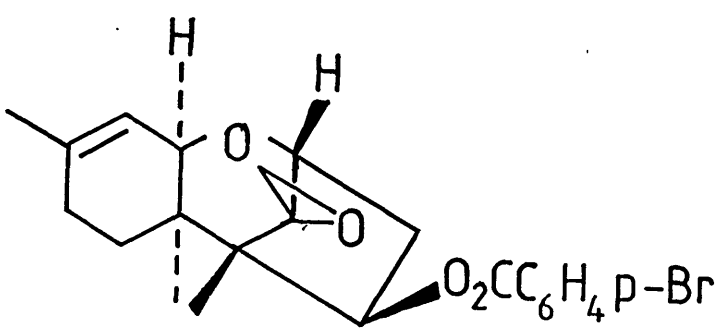
STRUCTURE

In 1967, Godtfredsen proposed[24] the name 'trichothecane' for the group of spiroepoxy-containing sesquiterpenoid compounds after trichothecin, the member first isolated by Freeman and Morrison. Since all the naturally occurring trichothecane compounds possess a double bond at C-9 and an epoxy ring at C-12,13, they are termed '12,13-epoxy-trichothec-9-enes'.

Initial work on the structure determination of the trichothecenes was reported from the laboratories of Freeman[25], Tamm[26] and Fishman,[27] Based on extensive chemical studies, these groups arrived at a similar but incorrect carbon framework, now known as the apotrichothecene skeleton, exemplified by Freeman's proposed structure for trichothecolone(1). However, in 1964, single-crystal X-ray analysis of the p-bromobenzoate derivative of trichodermol(2) showed the structure to be the tetracyclic epoxide characteristic of all the trichothecenes. Other workers in the field quickly revised their previous structural assignments and all then-known trichothecenes were correlated with trichodermol. The fact that nuclear magnetic resonance spectral analysis was just becoming widely used was an important factor in the recognition of the individual trichothecenes as a related group and in the elucidation of their correct structures.

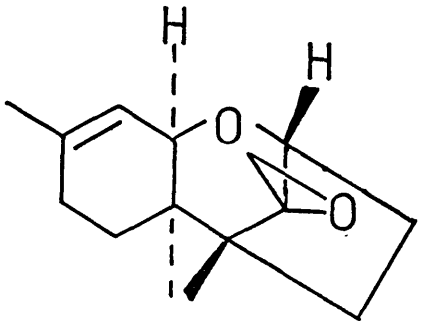


(1)



(2)

The basic skeleton (3) and numbering system (4) for the trichothecenes are as illustrated. The individual rings are designated, from left to right, A, B and C.



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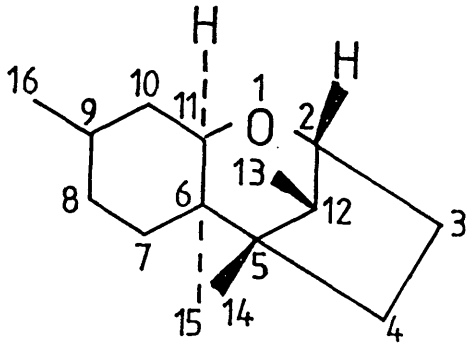
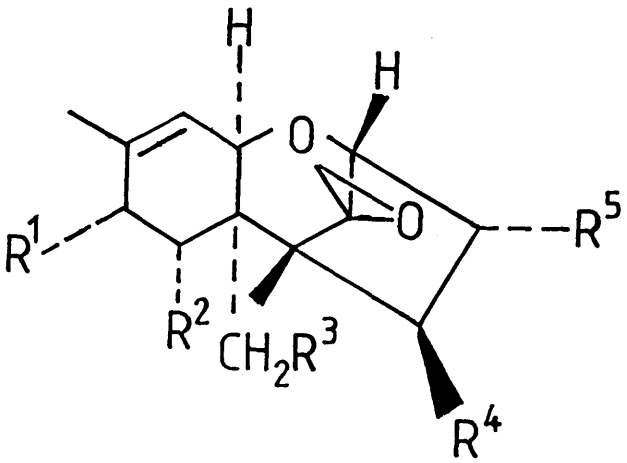


(4)

The trichothecenes can be sub-divided[1] into three distinct structural groups : simple trichothecenes, macrocyclic trichothecenes and the trichoverroids. The simple trichothecenes contain the basic mono- or polyhydroxylated sesquiterpene skeleton with none, one or more of the hydroxyl groups esterified by acetic, crotonic, isovaleric, lactic or β-hydroxyisovaleric acid. This grouping can be further sub-divided depending on the oxidation level at C-8: fully reduced (5, R^1 = H), possessing an 8α-hydroxyl group (5, R^1 = OH), or ketonic (6).



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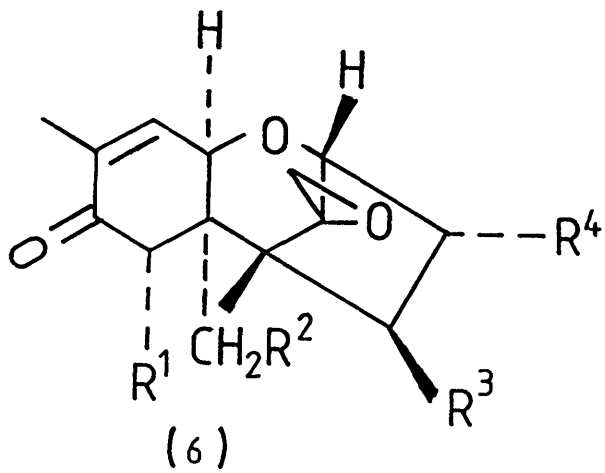
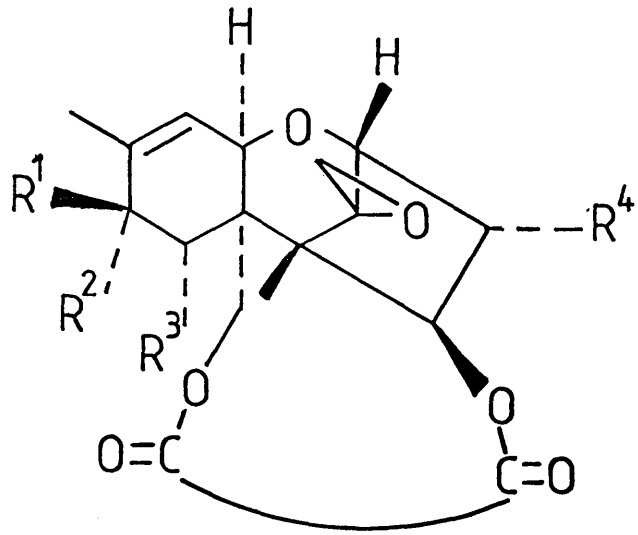


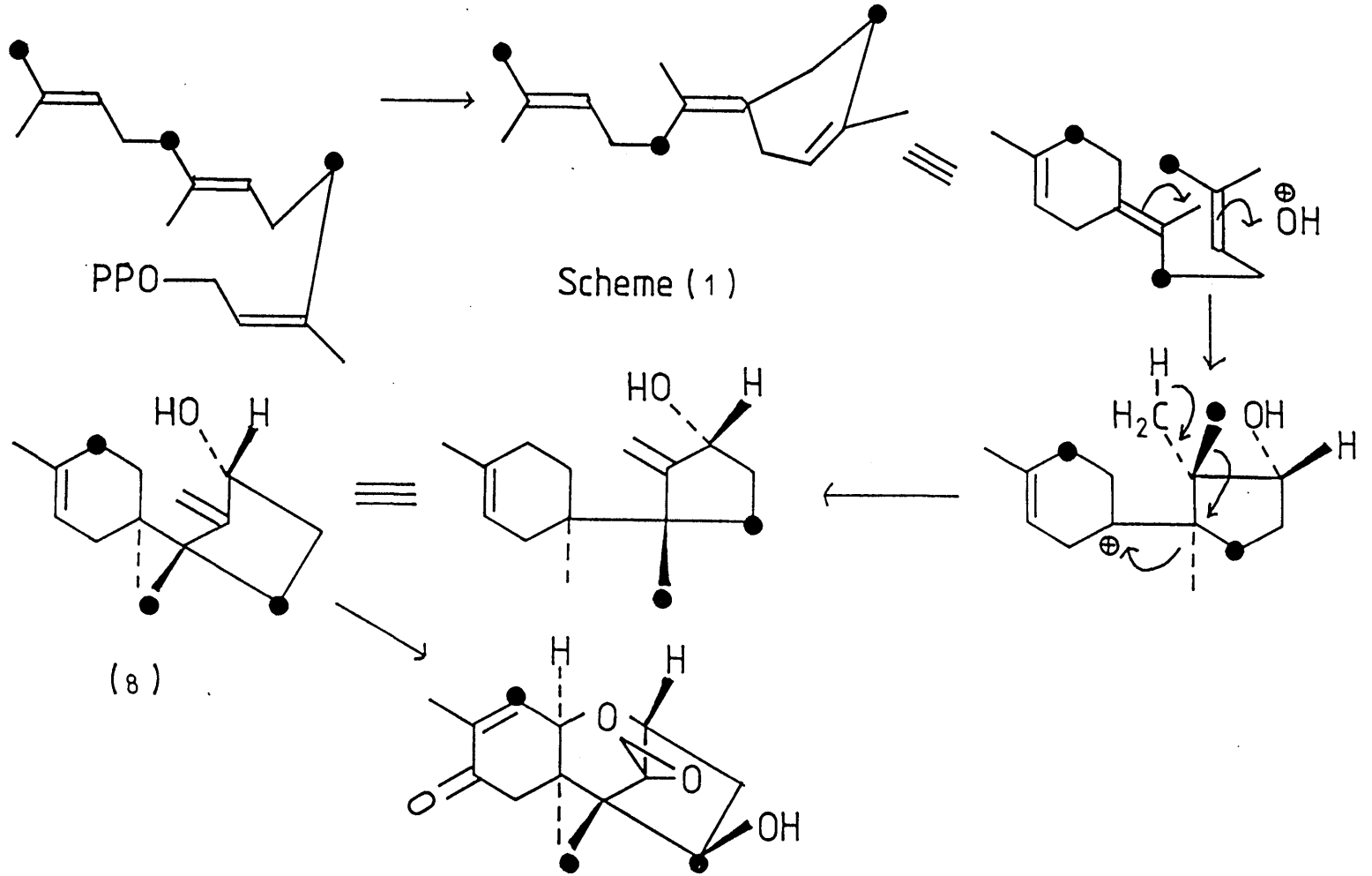
(6)

In the second structural group, the macrocyclic trichothecenes, the hydroxyl groups at C-4 and C-15 of the simple trichothecene skeleton are bridged by a di- or trilactidic ribbon. A variety of macrocyclic ester side chains differentiate one trichothecene from the other; their general structure is as illustrated (7).



(7)

The third group of trichothecenes are the trichoverroids. These are termed seco-macrocyclic trichothecenes having either partial or complete carbon chains at C-4 and C-15 characteristic of the macrocyclic compounds but lacking the ring-forming bond required to be fully macrocyclic.



Scheme (1)

(8)

THE LABELLED CARBON ATOMS COME FROM MEVALONIC ACID-2-^{14}C

BIOSYNTHESIS

A comprehensive review of the trichothecene biosynthesis will not be attempted here. However, a brief description is necessary in order to help the reader understand why certain routes, described later, were used in approaching trichothecene total syntheses.

At first sight, the 15 carbon skeleton of the trichothecene nucleus suggests that these compounds are sesquiterpenoid in origin. However, the basic tetracyclic nucleus (3) cannot be derived by the classical head-to-tail linking of three isopentane units. Nevertheless, the structure is consistent with the Ruzicka biogenetic isoprene[28] rule which allows 1,2-methyl migrations. The proposed mechanism for the biosynthesis of trichothecolone from cis, trans-farnesyl pyrophosphate is shown in scheme 1. Labelling studies[29] with mevalonate-2-^{14}C appear to be in agreement with the suggested double 1,2-methyl migration.

A key step in several trichothecene total syntheses is the biomimetic-type cyclisation of a suitably functionalised diene with the general skeletal arrangement as shown (8).

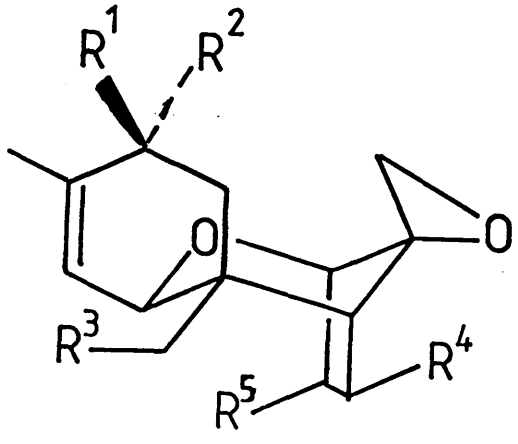
STRUCTURE ACTIVITY RELATIONSHIPS

All of the 12,13-epoxytrichothec-9-enes possess a potent inhibitory activity on protein synthesis in eukaryotes.

There is speculation[30] that the mode of action may involve the epoxide group acting as a bio-alkylating agent, through some form of intramolecularly assisted nucleophilic ring opening, induced by the interaction of the epoxide with an electrophilic site on an enzyme. The residual groups of the trichothecene nucleus are thought to play an important conformational role[31] in determining the relative activity.

Chemical modifications of the trichothecene structure add weight to these postulates. Hydrogenation of the olefinic bond in the trichothecene nucleus reduces biological activity.[31] Evidence for the necessity of the epoxide function was furnished by Grove and Mortimer[31] who examined a variety of transformation products of diacetoxyscirpenol for cytotoxicity. Compounds in which the epoxide had been removed by reduction or rearrangement were several times less toxic than the compounds from which they were produced.

A three dimension representation[32] of the trichothecene skeleton is illustrated (9).



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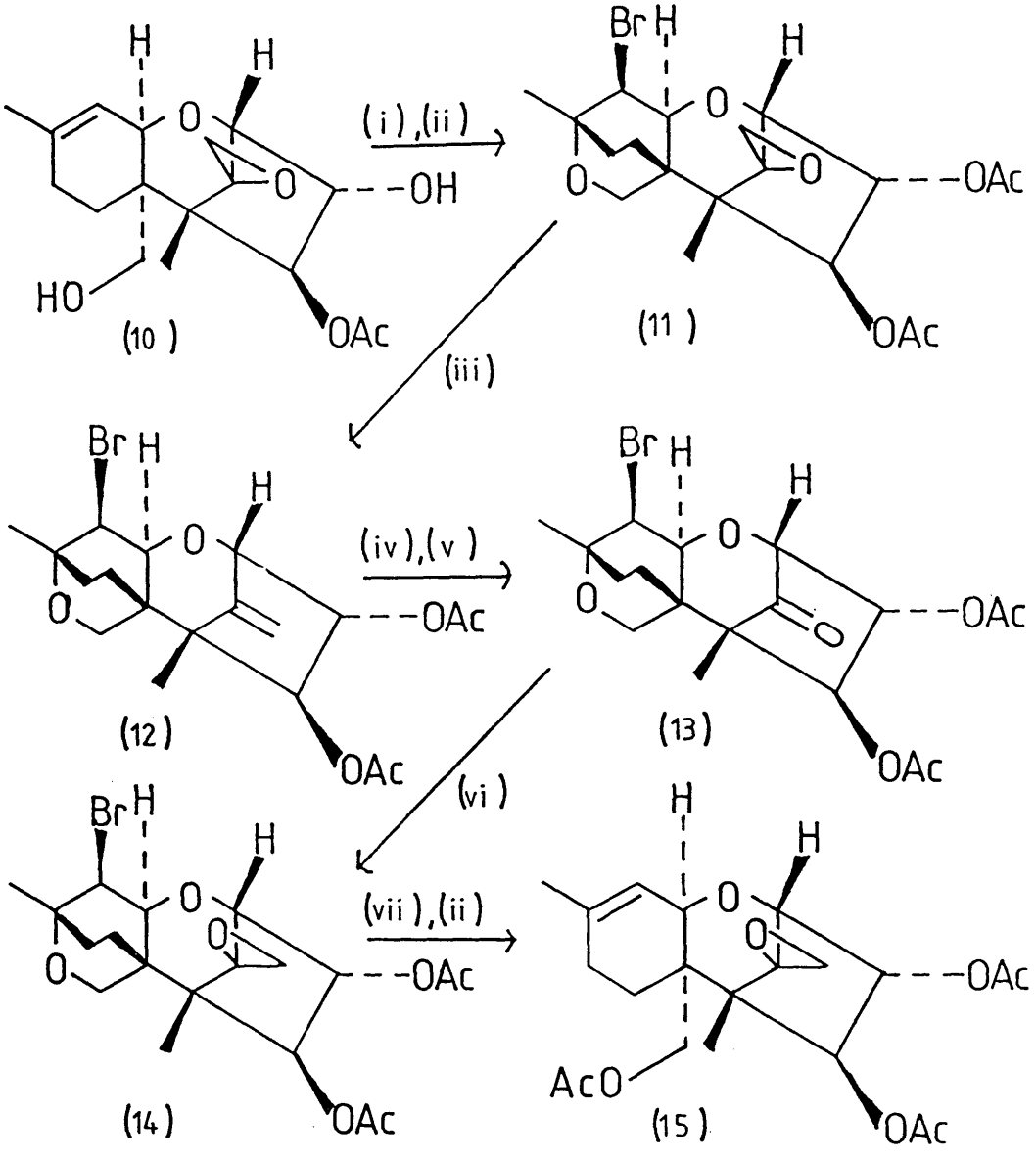
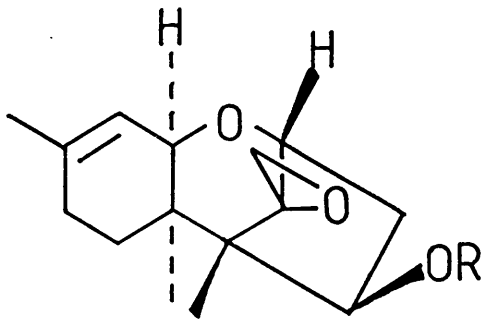


Scheme (2)

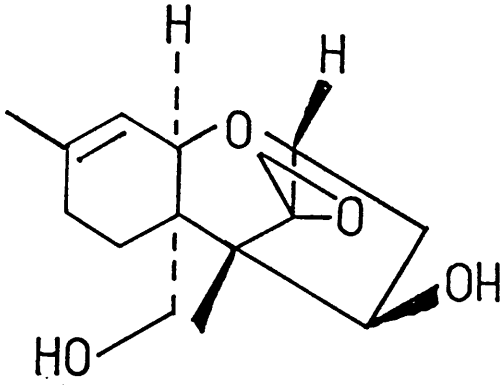
Reagents:-(i) NBS, MeCN; (ii) Ac_2O, Py; (iii) WCl_6, n-BuLi, THF ; (iv) O_3, CH_2Cl_2 ; (v) Et_3N ; (vi) $Me_2\overset{\oplus}{S}\overset{\ominus}{C}H_2$, THF ; (vii) Zn(Ag)

Derivatives in which the epoxide group remains but in which ring C is altered so as to permit nucleophilic attack on the rear side of the epoxide were also shown[33] to be devoid of cytotoxicity.

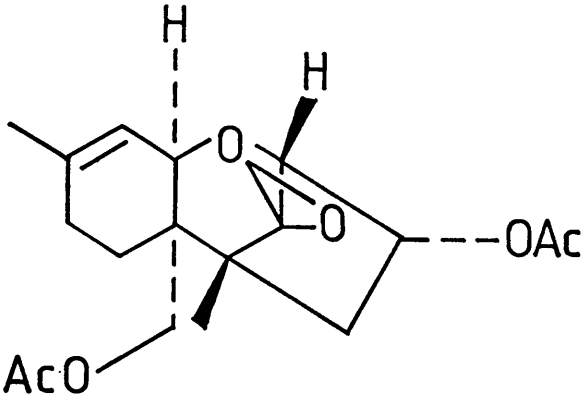
Additional evidence for the necessity of the epoxide has been provided by Colvin and Cameron[34,35] through chemical modifications (scheme 2). Removal of the epoxide with the Sharpless tungsten-based deoxygenating system[36,37], oxidative cleavage of the exomethylene olefin with ozone and formation of the epi-epoxide gave a trichothecene which, in dramatic contrast to the natural isomer, lacked significant biological activity. As all other functionality within the molecule remained unchanged, this finding emphasised the key role played by a correctly orientated epoxide group in providing the cytotoxicity of the trichothecenes.



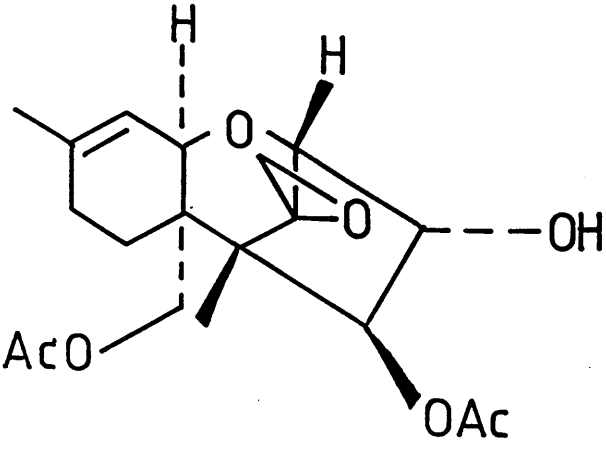
R=H, TRICHODERMOL (16)
R=Ac, TRICHODERMIN (17)



VERRUCAROL (18)



CALONECTRIN (19)



ANGUIDINE (20)

SYNTHETIC APPROACHES.

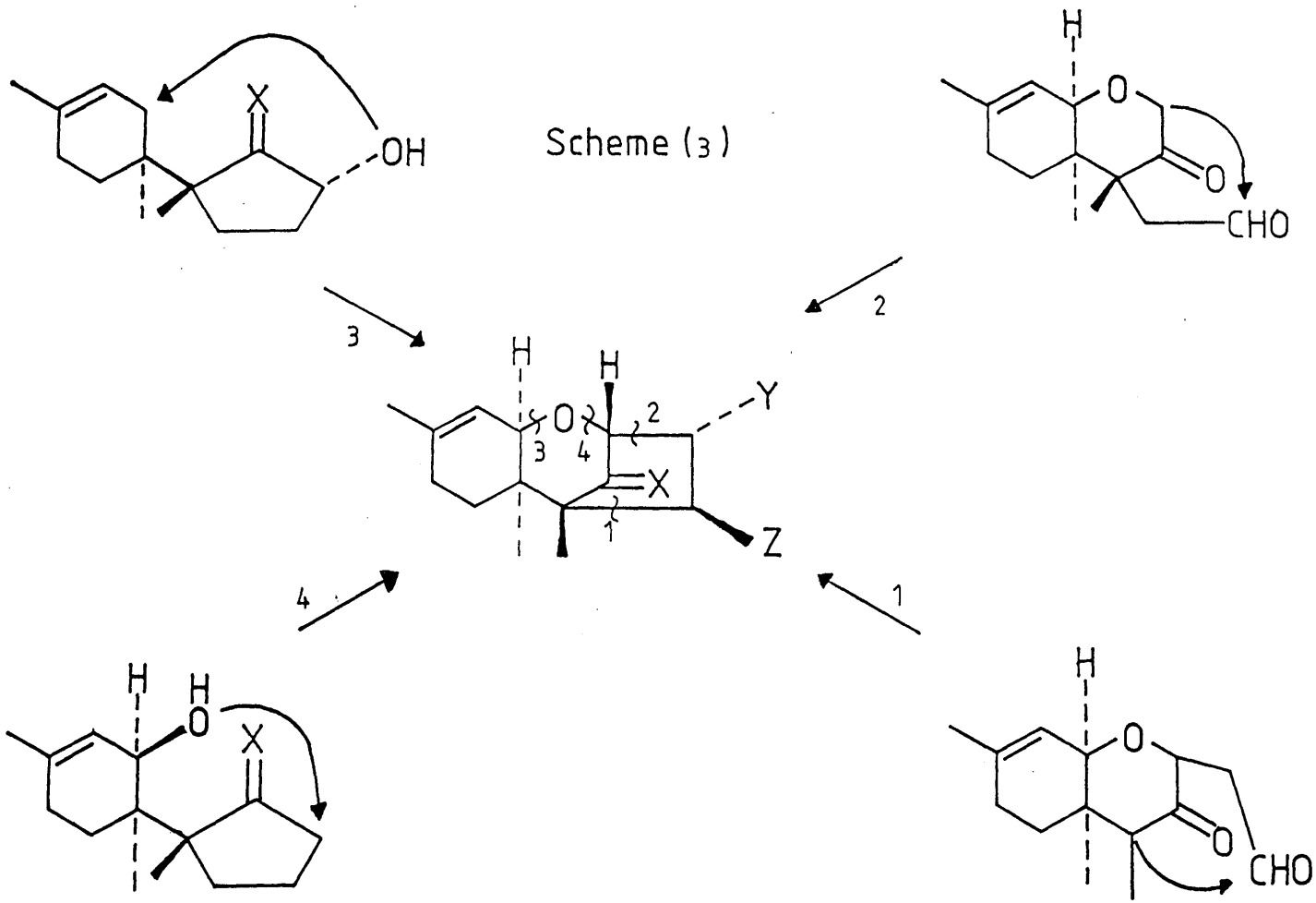
Most trichothecenes are difficult to obtain in significant amounts from culture broths. As a group, they therefore present a major synthetic challenge requiring both stereo- and regiocontrol for their successful construction. Total synthesis provides not only a means of producing analogues[38,39,40] to evaluate structure-activity relationships but also, by labelling specific sites within the molecule[41], it can aid the elucidation of metabolic pathways and routes of bio-elimination. The complexity of these naturally occurring toxins has aroused the attention of synthetic chemists to the extent that, in the last decade, more than 11 total syntheses of naturally occurring trichothecenes have been published.[42,43] In recent years, however, there has been a lull in total synthesis publication, possibly because most of the simpler members of the class have been constructed and also synthesis of the more highly oxygenated trichothecenes has proved too difficult. Attention now appears to be turning to natural trichothecene interconversions and modifications.[35,44,45]

Colvin, Raphael and Roberts achieved the first total synthesis[46] in 1971; the trichothecene in question was trichodermin (17), a mono-hydroxylated species. Following this success, a variety of other approaches to the tricyclic structure were described, but it was nine years later, in 1980, that the efforts of Still and Tsai[47], using an alternative strategy, climaxed in the synthesis of trichodermol (16).

In the next few years there was to be an explosion of work.

The first syntheses of polyhydroxylated trichothecenes were achieved simultaneously in 1982 by Schlessinger and Nugent[48] with the synthesis of verrucarol (18) and Kraus and coworkers[49] with the

Scheme (3)

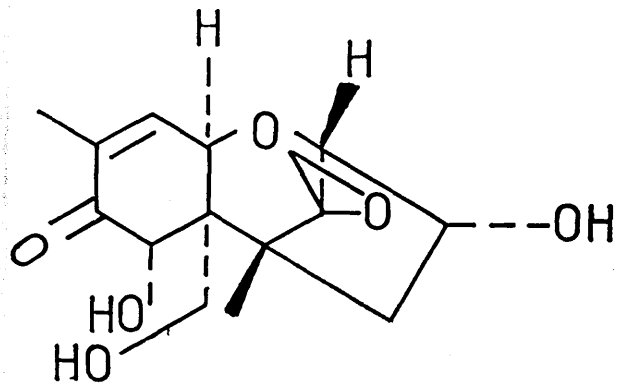


GROUP 3,4 BIOMIMETIC APPROACH

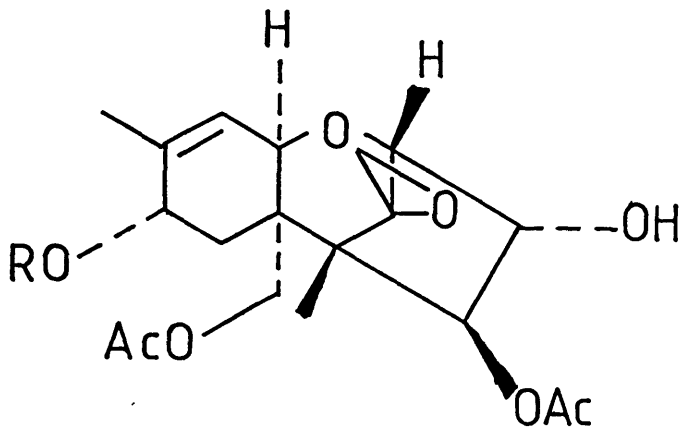
GROUP 1,2 ALDOL APPROACH

synthesis of calonectrin (19). Very soon thereafter, Trost and McDougal[50] along with Roush and D'Ambra[51] published alternative syntheses of verrucarol (18). The first trioxygenated trichothecene to be made by total synthesis was anguidine (20), prepared by Brooks.[52] Notably, this was the first example of an enantioselective synthesis in this area. More recently Pearson[53] has synthesised trichodermol (16).

Despite this intense research effort, the more complex trichothecenes, such as the 'Yellow Rain' toxins, deoxynivalenol (21) and T-2 toxin (22), have yet to yield to total synthesis.



DEOXYNIVALENOL (21)

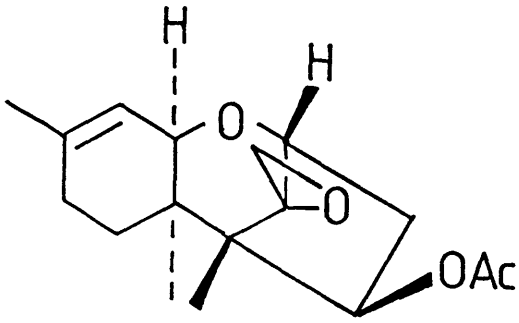


T-2 TOXIN (22)

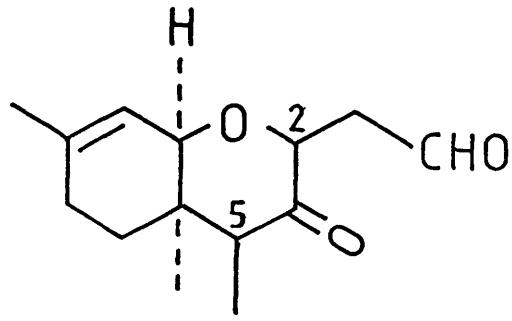
The eleven syntheses reported to date can be sub-divided into four categories, the divisions being based on the methods of cyclisation used to form the tricyclic ring system. Scheme 3 depicts this categorisation. Groups 1 and 2 (X = O, Y or Z = OH) form a subset which will be referred to as the aldol approach. Groups 3 and 4 (any number of variations X, Y, Z) form a subset which will be termed the biomimetic approach.

GROUP 1 ALDOL APPROACH

The group 1 aldol approach provided the first entry into the trichothecene skeleton with the stereoselective synthesis of racemic trichodermin[46] (17).



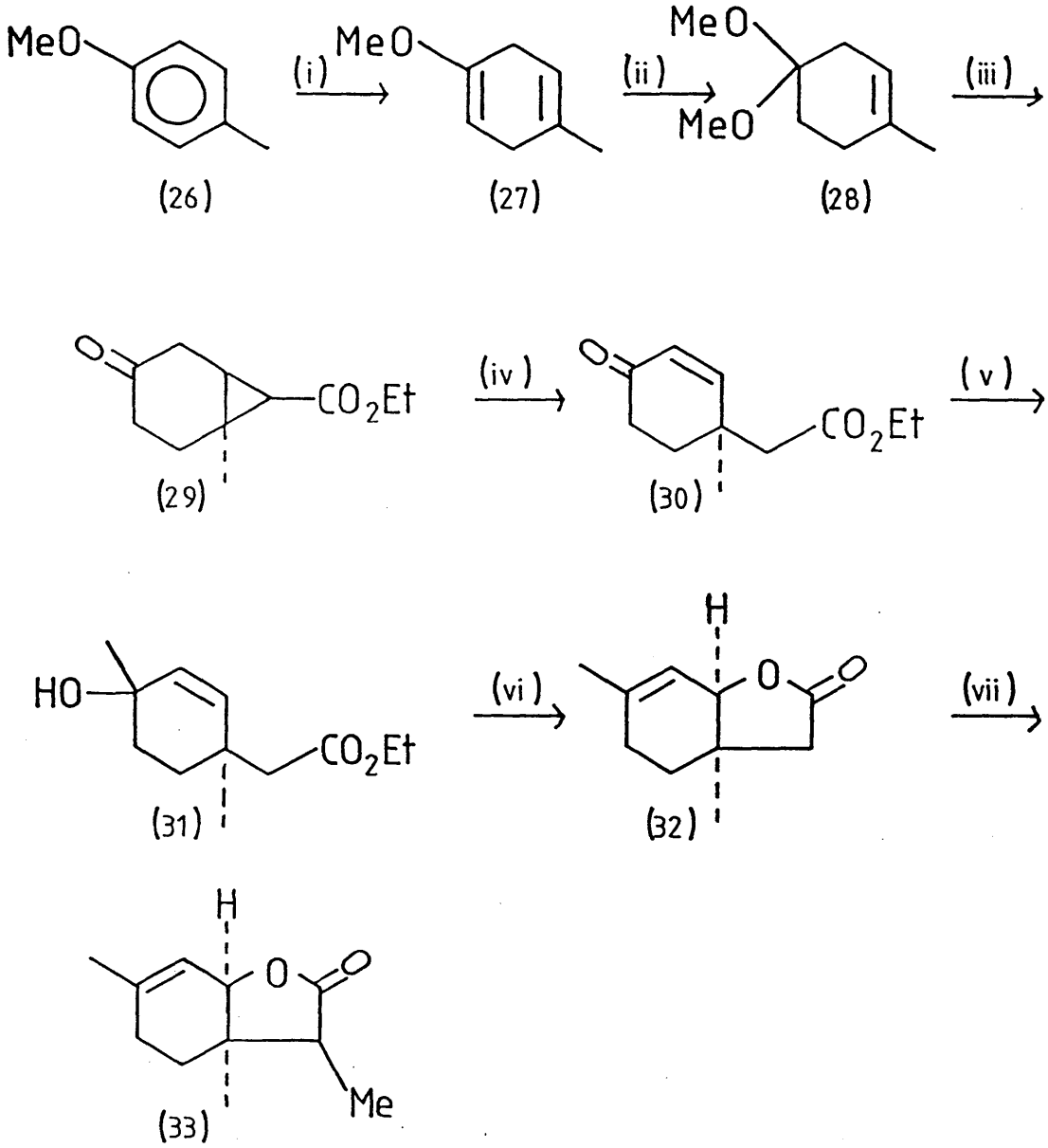
(17)



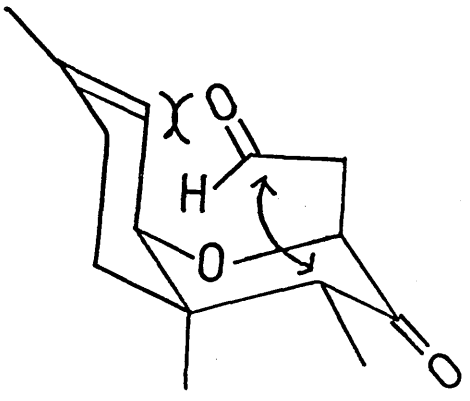
(23)

The initial concept was to preform a cis-fused AB ring system and then to create ring C by an intramolecular aldol cyclisation of keto-aldehyde (23). Although there was no stereochemical control at positions 2 or 5, it was felt that under aldol conditions epimerisation at these two centres would ensue giving rise to an equilibrium mixture of diastereoisomers.

Conformational analysis of the two possible conformers (24) and (25) indicated that the transition state (24) would be energetically less favoured due to non-bonded interactions.



Reagents :-(i) Birch-reduction
(ii) Acidic MeOH
(iii) $N_2=CHCO_2Et$, Cu Br ; TsOH , acetone
(iv) NaOAc, EtOH, reflux
(v) MeMgCl
(vi) 2N aq. NaOH ; 6N H_2SO_4
(vii) LDA , MeI



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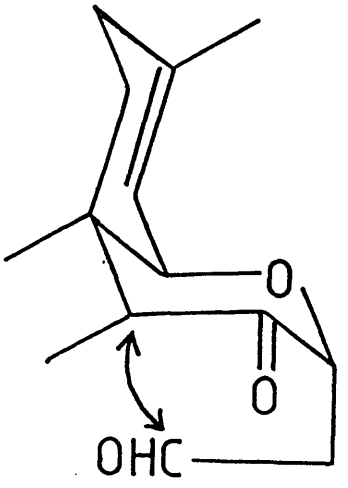


(25)

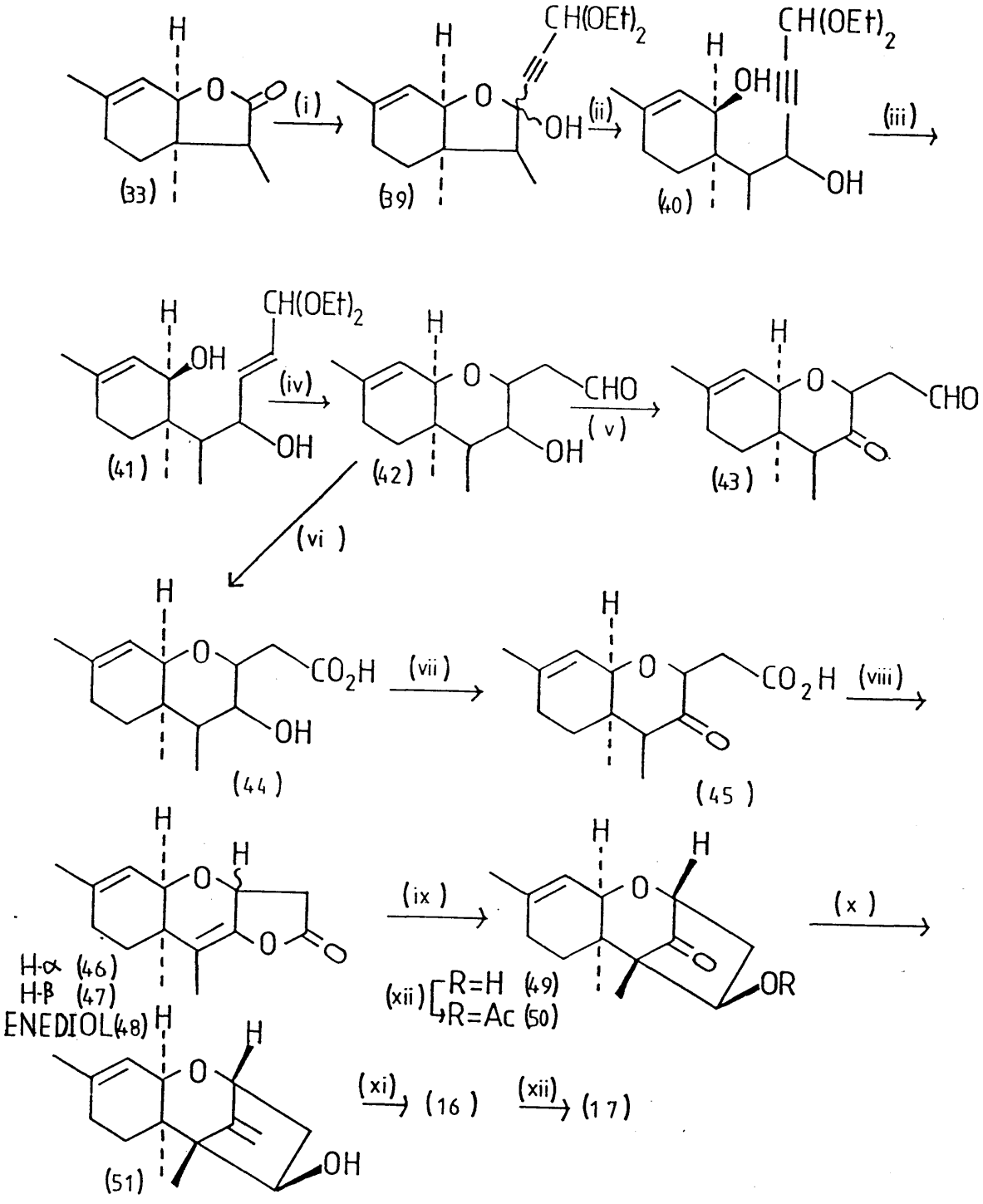
It was therefore hoped that the course of the aldolisation would proceed more rapidly with the component of the equilibrium mixture possessing the stereochemistry of (25) and thus lead to a product with relative stereochemistry corresponding precisely with that of trichodermin (17).

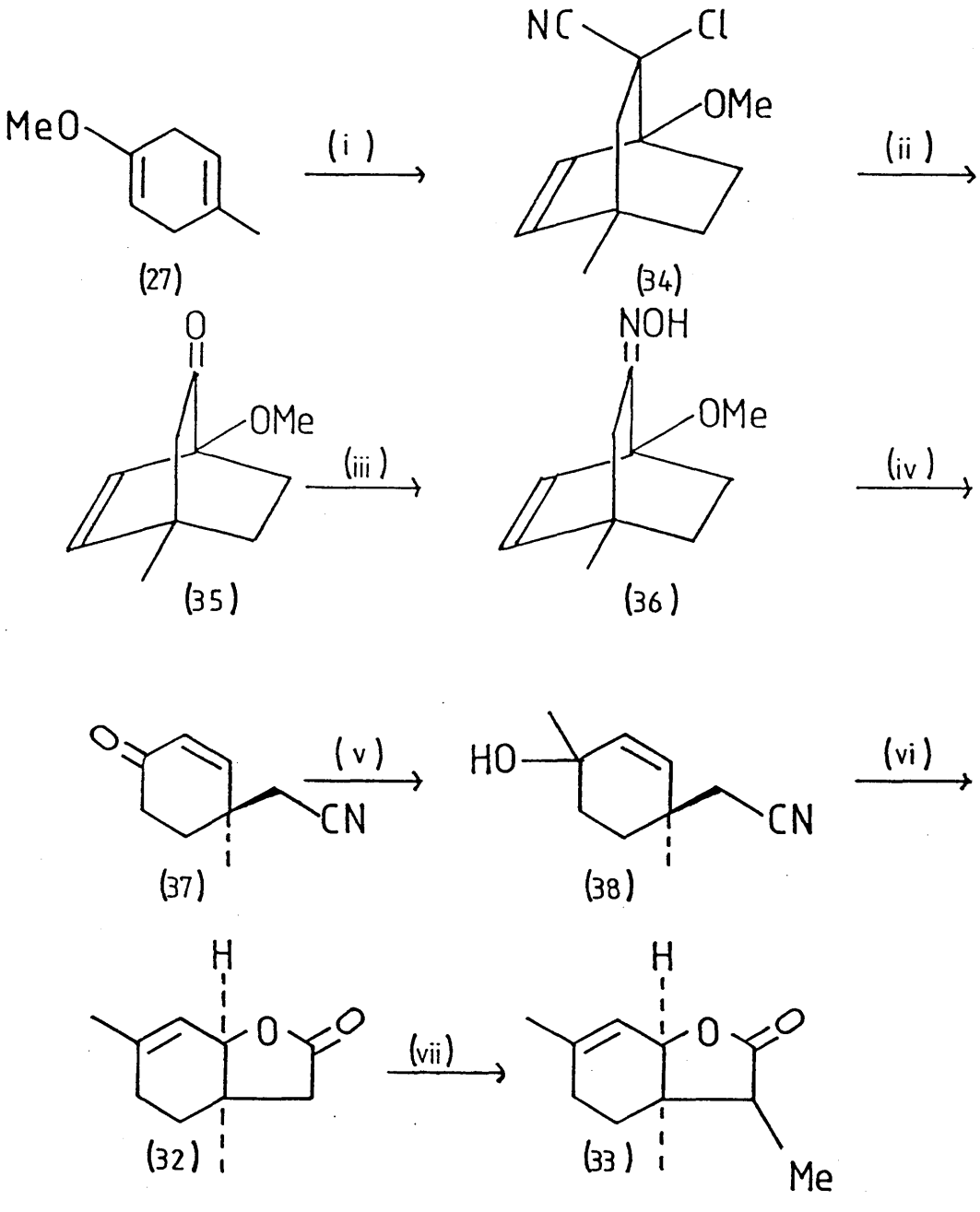
It was decided that the cis-fusion between the two six-membered rings should be built into the synthetic pathway as early as possible. Thus, the initial goal was the bicyclic γ-lactone (32), for which it had already been established[54] that the cis-stereoisomer was the thermodynamically favoured one.

Birch reduction of p-methoxytoluene (26) gave diene (27) from which two alternative routes were described leading to lactone (32).

In the first the dihydrocompound (27) was converted into dimethyl acetal (28). Reaction of (28) with ethyl diazoacetate gave the corresponding cyclopropane ester which was converted into the parent ketone (29) by trans-acetalisation. Base-induced fragmentation[55] of (29) gave the unsaturated keto-ester (30). Chemoselective

Reagents :- (i) Lithium-3,3-diethoxypropyne
(ii) $NaBH_4$
(iii) $Na/NH_3(l)$
(iv) NaOAc, AcOH
(v) CrO_3 /Py
(vi) CrO_3 /Py / H_2O
(vii) Jones Reagent
(viii) Ac_2O, NaOAc
(ix) $LiAlH(O^tBu)_3$
(x) Ph_3PCH_2
(xi) m-CPBA
(xii) Ac_2O, Py


(i)
(ii)
(iii)
(iv)
(v)
(vi)
(vii)
(viii)
(ix)
(x)
(xi)
(xii)
(16)
(17)
(33)
(39)
(40)
(41)
(42)
(43)
(44)
(45)
(46)
(47)
(48)
(49)
(50)
(51)
H-α
H-β
ENEDIOL
R=H
R=Ac
CH(OEt)2
CHO
CO2H
OH
OR



Reagents:- (i) 2-Chloroacrylonitrile, C_6H_6, Δ
(ii) 1·3eq. Na_2S, EtOH
(iii) $H_2NOH.HCl$, NaOAc
(iv) NaH, TsCl
(v) MeMgCl
(vi) HCl, MeOH
(vii) LDA, MeI

Grignard treatment gave the hydroxy-ester (31). Ester hydrolysis followed by acid treatment resulted in the formation of (32) via an anionotropic rearrangement.

The second route utilised a Diels-Alder reaction. Reaction of diene (27) with α-chloroacrylonitrile gave the bridged bicycle (34), the diene undergoing conjugation under the reaction conditions. Treatment of the adduct with sodium sulphide[56] gave the corresponding bicyclic ketone (35). Formation of oxime (36) was followed by an abnormal Beckmann rearrangement leading to keto-nitrile (37). Grignard treatment of (37) gave the corresponding tertiary alcohol (38) which, on acid hydrolysis, was converted into γ-lactone (32).

More recent publications have described alternative strategies to cis-fused lactones (32)[57] and (33).[58]

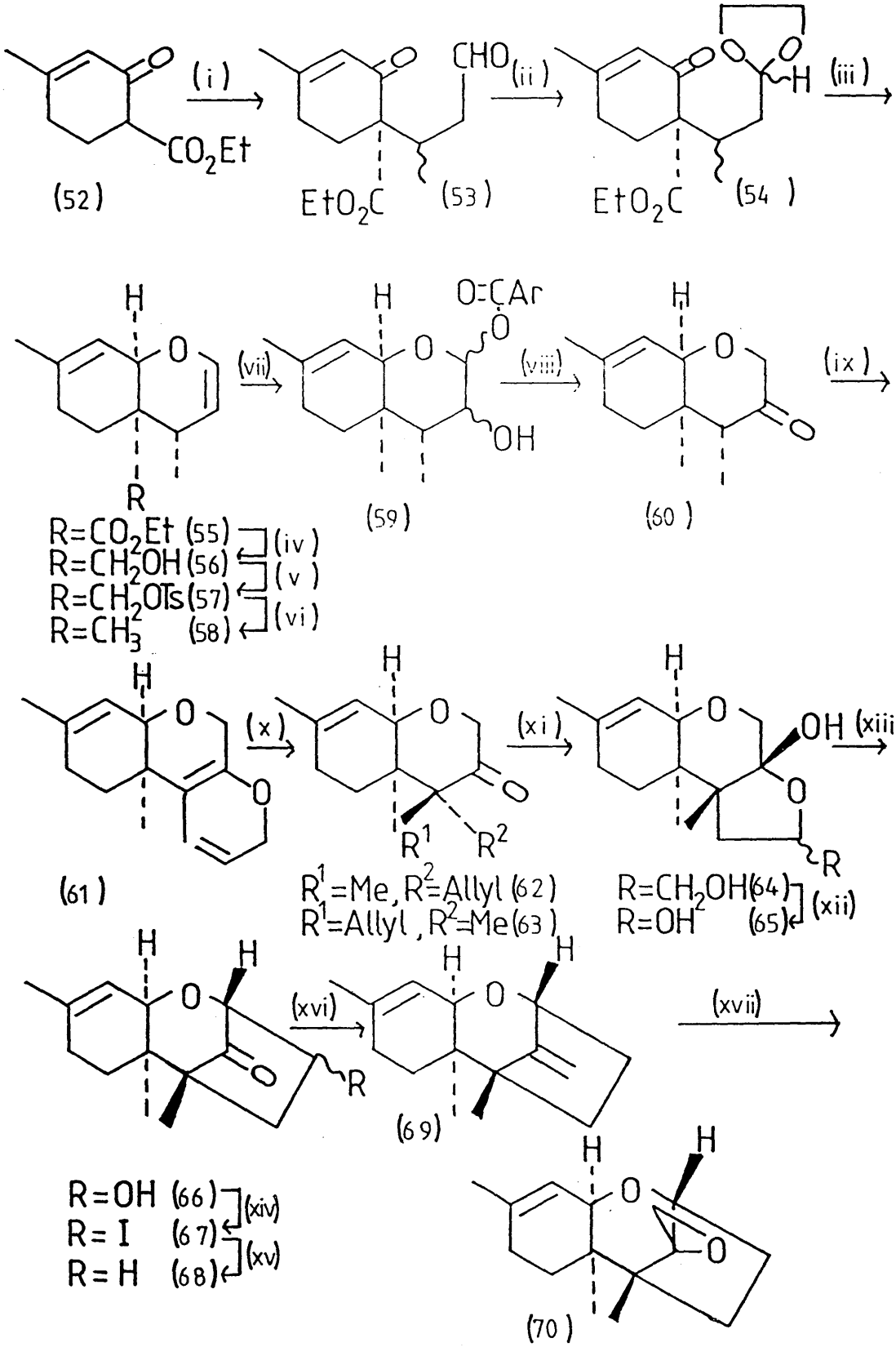
Alkylation of (32) with MeI gave the homologous γ-lactone (33) as a single methyl epimer. Interaction of (33) with the lithium salt of 3,3-diethoxypropyne gave (39). The acetylenic hemiacetal (39) was reduced to the corresponding diol (40). Sodium in liquid ammonia reduction gave the trans-alkene (41). Deprotection under mildly acidic conditions regenerated the aldehyde and at the same time induced an internal nucleophilic attack of the hydroxyl group on the enal to give the cis-fused bicyclic hydroxyaldehyde (42). Selective oxidation of (42) gave keto-aldehyde (43).

Despite extensive experimentation (43) could not be induced to undergo aldol cyclisation to the tricycle. To circumvent this stumbling block, the enol-lactones [(46) → (48)] were formed, effectively tying the two reactive sites together.

A two step oxidation of (42) gave keto-acid (45). Acetic

anhydride/sodium acetate treatment of (45) gave a mixture of enol lactones [(46), (47), (48)]. Reductive cyclisation[59] of the inseparable mixture gave the desired aldol product (49) in a low but readily reproducible yield. Acetylation followed by olefination gave (51). Hydroxyl directed epoxidation of the exomethylene alkene followed by acetylation gave trichodermin (17).

Reagents:- (i) (E)-MeCH=CHCHO, NaOMe
(ii) $(CH_2OH)_2$, H^+
(iii) Meerwein-Ponndorf reduction.
(iv) $LiAlH_4$
(v) TsCl, Py
(vi) $LiAlH_4$
(vii) m-CPBA
(viii) Triglyme, Py, Δ
(ix) NaH, Allyl bromide
(x) PhMe, Δ
(xi) OsO_4, $KClO_3$
(xii) $NaIO_4$
(xiii) NaOMe, MeOH
(xiv) Triphenylphosphite methiodide
(xv) Raney-Ni
(xvi) $Ph_3P=CH_2$
(xvii) m-CPBA


(i)
(ii)
(iii)
(52)
(53)
(54)
(vii)
(viii)
(ix)
(59)
(60)
R=CO2Et (55)
R=CH2OH (56)
R=CH2OTs (57)
R=CH3 (58)
(iv)
(v)
(vi)
(x)
(xi)
(xiii)
(61)
R1=Me, R2=Allyl (62)
R1=Allyl, R2=Me (63)
R=CH2OH (64)
R=OH (65)
(xii)
(xvi)
(xvii)
(69)
R=OH (66)
R=I (67)
R=H (68)
(xiv)
(xv)
(70)

GROUP 2 ALDOL APPROACH

The group 2 aldol approach has proved to be a more efficient entry into the trichothecene skeleton than the group 1 approach, which suffers from low yields in the crucial C-4 → C-5 bond forming reaction. It was developed in 1974 by Fujimoto and coworkers[60] in a total synthesis of racemic 12,13-epoxytrichothec-9-ene.

Keto-ester (52) was reacted with crotonaldehyde to give keto-aldehyde (53) which was converted into acetal (54). Meerwein-Ponndorf reduction of (54) gave the cis-fused pyran derivative (55). Deoxygenation to (58) was achieved via (56) and (57). Selective attack on the more electron rich double bond by m-CPBA produced a diastereoisomeric mixture of hydroxy-ester (59), which was pyrolysed to ketone (60). This compound could conceivably serve as an intermediate in either of the two aldol approaches depending on the regiochemistry of alkylation. However, alkylation of (60) with allyl bromide did not give rise to either of the two possible C-allylated products, the O-allylated compound (61) being obtained as sole product. Nevertheless, (61) was put to effective use. Claisen rearrangement of enol ether (61) gave a 2:1 mixture of allyl ketones (62) and (63). The two diastereoisomers were separated and the predominant isomer (62), with the correct C-5 stereochemistry, carried forward. Careful hydroxylation of (62) afforded diol (64) which was cleaved to yield the keto-aldehyde monohydrate (65). Aldol cyclisation of (65) using NaOMe gave a diastereoisomeric mixture of tricyclic ketol (66). Ketol deoxygenation was accomplished by a two-step process ; triphenylphosphite methiodide to convert the ketol into the keto-iodide and removal of the halogen with Raney-Ni to give ketone (68). Wittig reaction of (68) with

Reagents:-

(i) TBDMS-Cl, Imidazole, DMF

(ii) K_2CO_3, MeOH

(iii) $PhCH_2\overset{+}{N}Me_3\bar{O}H$

(iv) $ClOCCH_2CN$

(v) DBN

(vi) DIBAH

(vii) Et_3SiH, $BF_3.Et_2O$

(viii) DIBAH

(ix) $NaClO_2$, t-BuOH

(x) 1. $ClCO_2Et$, Et_3N 2. NaN_3 3. $\triangle$ 4. OH^- 5. H^+

(xi) n-Bu_4NF

(xii) $BrCOCH_2Br$

(xiii) Me_3SiI, $(Me_3Si)_2NH$

(xiv) n-Bu_4NF

(xv) 1. LiOH 2. CH_2N_2

(xvi) TBDMS-ClO_4, MeCN

(xvii) $LiAlH_4$

(xviii) DMSO, $(COCl)_2$, Et_3N

(xix) NaOMe, MeOH

(xx) $CH_2=CHOEt$, PPTS

(xxi) Ph_3PCH_2

(xxii) PPTS, MeOH

(xxiii) PCC, CH_2Cl_2

(xxiv) n-Bu_4NF

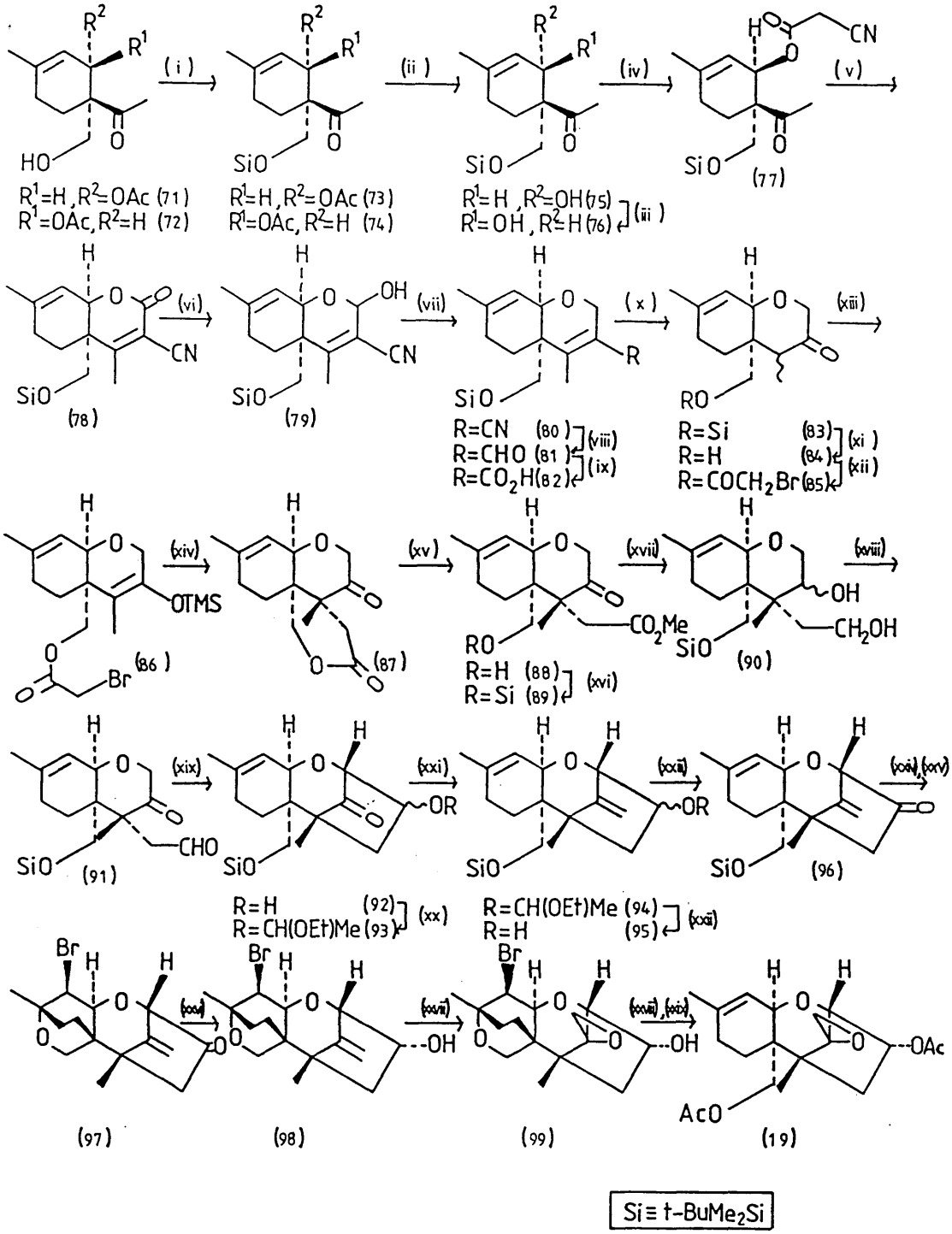
(xxv) NBS, MeCN

(xxvi) $NaBH_4$

(xxvii) CF_3CO_3H

(xxviii) Zn/Ag

(xxix) Ac_2O, DMAP, CH_2Cl_2


R1=H, R2=OAc (71)
R1=OAc, R2=H (72)
R1=H, R2=OAc (73)
R1=OAc, R2=H (74)
R1=H, R2=OH (75)
R1=OH, R2=H (76)
(77)
(78)
(79)
R=CN (80)
R=CHO (81)
R=CO2H (82)
R=Si (83)
R=H (84)
R=COCH2Br (85)
(86)
(87)
R=H (88)
R=Si (89)
(90)
(91)
R=H (92)
R=CH(OEt)Me (93)
R=CH(OEt)Me (94)
R=H (95)
(96)
(97)
(98)
(99)
(19)
Si ≡ t-BuMe2Si

methylene triphenylphosphorane gave the corresponding exomethylene compound (69) which was treated with m-chloroperbenzoic acid to afford (±)-12,13-epoxytrichothec-9-ene (70). In the absence of hydroxyl-aided epoxidation the final epoxidation of diene (69) was complicated by accompanying oxidation of the 9,10-alkene. In an attempt to circumvent this problem, (68) was treated with the methylene transfer agent dimethyl sulphonium methylide. However, this yielded the unnatural 12,13-epoxide, a result which had been reported previously.[61] Although the key aldol cyclisation in Fujimoto's route was high yielding, there was only modest stereocontrol at the Claisen rearrangement step.

An alternative strategy devised by Kraus and Roth[49] also utilised the group 2 aldol approach but by a cleverly conceived intramolecular process, the two carbon bridge of ring C was installed stereospecifically [(86) → (87)].

Lewis acid promoted Diels-Alder reaction between 1-acetoxy-3-methylbutadiene and 3-(hydroxymethyl)-3-buten-2-one afforded a diastereoisomeric mixture of acetoxy ketones (71) and (72). Saponification of the acetates (73) and (74) gave a mixture of hydroxyketones (75) and (76); hydroxy ketone (75) could be equilibrated by a retroaldol-aldol process to a 1:1 mixture of (75) and (76) from which the desired β-epimer (76) could be readily separated. Intramolecular Knoevenagel cyclisation of (77) gave (78). Reduction of (78) with DIBAH afforded an unstable lactol (79) which could be reduced to the allylic ether (80) with triethylsilane and boron trifluoride etherate.[62] DIBAH reduction of (80) gave aldehyde (81). Aldehyde (81) was oxidised to acid (82), which was transformed into the desired hydroxy ketone (84) by Curtius

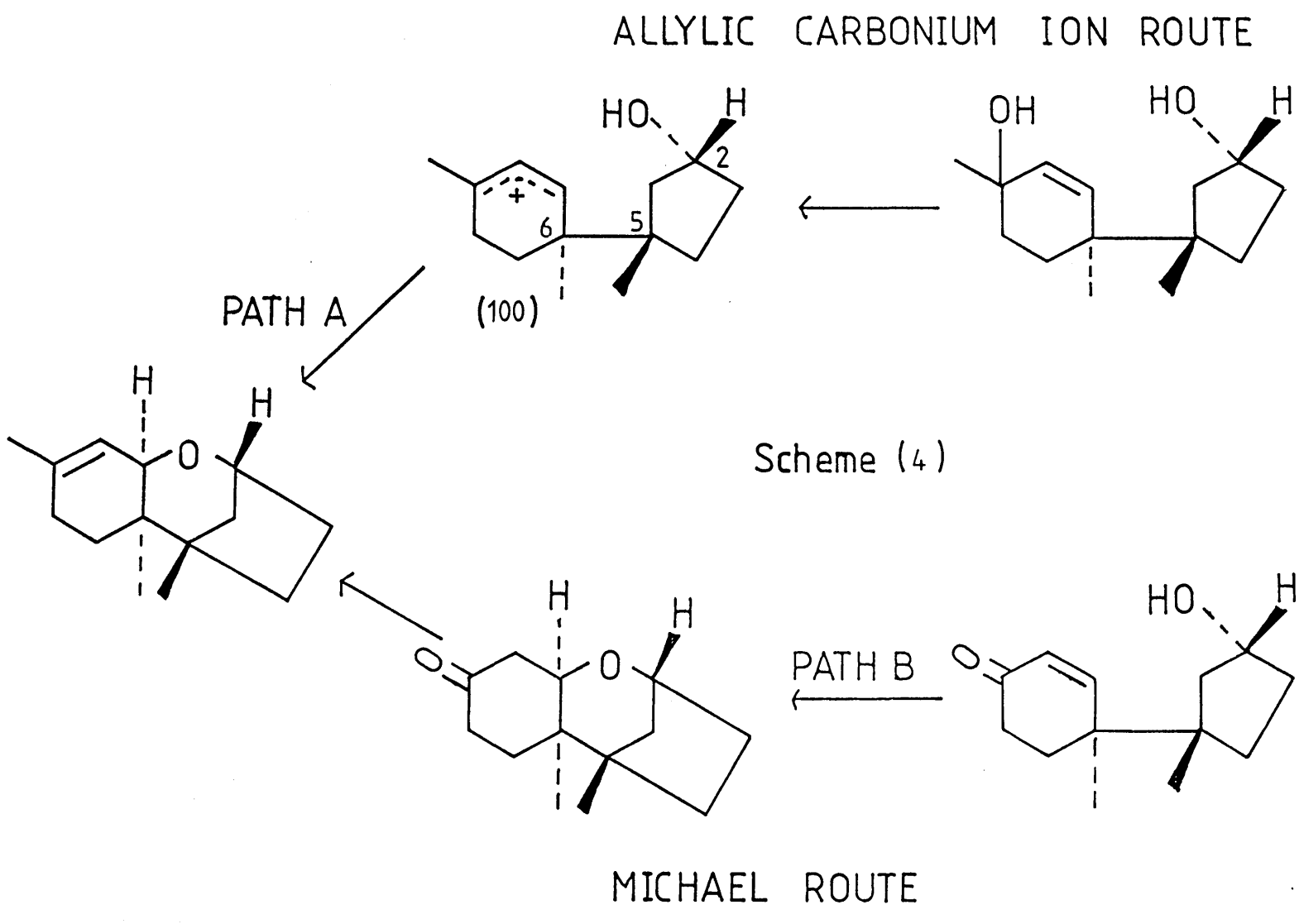
degradation,[63] Ketol (84) was acylated with bromoacetyl bromide and the resulting α-bromo keto-ester (85) was transformed into the silyl enol ether (86),

The crux of the synthetic strategy now hinged on intramolecular delivery of the two-carbon fragment, ensuring the correct relative stereochemistry and setting the stage for the construction of the tricyclic system.

Fortunately cyclisation of (86) to keto-lactone (87) could be effected with fluoride ion. Keto-lactone (87) was hydrolysed and esterified with diazomethane to give the unstable hydroxy ester (88). Protection[64] of the free alcohol as its silyl ether (89) followed by careful reduction furnished diol (90), which was oxidized to keto-aldehyde (91) using Swern's reagent.[65] Following Fujimoto's methodology, reaction of keto-aldehyde (91) with excess sodium methoxide in refluxing methanol afforded a mixture of epimeric ketols (92) in a ratio of 6:1. After alcohol protection, the exomethylene alkene was introduced as previously described to furnish (94). Alcohol deprotection and PCC oxidation provided ketone (96). Conscious of the lack of regiocontrol in epoxidation of dienes of the type (96), the 9,10-trisubstituted alkene was protected by bromo ether formation [66]. As expected, hydride reduction of ketone (97) was highly stereoselective, taking place from the more accessible exo face of the bicyclo[3.2.1]octane subunit. Epoxidation was accomplished with buffered trifluoroperacetic acid to give (99). Regeneration of the 9,10-alkene and finally acetylation then provided calonectrin (19).

The group 2 aldol routes just described, Fujimoto's 19 stage synthesis of 12,13-epoxytrichothec-9-ene (70) and Kraus' heroic 31 stage

synthesis of calonectrin (19) both illustrate that the group 2 approach can provide a viable entry to the trichothecene skeleton. Kraus has also indicated his intention to elaborate the olefinic ketone (96) to both anguidine (20) and verrucarol (18). Colvin and Thom, again using group 2 methodology, have reported[67] their progress towards the total synthesis of deoxynivalenol, one of the more complex highly oxygenated trichothecenes. At present, this total synthesis is tantalisingly close to completion.


ALLYLIC CARBONIUM ION ROUTE
HO
H
OH
HO
H
2
6
5
(100)
PATH A
H
H
O
H
H
O
PATH B
HO
H
MICHAEL ROUTE

Scheme (4)

GROUP 3 BIOMIMETTIC APPROACH

To date the group 3 biomimetic approach has enjoyed the greatest popularity with five successful total syntheses and numerous analogue syntheses. Cyclisation can proceed by either of two routes (scheme 4); the hydroxyl in ring C can quench an allylic carbonium ion (Path A) or it can add conjugatively to an enone (Path B). When the cyclisation proceeds *via* an allylic carbonium ion (100), the desired 9,10-alkene is obtained directly. If, however, it proceeds *via* the Michael route, the ketone so obtained must be transformed into the 9,10-alkene, a process which shows good, if incomplete, regioselectivity.[47]

Masuoka, Kamikawa and Kubota reported[68] that for either of the two routes to proceed the C-2 alcohol must have the correct relative stereochemical orientation since the highly stereospecific nature of the cyclisation depends on favourable orbital overlap during the addition (Figure 1).

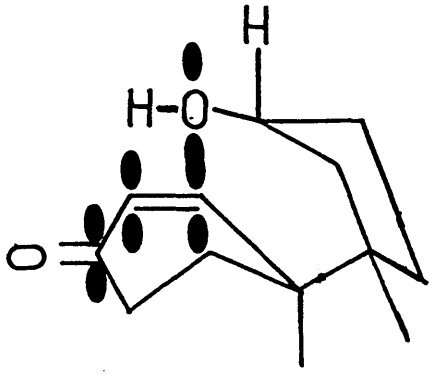
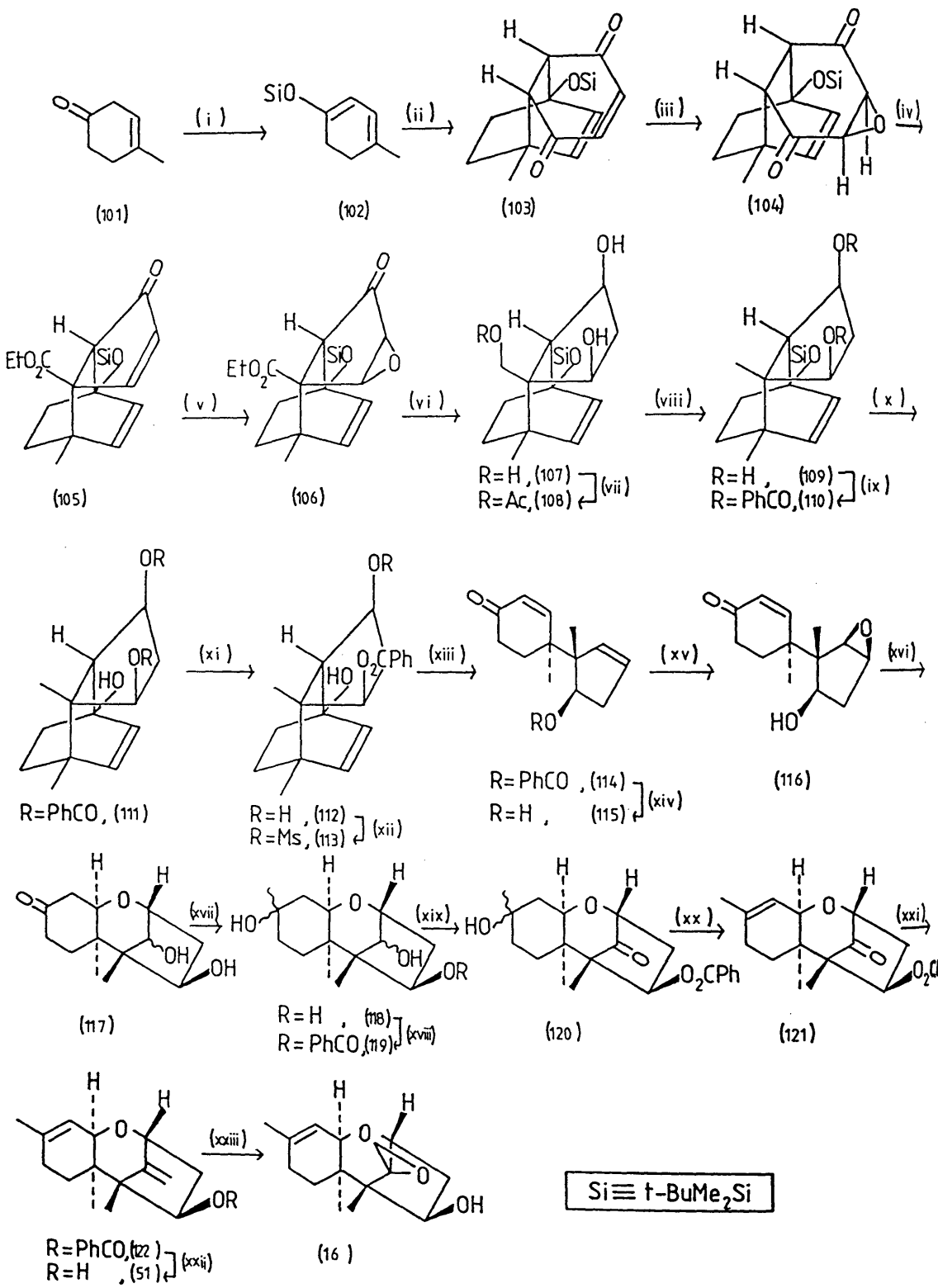


FIGURE (1)

Consequently, any synthetic strategy must control the relative stereochemistry not only at the two quaternary centres, C-5 and C-6, but also at the C-2 alcohol position.

For the purposes of this report the Michael route and the allylic carbonium ion route will be examined separately.

Reagents:- (i) LDA, THF/HMPA, TBDMSCl
(ii) p-Benzoquinone, C_6H_6
(iii) TBHP, Triton B
(iv) NaOH, EtOH
(v) TBHP, Triton B
(vi) $Li/NH_3(l)$
(vii) Ac_2O, Py
(viii) hν, deoxygenated HMPT
(ix) PhCOCl, Py
(x) n-Bu_4NF, THF
(xi) K_2CO_3, MeOH
(xii) MsCl, Et_3N
(xiii) NaH, THF
(xiv) K_2CO_3, MeOH
(xv) TBHP, $VO(acac)_2$
(xvi) 2% aq H_2SO_4
(xvii) MeLi, THF
(xviii) PhCOCl, Py
(xix) $CrO_3.Py_2$, CH_2Cl_2
(xx) $POCl_3$, Py
(xxi) Ph_3PCH_2
(xxii) K_2CO_3, MeOH
(xxiii) m-CPBA


(i)
(ii)
(iii)
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(vi)
(vii)
(viii)
(ix)
(x)
(xi)
(xii)
(xiii)
(xiv)
(xv)
(xvi)
(xvii)
(xviii)
(xix)
(xx)
(xxi)
(xxii)
(xxiii)
(101)
(102)
(103)
(104)
(105)
(106)
R=H, (107)
R=Ac, (108)
R=H, (109)
R=PhCO, (110)
R=PhCO, (111)
R=H, (112)
R=Ms, (113)
R=PhCO, (114)
R=H, (115)
(116)
(117)
R=H, (118)
R=PhCO, (119)
(120)
(121)
R=PhCO, (122)
R=H, (51)
(16)
Si≡ t-BuMe2Si

MICHAEL ROUTE

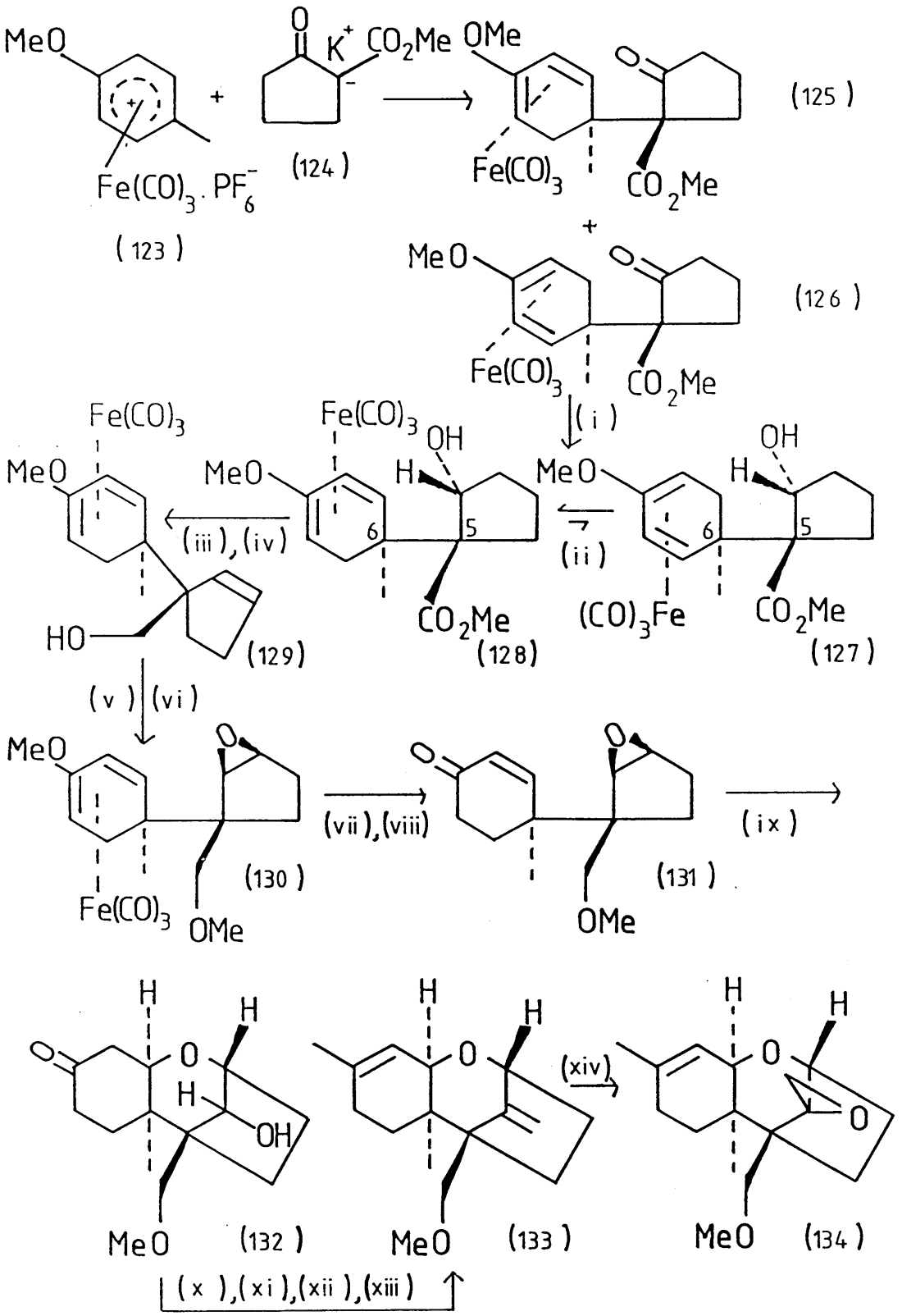
Although this route has been used successfully on two occasions, once for the synthesis of a natural trichothecene[47] and once for a trichothecene analogue,[69] each group has adopted a different strategy in establishing the relative stereochemistries at the three critical centres.

The first to employ the Michael route, Tsai and Still reported the second successful total synthesis of trichodermol (16). Stereochemistry at the two quaternary centres was controlled by an elegant cycloaddition-fragmentation sequence.

Cycloaddition of quinone with the cyclohexadienyl silyl ether (102) gave a high yield of the expected endo-adduct (103). By a cleverly conceived process, the dienone ring was contracted[70]; initial epoxidation followed by treatment with base gave the cyclopentenone system (105) having the correct ring size for ring C and capable of being elaborated and unmasked later in the synthesis. Stereospecific epoxidation of the enone gave the α,β-epoxy ketone (106). Reduction of (106) gave the triol (107) possessing the correct C-4 hydroxyl stereochemistry. The primary alcohol was deoxygenated[71] to give (109) which by a series of protection and selective deprotection steps furnished diol (112). Mesylation of the secondary alcohol followed by treatment with sodium hydride resulted in smooth fragmentation of the hydroxymesylate to give the advanced intermediate (114) in which the relative stereochemistry of the two isolated rings was now fixed.

The plan was to trans-hydroxylate the C-2, C-12 alkene. However, as the alkene proved to be relatively unreactive towards peracids, (114) was debenzoylated and the free hydroxyl used to direct the epoxidation.

Reagents:- (i) $NaBH_4$
(ii) p-TSA
(iii) $SOCl_2$ / Py
(iv) $LiAlH_4$
(v) m-CPBA
(vi) NaH / MeI
(vii) $Et_3\overset{+}{N}\overset{-}{O}$
(viii) H_3O^+
(ix) 2% aq H_2SO_4
(x) MeLi
(xi) $CrO_3.Py_2$
(xii) $POCl_3$, Py
(xiii) Ph_3PCH_2
(xiv) m-CPBA


MeO
Fe(CO)3. PF6−
(123)
(124)
K+ CO2Me
OMe
Fe(CO)3
CO2Me
(125)
(126)
(i)
(ii)
(iii), (iv)
(v)
(vi)
(vii), (viii)
(ix)
(x), (xi), (xii), (xiii)
(xiv)
OH
HO
(CO)3Fe
(127)
(128)
(129)
(130)
(131)
(132)
(133)
(134)

The synthesis hinged on being able to open the C-2, C-12 β-epoxide in such a way that the newly added hydroxyl at C-2 would have the α-configuration required for subsequent cyclisation.

Fortunately, treatment of (116) with dilute H_2SO_4 resulted in the direct formation of the bridged tricyclic intermediate (117), via the trans-C-2α, C-12β-diol.

Ketone (117) was treated with methyl lithium to give triol (118). Selective benzoylation followed by oxidation gave (120), which underwent regioselective dehydration to give a 7:1 mixture of olefins with the desired regioisomer predominating. The final elaboration to trichodermol (16) was carried out as for trichodermin.

Pearson and Ong have also used the Michael route for the synthesis of a trichothecene analogue (134). Although their approach was modelled on Still's epoxide-opening-cyclisation sequence [(116) → (117)], a novel aspect of their work was the method used to control the C-5, C-6 stereochemistry.

Reaction of the β-keto-ester enolate (124) with tricarbonyl-(4-methoxy-1-methylcyclohexadienylium) iron hexafluorophosphate (123) gave a 1:1 mixture of the two diastereoisomers (125) and (126), setting up, in one step, the correct relative stereochemistry of the two quaternary centres. Reduction of the mixture gave complexes (127) and (128) which could be readily separated. As double bond migration in the cyclohexadienyl ring serves to invert the absolute stereochemistry at C-6, the separated complex (127) with the incorrect stereochemistry was treated with a catalytic amount of acid to establish equilibrium. Consequently, although the original alkylation had yielded both (125) and (126), an 80% yield of the diastereoisomer (128) could be obtained

by this means of equilibration.

Dehydration of the secondary alcohol, followed by reduction of the methyl ester gave (129). Hydroxyl-directed epoxidation using the Sharpless procedure[72] and then alcohol protection gave (130). Decomplexation gave enone (131) which was subjected to glycol formation using aqueous H_2SO_4, producing (132) directly. Subsequent elaboration to analogue (134) followed Still's methodology, although in the absence of hydroxyl-direction the final epoxidation had to be strictly controlled to avoid formation of diepoxide.

Reagents:-(i) $h\nu$, Et_2O

(ii) 50% aq AcOH

(iii) $(CH_2SH)_2$, $BF_3.Et_2O$

(iv) NaH , $(EtO)_2CO$

(v) CH_2O, Et_2NH , $Et_2NH.HCl$

(vi) $B(OH)_3$

(vii) $NaBH_4$

(viii) Ac_2O , Py

(ix) $HgCl_2$, $CdCO_3$

(x) OH^-

(xi) MsCl , Py

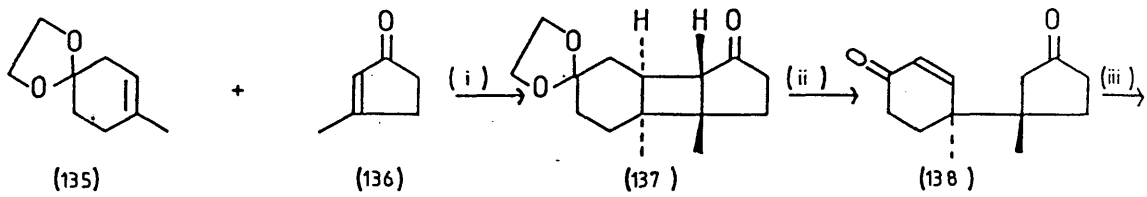
(xii) Et_4 NOAc

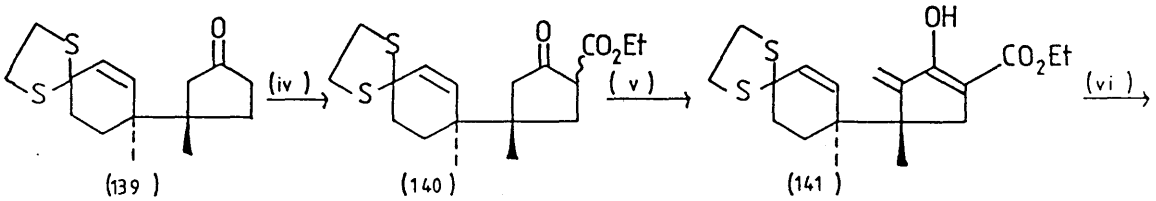
(xiii) MeMgI

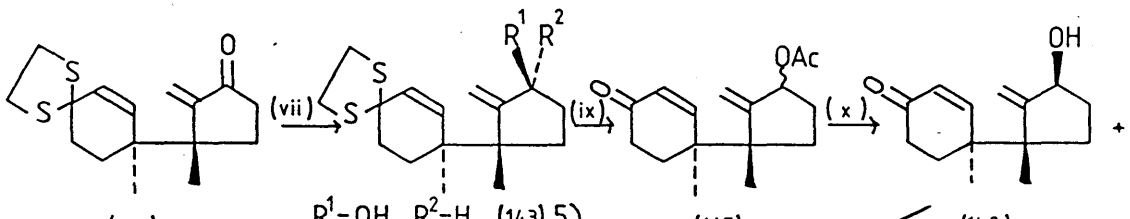
(xiv) OH^-

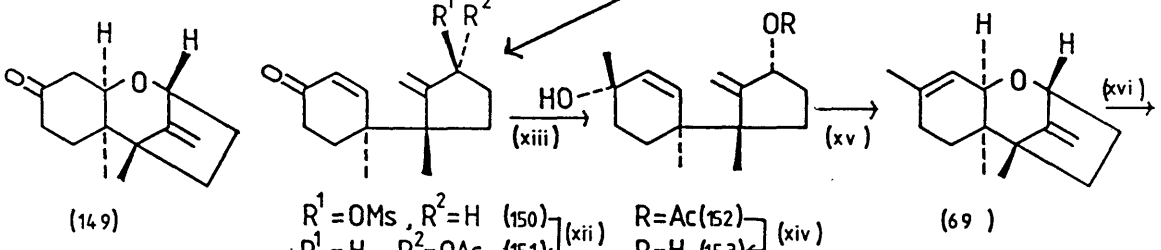
(xv) H_3O^+

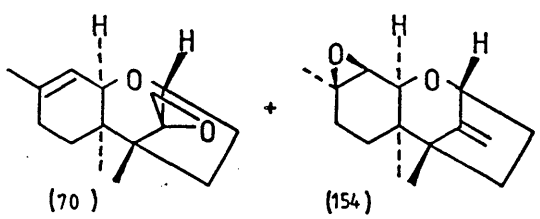
(xvi) m-CPBA


(135)
(136)
(i)
(137)
(ii)
(138)
(iii)


(139)
(iv)
(140)
CO2Et
(v)
(141)
OH
CO2Et
(vi)


(142)
(vii)
R1 R2
(ix)
OAc
(147)
(x)
OH
(148)
R1=OH, R2=H (143) 5
R1=H, R2=OH (144) 1
R1=OAc, R2=H (145)
R1=H, R2=OAc (146)
(viii)
(xi)


(149)
R1 R2
HO
(xiii)
OR
(xv)
(xvi)
(69)
R1=OMs, R2=H (150)
R1=H, R2=OAc (151)
(xii)
R=Ac (152)
R=H (153)
(xiv)


(70)
(154)

ALLYLIC CARBONIUM ION ROUTE

The general strategy for this route was developed by Masuoka, Kamikawa and Kubota[68,73] in a synthesis of 12,13-epoxytrichothec-9-ene (70).

Irradiation of a mixture of 3-methylcyclopent-2-en-1-one (136) and 4-methylcyclohex-3-en-1-one ethylene ketal (135) gave rise to a complex mixture of products from which (137) could be isolated in 16% yield. Treatment of (137) with 50% aqueous acetic acid resulted in deprotection of the ketal and fragmentation to give adduct (138) with the correct C-5, C-6 relative stereochemistry. Selective thioketalisation of the enone gave (139). Since direct methylenation of C-12 was unsuccessful using a variety of techniques, ketone (139) was subjected to α-methylenation using a method developed by Miller and Smith.[74] Alkene (141) so obtained was transformed into enone (142). Hydride reduction of (142) gave a mixture of epimeric alcohols; acetylation followed by desulphurisation gave acetate (147). Saponification furnished both the β-allylic alcohol (148) and the tricycle (149), emphasising the fact that only the α-alcohol can add[68] to the α,β-unsaturated ketone. The β-allylic alcohol was transformed into the 2α-acetate by a two step process involving mesylation followed by displacement with tetraethylammonium acetate. Reaction of (151) with methylmagnesium iodide followed by alkaline hydrolysis gave diol (153) which on acidification gave diene (69) as a single compound. Oxidation of (69) with m-CPBA gave a mixture of the two epoxides (70) and (154).

Although this synthesis provided an authentic sample of the natural toxin, it had 3 major disadvantages.

Reagents:-(i) $MeCOCH=CH_2$, Py

(ii) TsOH , AcOH

(iii) $NaBH_4$

(iv) $CH_2=CMe_2$, $BF_3.Et_2O$

(v) LDA , TMSCl

(vi) m-CPBA

(vii) O_3 , $NaIO_4$, CrO_3

(viii) Ph_3PCH_2

(ix) cat. SeO_2 , TBHP

(x) TsOH, CH_2Cl_2

(xi) LDA , CH_2O

(xii) $MeOCH=CHC(OTMS)=CH_2$

(xiii) Amberlite IR-120

(xiv) MeLi, THF

(xv) $LiAlH_4$

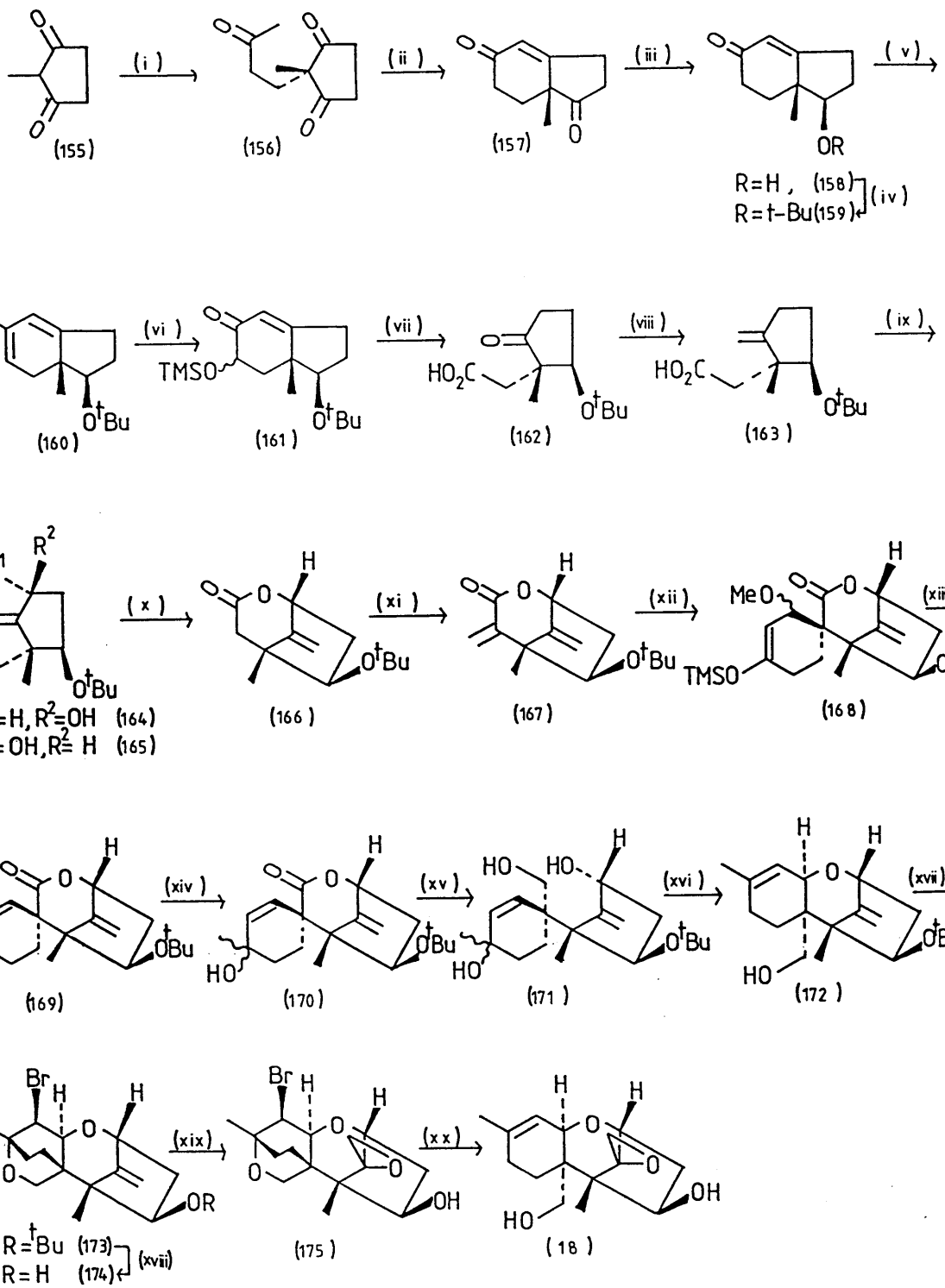
(xvi) cat. TsOH

(xvii) NBS , acetone

(xviii) $TiCl_4$

(xix) m-CPBA

(xx) Na , $EtNH_2$, THF


(155)
(i)
(156)
(ii)
(157)
(iii)
R=H, (158)
R=t-Bu (159)
(iv)
(v)
TMSO
(160)
(vi)
(161)
(vii)
(162)
(viii)
(163)
(ix)
R1=H, R2=OH (164)
R1=OH, R2=H (165)
(x)
(166)
(xi)
(167)
(xii)
MeO
TMSO
(168)
(xiii)
(169)
(xiv)
(170)
(xv)
(171)
(xvi)
(172)
(xvii)
R=tBu (173)
R=H (174)
(xviii)
(xix)
(175)
(xx)
(18)

1. The initial photoaddition produced a variety of compounds and was low yielding in (137).

2. Reduction of (142) gave the wrong C-2 alcohol which had to be inverted.

3. Epoxidation of the 12,13-alkene was competitive with oxidation of the 9,10-alkene.

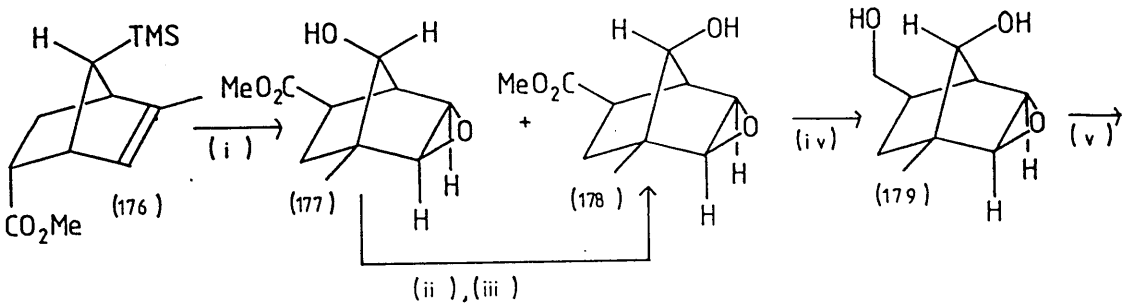
Schlessinger and Nugent also employed the group 3 allylic carbonium ion route to synthesise verrucarol (18), but by utilising an alternative approach, they eliminated the problems previously encountered in the synthesis of 12,13-epoxytrichothec-9-ene (70). Additionally the synthesis of (18) is *via* a route which has the potential[75] to be extended to allow the preparation of verrucarol in optically active form.

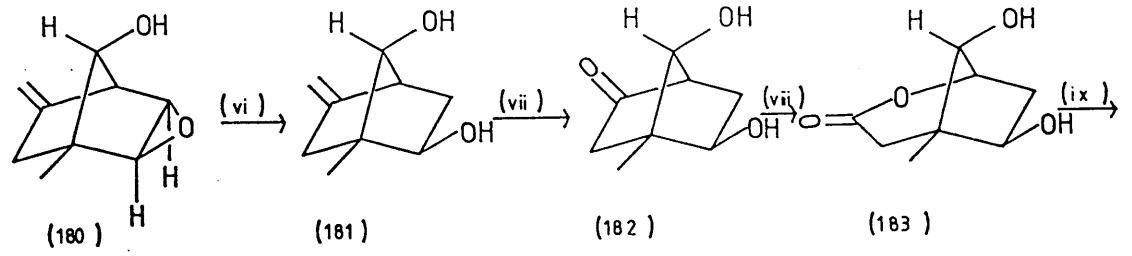
Robinson annelation of (155) with methyl vinyl ketone gave dione (157). Selective hydride reduction of (157) from the less hindered face gave alcohol (158) thereby establishing the C-4 hydroxyl stereochemistry. After hydroxyl protection, α-oxidation of the enone followed by ozonolysis and oxidative work-up furnished keto-acid (162), which was converted into exocyclic alkene (163). Allylic oxidation afforded a mixture of alcohols in which the desired α-epimer predominated in a ratio of 5:1. The orientation of the alcohol was confirmed by lactone formation to give (166). Treatment of the enolate derived from (166) with monomeric formaldehyde afforded the key intermediate (167).

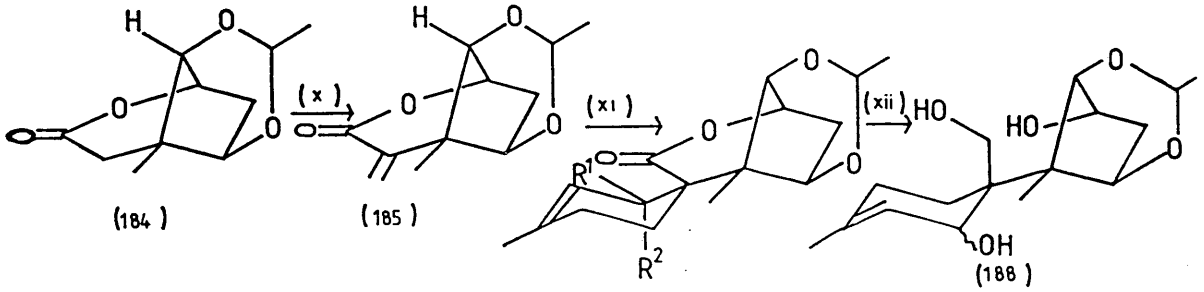
Stereocontrol at C-5, C-6 was achieved by means of a Diels-Alder reaction. Because of the shape of the bicyclic lactone, combination of (167) and Danishefsky's diene resulted in exclusive

attack of the diene from the less hindered top face of the enone component, thereby controlling the stereochemistry at the critical centres. The silyl enol ether (168) was hydrolysed and the enone so obtained treated with methyl lithium to afford alcohol (170). Hydride reduction of (170) furnished triol (171) which underwent smooth acid-catalysed cyclisation to give (172). Since epoxidation of diene (172) proved to be non-regiospecific even in the presence of the free C-4β hydroxyl, the 9,10-alkene was protected as its bromoether (173). Removal of the tert-butyl protecting group followed by stereospecific epoxidation converted (174) into (175). Finally regeneration of the trisubstituted olefin gave verrucarol (18).

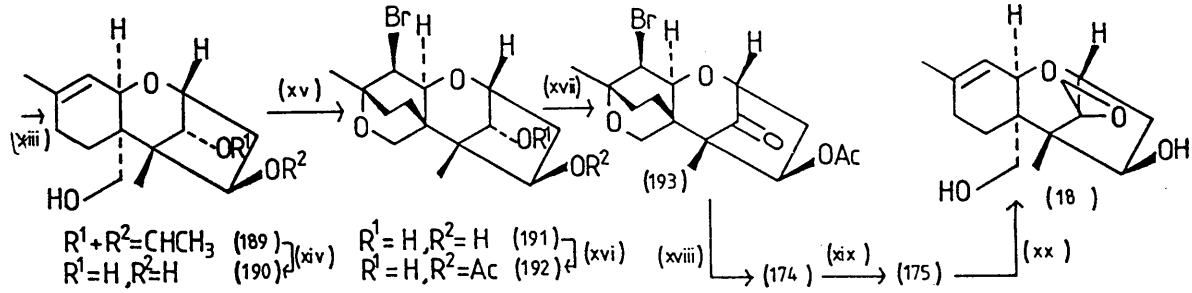
Reagents :-(i)3,5-Dinitroperoxybenzoic acid, $NaHCO_3$
(ii)a.TFAA, Me_2SO b.Et_3N
(iii)$NaBH_4$
(iv)$LiAlH(OMe)_3$
(v)a.o-Nitrophenylselenocyanate, $n\text{-}Bu_3P$
b.m-CPBA
(vi)Li, $(CH_2NH_2)_2$
(vii)a.O_3 b.Me_2S
(viii)m-CPBA
(ix)$MeCH(OMe)_2$, TsOH
(x)LDA, CH_2O
(xi)$AcOCH{=}CHC(Me){=}CH_2$, PhMe
(xii)$LiAlH_4$
(xiii)PPTS, C_6H_6
(xiv)1M HCl
(xv)NBS, MeCN
(xvi)Ac_2O, Py
(xvii)Jones oxidation
(xviii)Ph_3PCH_2
(xix)m-CPBA
(xx)Zn/Ag







$R^1 = H, R^2 = OAc$ (186) 1
$R^1 = AcO, R^2 = H$ (187) 3



$R^1 + R^2 = CHCH_3$ (189) ┐(xiv)
$R^1 = H, R^2 = H$ (190) ┘

$R^1 = H, R^2 = H$ (191) ┐(xvi)
$R^1 = H, R^2 = Ac$ (192) ┘

(xviii) → (174) → (175) → (xx)
(xix)

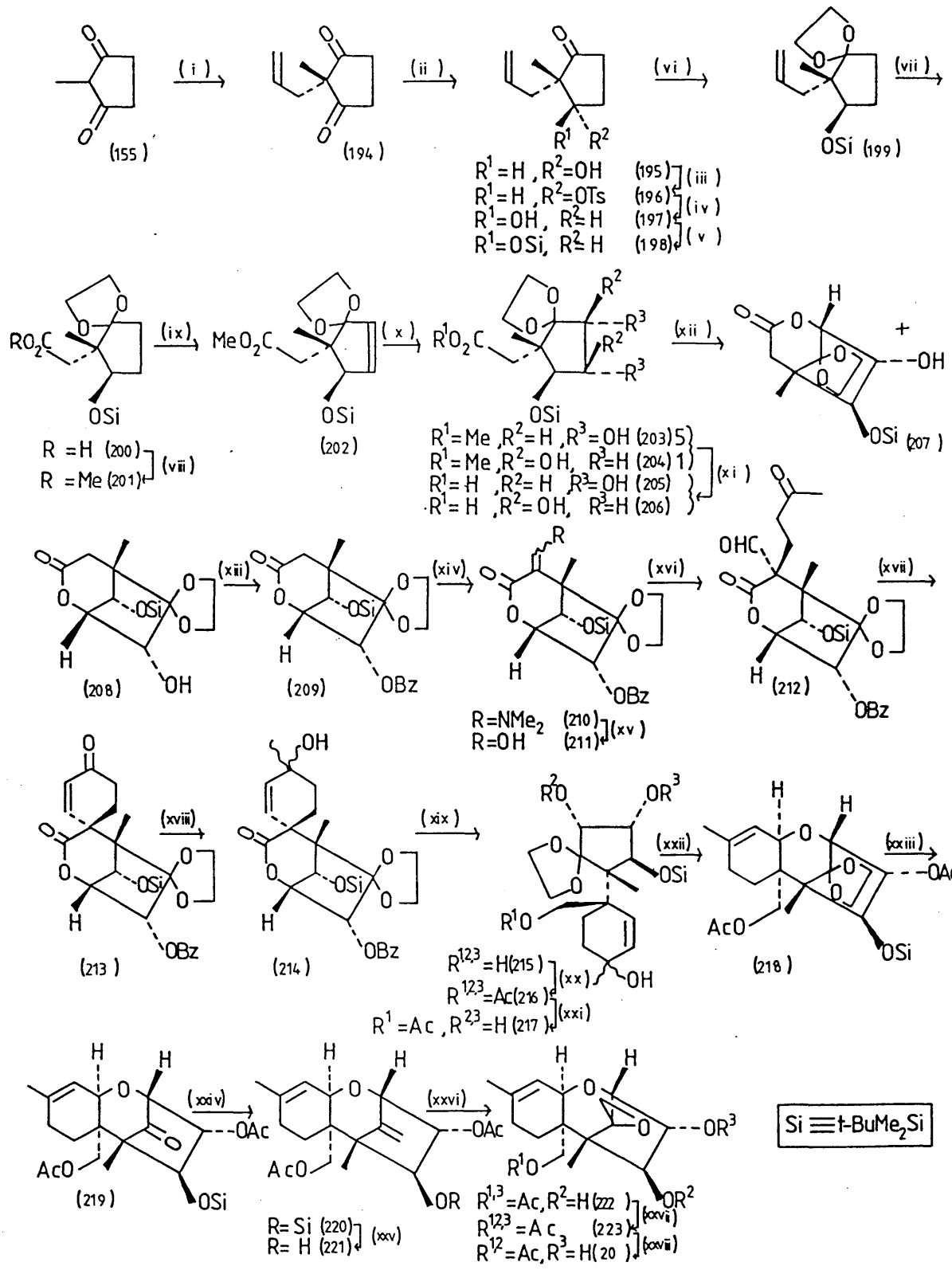
In a series of publications[51,76,77] Roush and D'Ambra developed another group 3 biomimetic sequence finally culminating in a synthesis of verrucarol (18).

Diels-Alder reaction between methyl acrylate and methyl trimethylsilylcyclopentadiene gave the bicyclo[2.2.1]heptene (176) as the major product. The ability of silicon to stabilise β-carbocations was then demonstrated by a silyl-controlled Wagner-Meerwein rearrangement[78] which furnished the bicyclo[2.2.1]heptanols (177) and (178). The epimeric relationship between (177) and (178) was established by oxidation of (177) with Swern's reagent followed by hydride reduction. Ester reduction was accomplished using $LiAlH(OMe)_3$[79] to give diol (179). Selective dehydration of the primary alcohol using Grieco's method[80] gave the exomethylene alkene (180) and thence alcohol (181). Oxidative cleavage to ketone (182), followed by Baeyer-Villiger oxidation afforded lactone (183). After diol protection, α-methylenation was achieved in a similar manner to that adopted by Schlessinger.

Spiroannelation of the key intermediate (185) was achieved by a Diels-Alder reaction which resulted in attack from the less hindered β-face due to the sterically biased nature of the bicyclic intermediate (185). In this way the relative stereochemistry at the two quaternary centres, C-5 and C-6, was controlled. The mixture of cycloadducts (186) and (187) was then reduced and the resulting triol treated with acid to afford ethylidene acetal (189) and the deprotected product (190).

Conversion of (190) into bromoether (191), followed by selective acetylation of the 4β-hydroxyl group gave (192); this was oxidised with Jones' reagent to ketone (193). The 12,13-alkene was introduced by means of a Wittig reaction, with the final synthetic steps following established protocol.

Reagents:-(i)NaOH, Allyl bromide
(ii)Dry active Bakers yeast
(iii)TsCl, Py
(iv)KNO_2
(v)TBDMS-Cl, DMAP, Imidazole, DMF
(vi)$(EtO)_3CH$, TsOH, $(CH_2OH)_2$
(vii)$KMnO_4$, $NaIO_4$
(viii)CH_2N_2
(ix)a.$PhNMe_3Br_3$ b.DBU
(x)OsO_4, NMMO
(xi)KOH
(xii)Ac_2O
(xiii)PhCOCl, Py
(xiv)$HC(NMe_2)_3$
(xv)AcOH, NaOAc
(xvi)$MeCOCH=CH_2$
(xvii)a.LDA b.MsCl, Imidazole
(xviii)MeLi
(xix)$LiAlH_4$
(xx)Ac_2O, Py
(xxi)NH_4OH, MeOH
(xxii)a.cat.TsOH b.Ac_2O, Py
(xxiii)1N HCl
(xxiv)Ph_3PCH_2
(xxv)n-Bu_4NF
(xxvi)m-CPBA
(xxvii)Ac_2O, Py
(xxviii)NH_4OH, MeOH


(155)
(i)
(194)
(ii)
(vi)
(vii)
(199)
R¹=H, R²=OH (195)
R¹=H, R²=OTs (196)
R¹=OH, R²=H (197)
R¹=OSi, R²=H (198)
(iii)
(iv)
(v)
(ix)
(x)
(xii)
(207)
R=H (200)
R=Me (201)
(viii)
(202)
R¹=Me, R²=H, R³=OH (203)
R¹=Me, R²=OH, R³=H (204)
R¹=H, R²=H, R³=OH (205)
R¹=H, R²=OH, R³=H (206)
(xi)
(208)
(xiii)
(209)
(xiv)
(xvi)
(212)
(xvii)
R=NMe₂ (210)
R=OH (211)
(xv)
(213)
(xviii)
(214)
(xix)
R¹²³=H (215)
R¹²³=Ac (216)
R¹=Ac, R²³=H (217)
(xx)
(xxi)
(xxii)
(218)
(xxiii)
(219)
(xxiv)
(xxvi)
R=Si (220)
R=H (221)
(xxv)
R¹³=Ac, R²=H (222)
R¹²³=Ac (223)
R¹²=Ac, R³=H (20)
(xxvi)
(xxvii)
Si ≡ t-BuMe₂Si

To date the most highly oxygenated trichothecene to be prepared is the cytostatic agent anguidine (20). The synthesis, reported in 1982 by Brooks, Grothaus and Mazdiyasni[52,81], was notable in that it represented the first chiral synthesis of a trichothecene. The strategy to form the tricyclic skeleton paralleled the 5 routes just described, namely, the addition of an A-ring unit to a fully functionalised C-ring, followed by an intramolecular cyclisation to provide the B-ring and thus complete the tricyclic skeleton.

Treatment of 2-allyl-2-methylcyclopentane-1,3-dione (194) with actively fermenting bakers' yeast effected a stereoselective microbial reduction of one of the two enantiotopic homomorphic carbonyl groups to provide the chiral starting material, (2S,3S)-2-allyl-3-hydroxy-2-methylcyclopentanone (195). Although the hydroxyl configuration in (195) was opposite to that required, inversion was achieved by treatment of the corresponding tosylate (196)with potassium nitrite. Protection of the hydroxyl and ketone functions was followed by oxidative cleavage of the alkene to provide the carboxylic acid (200) and thence methyl ester (201). Bromination/dehydrobromination[82] gave alkene (202), osmium tetroxide catalysed oxidation of which gave a 5:1 mixture of the two isomeric vicinal cis-diols. The major isomer (203) was lactonised to give a 1:3 mixture of the bicyclic lactones (207) and (208). Separation of the derived benzoates followed by α-formylation furnished (211). Control of the relative C-5, C-6 stereochemistry was achieved by Robinson annelation of (211) with methyl vinyl ketone, exo-addition taking place as expected due to the bicyclo[3.2.1]octane framework. Intramolecular aldol condensation[83] led to the enone (213), 1,2-addition of methyl lithium providing the allylic alcohol (214). Hydride reduction of the A/C ring unit gave tetraol (215).

Although tetraol (215) could not be cyclised directly due to competing reactions, a series of protection and selective deprotection steps allowed formation of (217), which readily cyclised on acid treatment to give tricycle (218) as the sole product. Removal of the ketal gave the ketone which was transformed into epoxide (222). Selective acetate saponification completed this synthesis of anguidine (20).

Reagents:- (i) $HOCH_2CH=CHCH_2Cl$, Δ

(ii) $KMnO_4$

(iii) CH_2N_2

(iv) DBU, C_6H_6

(v) $CH_2=C(Me)CH=CHOTMS$, neat, Δ

(vi) Mesitylene, Δ

(vii) $NaBH_4$

(viii) $CrO_3.Py_2$

(ix) Hot tube 470°C (flash vacuum thermolysis)

(x) a. Lithium 2,2,6,6-tetramethylpiperidide, TMSCl
b. Br_2.dioxane

(xi) TFA, H_2O

(xii) $n-Bu_4NF$

(xiii) Ph_3PCH_2

(xiv) DIBAH

(xv) TBDMS-Cl, DMAP

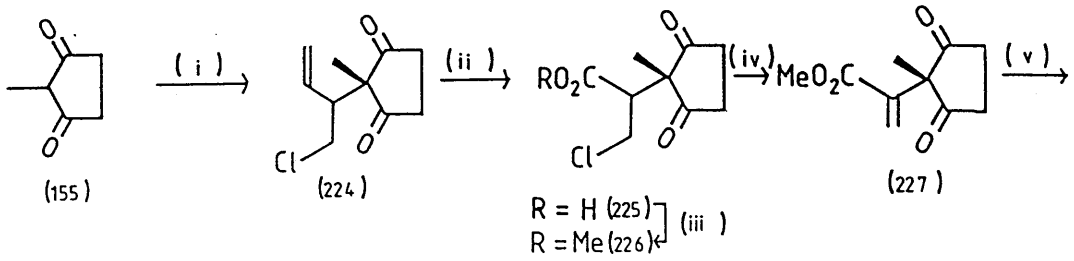
(xvi) TsCl, Py

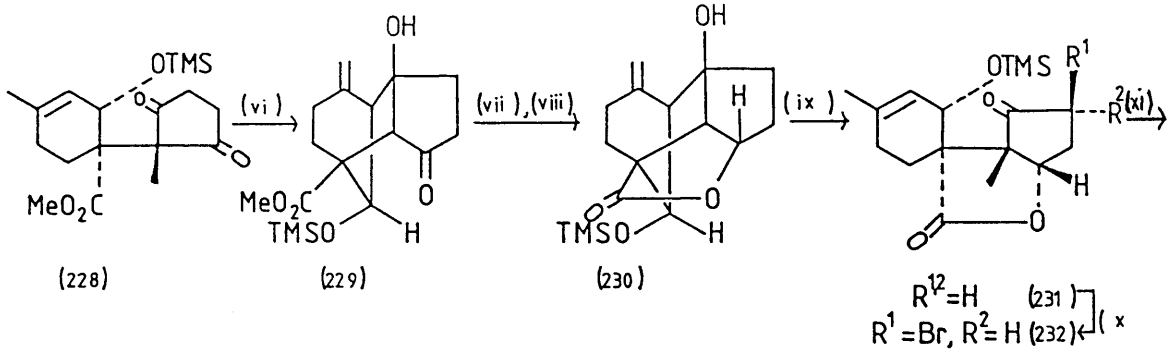
(xvii) $EtCO_2Cs$, 1,3-Dimethylimidazolinone, Δ

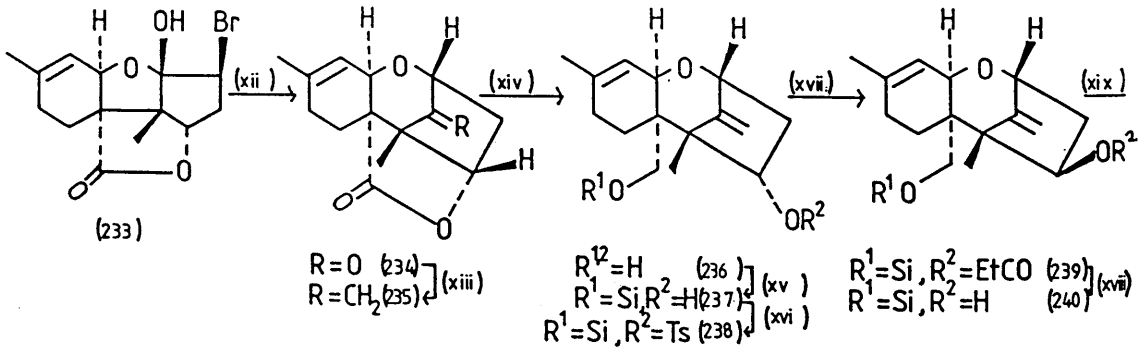
(xviii) K_2CO_3, MeOH

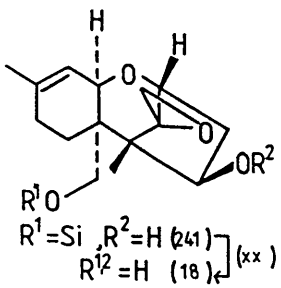
(xix) $Mo(CO)_6$, TBHP

(xx) $n-Bu_4NF$


(i)
(ii)
(iii)
(iv)
(v)
(155)
(224)
R = H (225)
R = Me (226)
(227)


(vi)
(vii), (viii)
(ix)
(xi)
(228)
(229)
(230)
R12=H (231)
R1=Br, R2=H (232)
(x)

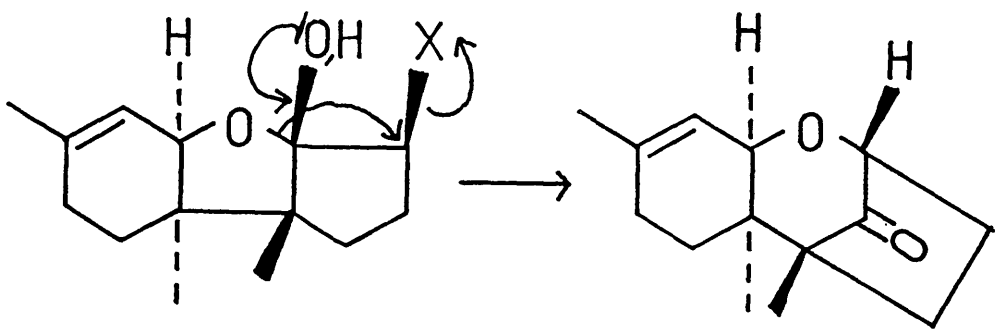

(xii)
(xiii)
(xiv)
(xv)
(xvi)
(xvii)
(xviii)
(xix)
(233)
R=O (234)
R=CH2 (235)
R12=H (236)
R1=Si, R2=H (237)
R1=Si, R2=Ts (238)
R1=Si, R2=EtCO (239)
R1=Si, R2=H (240)


R1=Si, R2=H (241)
R12=H (18)
(xx)

Si ≡ t-BuMe$_2$Si

GROUP 4 BIOMIMETIC APPROACH.

The group 4 cyclisation route was first explored by Anderson and co-workers[38,39] with the construction of two trichothecene model systems. These earlier workers were able to avoid the problem of control of the C-11 stereochemistry, which determines the A/B ring fusion, by using aromatic analogues. However, later workers were able to demonstrate complete control[50,84] at C-11 thus allowing the synthesis of both trichothecene and 11-epi-trichothecene skeletons. The key step in the group 4 route is rearrangement of a bicyclo[3.3.0] octane subunit to a bicyclo[3.2.1]octane subunit (scheme 5).



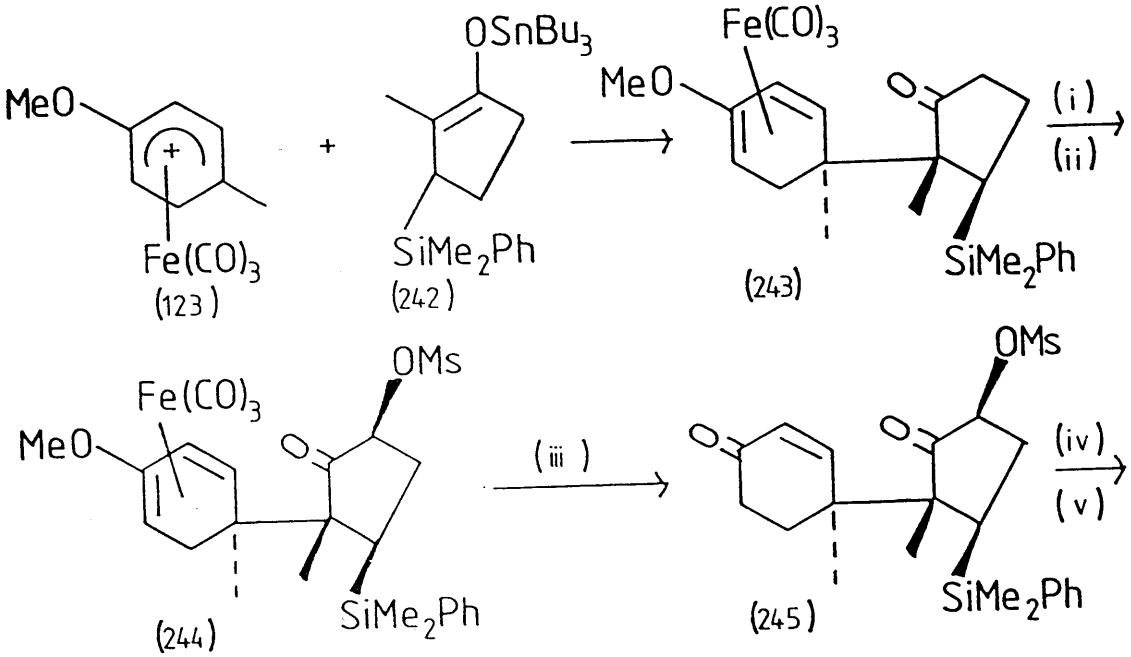
Scheme (5)

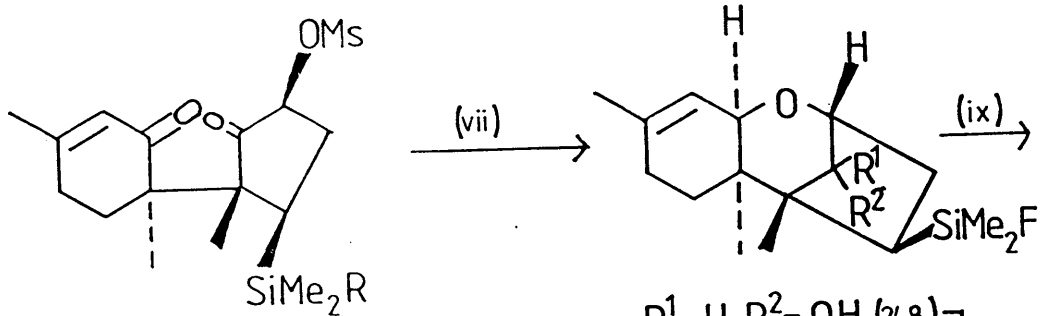
Trost and McDougal adopted Diels-Alder cycloaddition to create the A/C ring system. Reaction of (227) with (1-trimethylsiloxy)-3-methylbuta-1,3-diene at 130°C gave the anticipated adduct. Unexpectedly, further heating of this initial adduct to 155°C triggered an intramolecular ene reaction, yielding the tricyclic compound (229). Conformational analysis revealed that only one of the two diastereotopic carbonyl groups could align itself properly to undergo the ene reaction. Consequently this served as a means of

differentiation of the two ketones. Maintenance of this differentiation was realised upon reduction, lactonisation and pyrolysis, the last step effecting a retro-ene reaction and furnishing the modified Diels-Alder adduct (231).

Bromination of (231) gave the α-bromo ketone (232) which, on treatment with trifluoroacetic acid, gave hemiketal (233). Inversion of the C-11 stereochemistry was assumed to have taken place via intramolecular trapping of the cyclohexenyl cation by a hydrated form of the ketone. The key cyclisation was then accomplished using fluoride ion catalysis to give (234). Olefination followed by lactone reduction gave diol (236). A series of selective protection steps then led to tosylate (238)which, upon displacement with inversion using cesium propionate, gave ester (239). Molybdenum-based epoxidation resulted in exclusive formation of the 12,13-epoxide without necessitating 9,10-alkene protection. Simple desilylation finally yielded the target molecule, verrucarol (18).

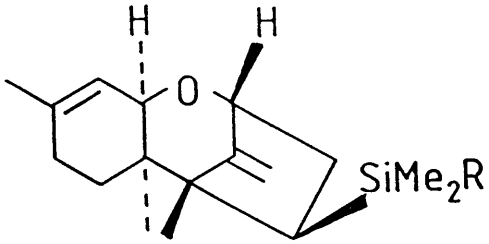
Reagents:– (i) LDA, MoOPH
(ii) MsCl, Py
(iii) $CuCl_2$, EtOH
(iv) MeMgBr
(v) PCC, CH_2Cl_2
(vi) $HBF_4.Et_2O$
(vii) $NaBH_4$
(viii) PCC, CH_2Cl_2
(ix) Ph_3PCH_3Br/KO^tBu, ^tBuOH
(x) nBu_4NF
(xi) H_2O_2, KF, $NaHCO_3$
(xii) m-CPBA





R=Ph (246)
R=F (247) (vi)

R1=H, R2=OH (248)
R1, R2=O (249) (viii)



(xi) → (51) (xii) → (16)

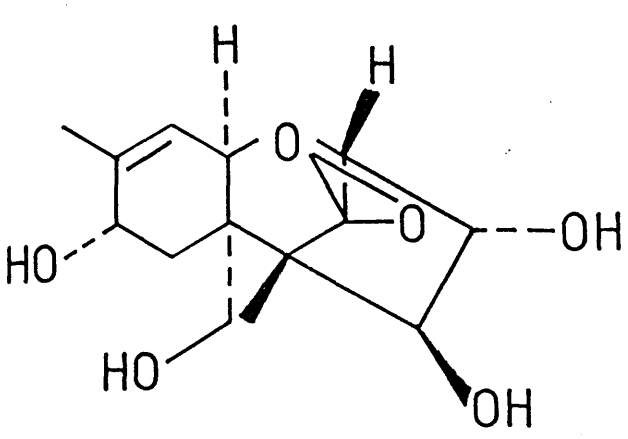
R=O^{t}Bu (250)
R=OH (251) (x)

The most recently reported total synthesis was published by Pearson and co-workers[53] in 1989. Although the third synthesis of trichodermol, it is the shortest to date requiring only 16 steps from 4-methylanisole. The strategy is similar to that employed in the previously reported[69] synthesis of the trichothecene analogue (134) but for the initial C-C bond forming step utilises the regiocontrolled addition of a tin enolate[89] to a cyclohexadienyl-iron complex.

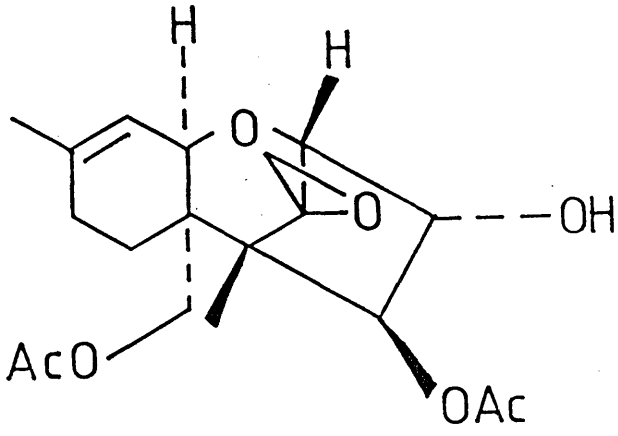
Reaction of tin enolate (242) with (123) afforded ketone (243). Hydroxylation followed by mesylation furnished complex (244). Decomplexation afforded enone (245), methylation and oxidative rearrangement of which gave enone (246). Silyl modification followed by reduction of the enone proceeded with accompanying intramolecular displacement of the mesylate to give (248). Oxidation then gave ketone (249), which was subjected to Wittig olefination, producing (250). Conversion of (251) into (51) was accomplished by treatment with $nBu_4^+N\ F^-$ followed by oxidative cleavage, with retention, of the C-Si bond. Hydroxyl-directed epoxidation of (51) gave trichodermol (16).

DISCUSSION

The ultimate goal of this research is to synthesise the complex trichothecene, T-2 tetraol (252).



T-2 TETRAOL (252)

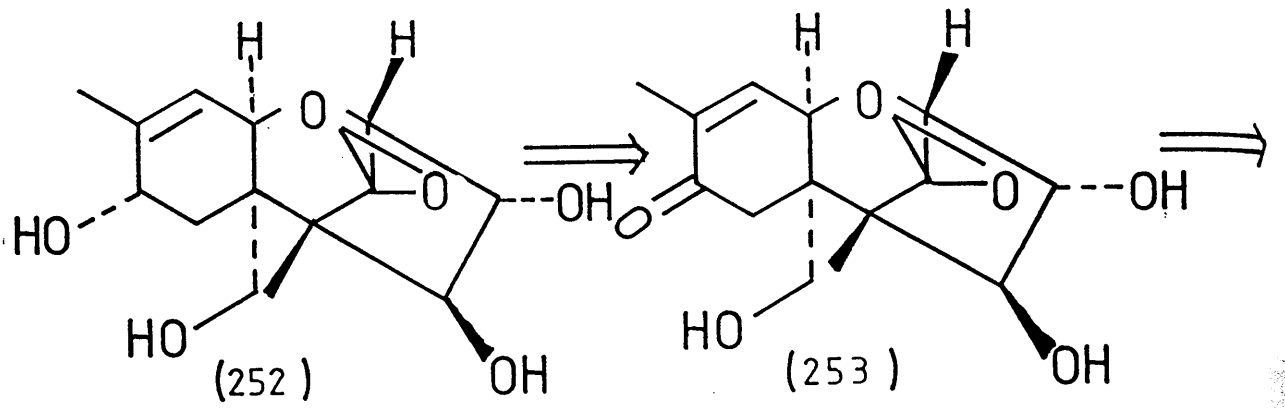


ANGUIDINE (20)

T-2 tetraol is one of the most highly oxygenated trichothecenes and as a consequence its synthesis presents considerable difficulties. In addition to the general tricyclic skeleton, spiro-epoxide and 9,10-alkene, the proposed synthetic pathway must be capable of being adapted to permit the introduction of the allylic α-alcohol in ring A and the trans-3α, 4β-diol system in ring C.

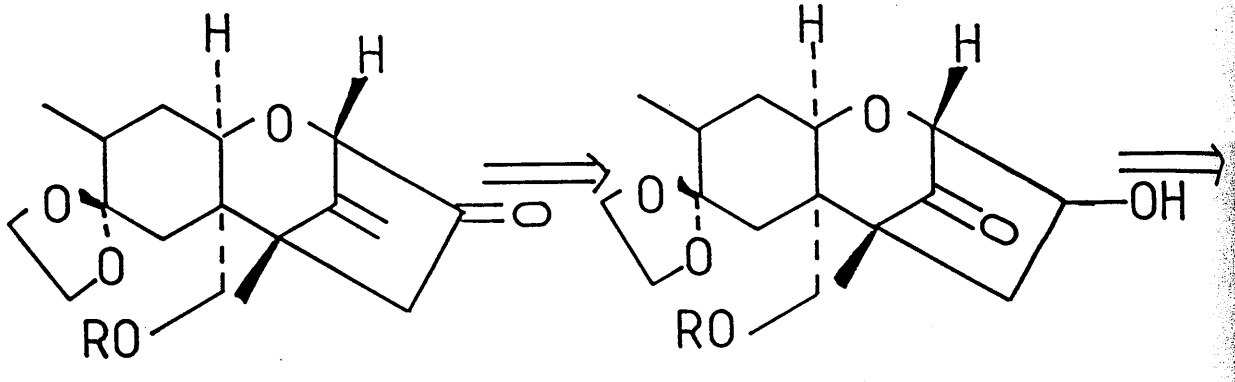
As described in the Introduction, Brooks constructed[52] anguidine (20) via a group 3 biomimetic cyclisation process, but encountered difficulties in attempting to cyclise a polyol precursor. It was envisaged that if a similar protocol were used to construct T-2 tetraol, the additional ring A hydroxyl group would complicate the cyclisation further and present insurmountable difficulties.

Colvin and Thom have reported[67] the synthesis of an advanced



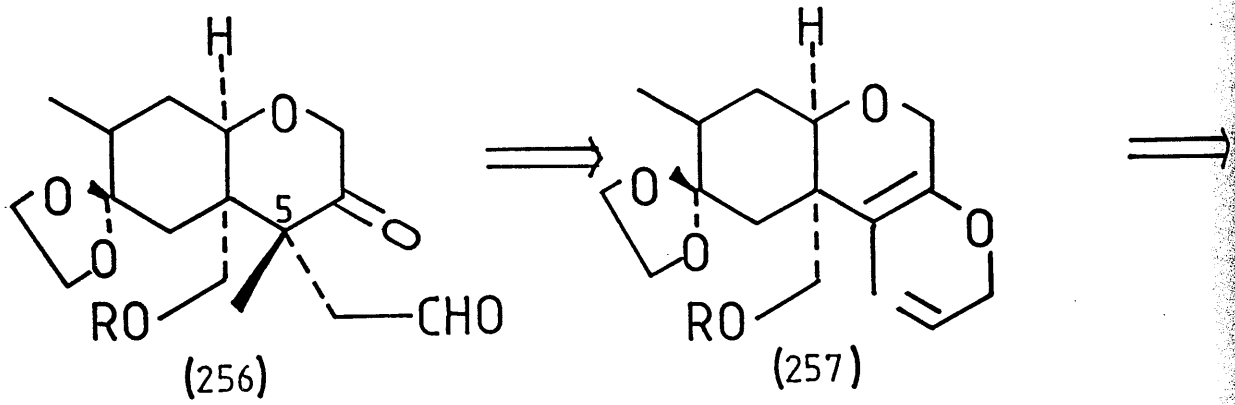
(252)

(253)



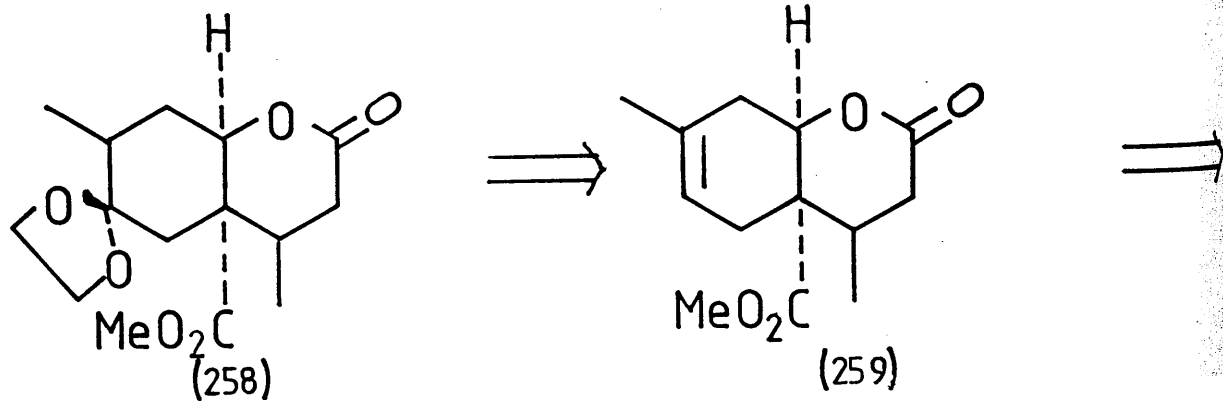
(254)

(255)



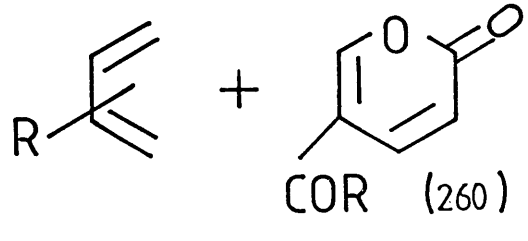
(256)

(257)



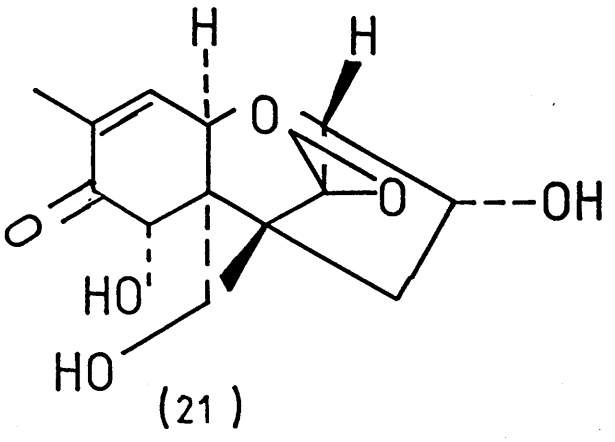
(258)

(259)



(260)

Scheme (6)

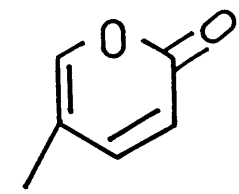


(21)

trichothecene intermediate *en route* to their primary target, vomitoxin (21). Vomitoxin, like T-2 tetraol, is a polyoxygenated trichothecene with a highly functionalised A ring. The authors proposed to construct vomitoxin *via* a group 2 aldol cyclisation using a Diels-Alder reaction to generate the *cis*-fused AB ring system; it was hoped that this methodology could be extended to the synthesis of T-2 tetraol.

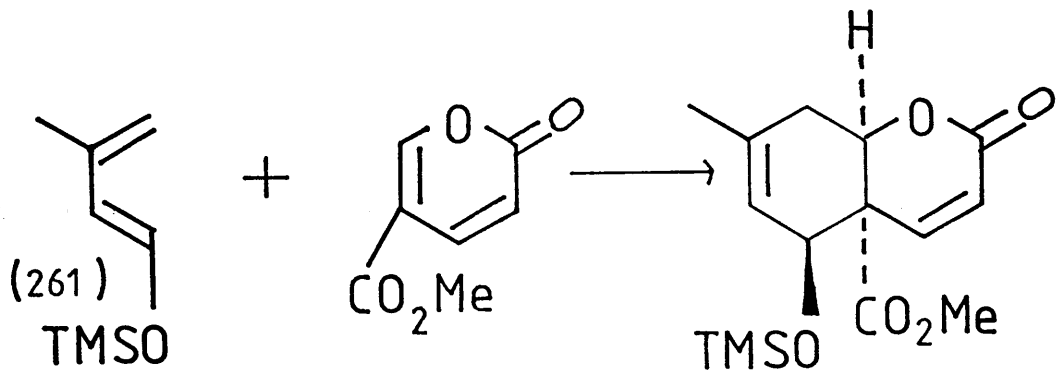
The proposed synthetic strategy to construct (252) consisted of two main elements; the first a Diels-Alder reaction to form simultaneously ring A and ring B, the second an aldol reaction to create ring C. With the basic carbon skeleton in place, simple transformations would then be used to install the peripheral groups.

A retrosynthetic analysis (Scheme 6) indicated that the ring A allylic α-alcohol could be formed by stereoselective reduction of enone (253). The spiro-epoxide would be installed by stereospecific epoxidation using the 4β-hydroxyl as a directing group. An extensive model study showed that the *trans*-3α,4β-diol could be generated by stereospecific α-oxidation, followed by hydride reduction, of ketone (254). Differentiation between ring A and ring C ketonic functionality would be established at an early stage and maintained until the introduction, at the required moment, of the α,β-unsaturated ketone by deprotection and dehydrogenation. The scheme envisaged employment of an aldol reaction of keto-aldehyde (256) to create (255), with the C-5 stereochemistry being established by [3,3] sigmatropic rearrangement of allyl enol ether (257). Lactone (258) could be converted into dihydropyran (257) by oxidation, allylation and reductive removal of the lactonic carbonyl. Introduction, and



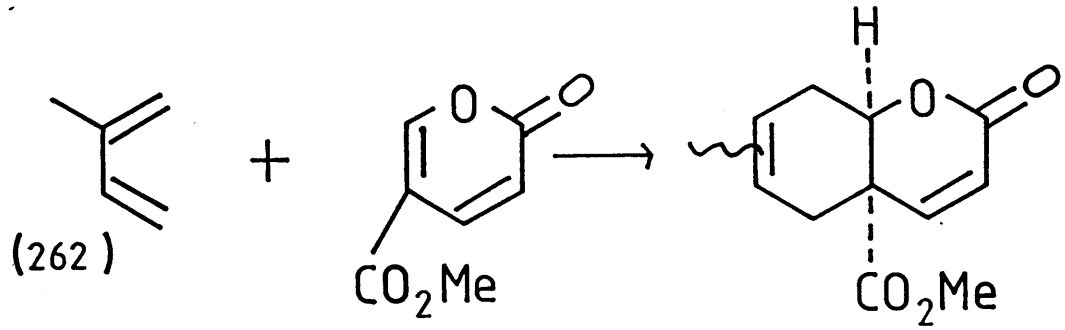
COR

R=OH,OMe,Cl (260)

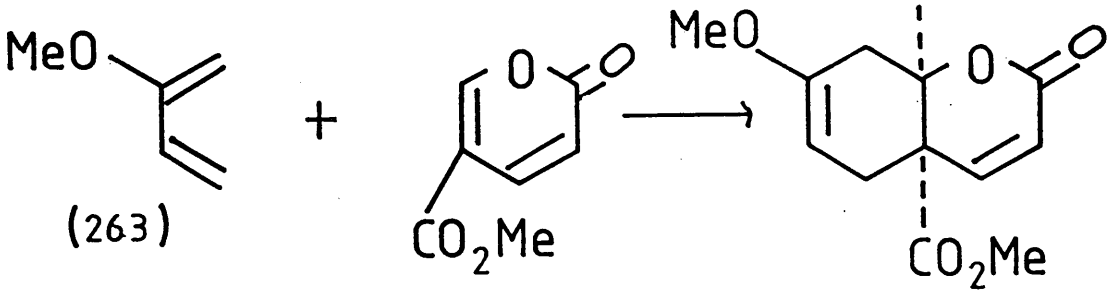


(261)

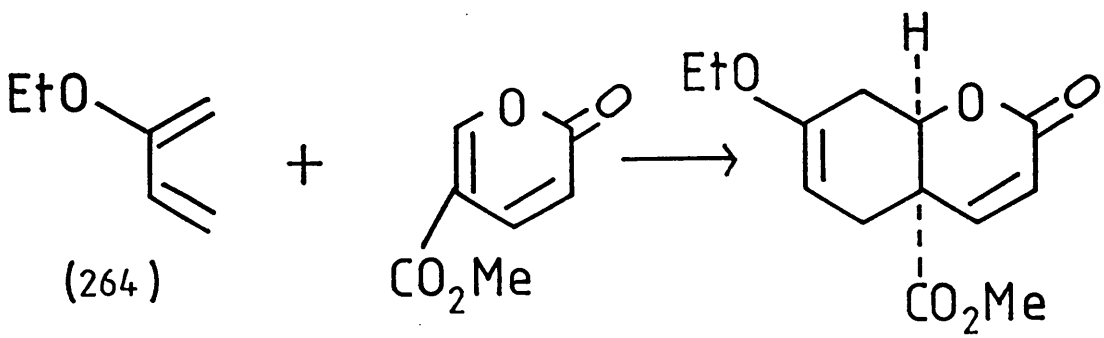
TMSO



(262)



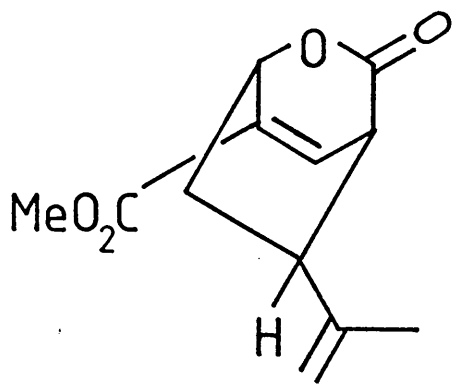
(263)



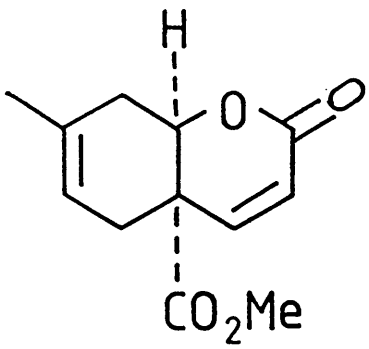
(264)

suitable protection, of ring A oxygen functionality would be achieved by manipulation of alkene (259). A cycloaddition reaction between a coumalic acid derivative (260) and a suitably functionalised buta-1,3-diene would be used to form the basic AB skeleton.

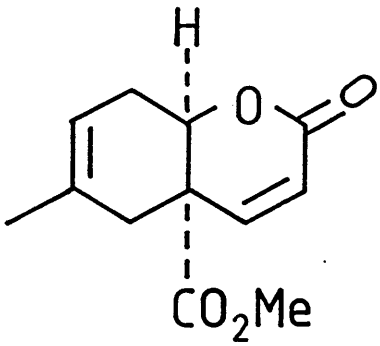
Diels-Alder cycloadditions are a major feature of many trichothecene total syntheses. The Diels-Alder reaction is one of the best methods for the unambiguous construction of a cis-fused decalin ring system and several reports have appeared which deal specifically with this in the creation of the AB portion of the trichothecene skeleton.[90,91,92,93] Coumalic acid derivatives (260) have found favour for the dienophile portion since when they are employed the useful pyran-enone system results, although a number of manipulations are needed to convert the Diels-Alder adducts into more useful synthetic intermediates. As diene partners, the substituted butadienes [(261) → (264)] have all been used; some, however, show better regioselectivity than others. In general alkoxy- and silyloxy- substituted butadienes give better regioselectivity than do simpler alkyl-substituted dienes. Nevertheless, the diene of choice for this project was isoprene. The reasons for this were two-fold; firstly, isoprene is relatively cheap and the initial reaction could be performed on a large scale; and, secondly, the C-9 skeletal methyl of T-2 tetraol results directly from the cycloaddition. Although this could also be achieved, and with higher regioselectivity, using diene (261), the formation of this diene[94] is labour intensive and the adduct so obtained would require subsequent deoxygenation. It has been shown[62] that in Lewis acid-mediated deoxygenation reactions of allylic alcohols of this type the product alkene can undergo



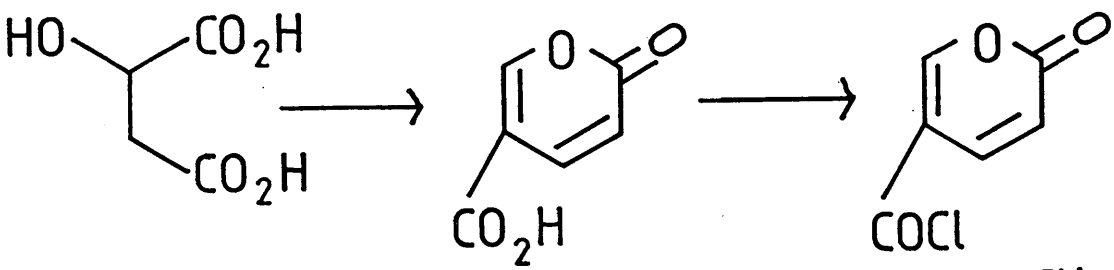
(265)



(266)



(267)



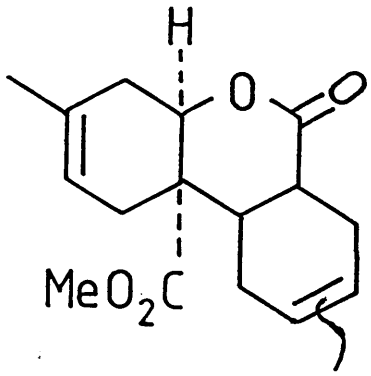
(268) (269) (260,R=Cl)

undesired isomerisation due to the intermediacy of a resonance-stabilised allyl cation.

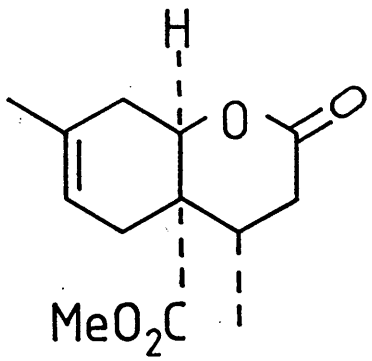
Cycloaddition of isoprene with methyl coumalate has been well documented.[91,95,96] In addition to the expected regioisomeric products, it has been reported[93] that methyl coumalate can also act as the 4π component in the cycloaddition, giving rise to (265). Brown and Colvin have established[93] that the major regioisomer in the thermal combination of isoprene and methyl coumalate is (266). Moreover, they reported that by lowering the energy of the LUMO of the dienophile by using coumalyl chloride they could improve the regioselectivity of the addition and minimise formation of (265).

Building on this ground work,[97] the preparation of coumalyl chloride (260, R=Cl)[99] was carried out. Coumalic acid (269) was prepared from malic acid by von Pechmann's synthesis.[98] Initial attempts to form the acid chloride proved unsuccessful, with black tars being obtained on several occasions. ^{1}H N.m.r. spectral analysis of the starting acid indicated the presence of water. To remove the water the crude coumalic acid was recrystallised from methanol; care, however, was required to avoid esterification. Treatment of the recrystallised acid with an excess of thionyl chloride then furnished acid chloride (260, R=Cl) in yields typically greater than 75%.

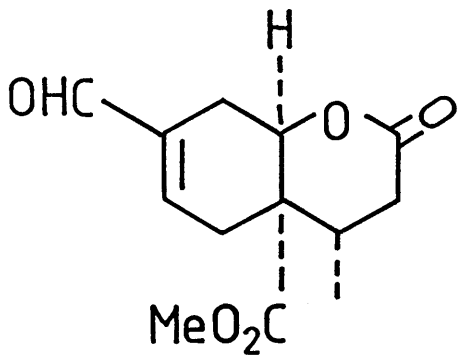
Following the documented literature,[93] cycloaddition of coumalyl chloride with a four-fold excess of isoprene and conversion of the intermediate into its methyl ester surprisingly did not produce the expected adducts (266) and (267). The major product



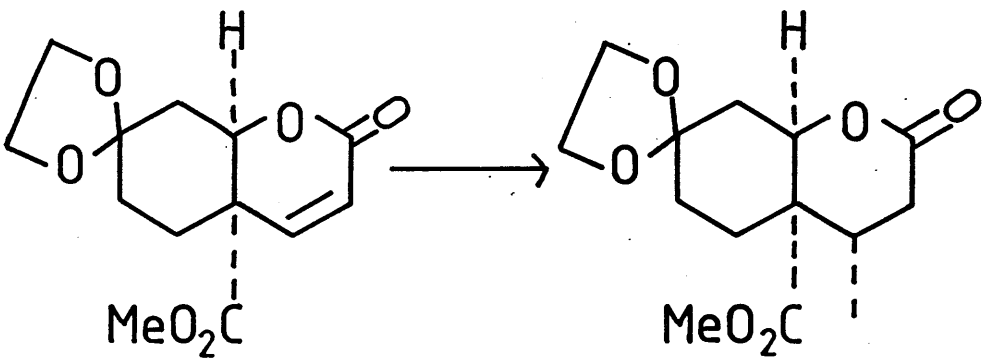
(270)



(259)



(271)

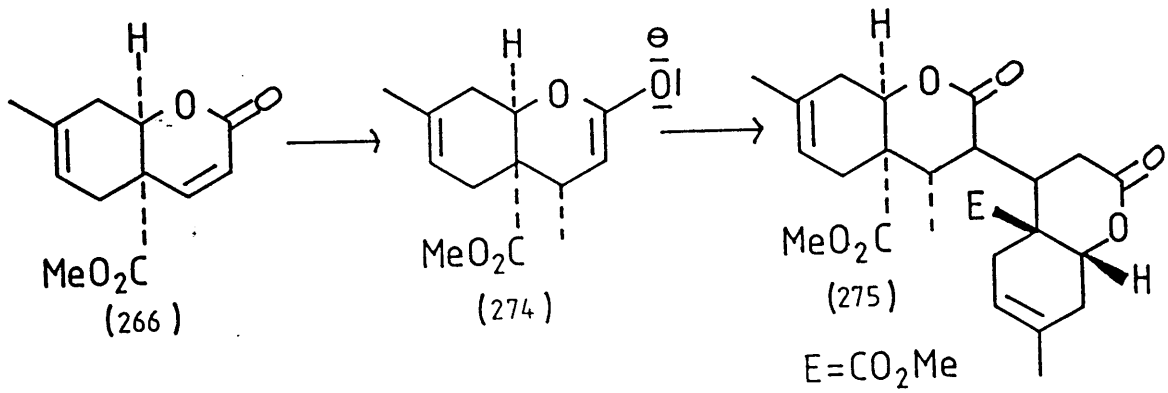


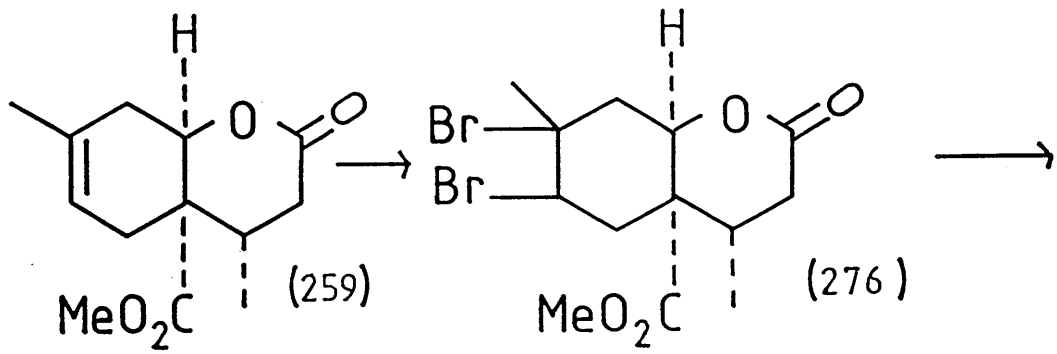
(272) (273)

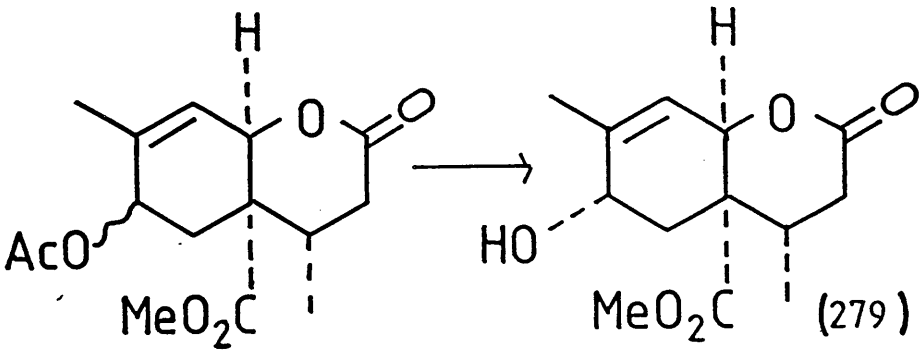
proved to be adduct (270) which lacked the anticipated enone AB quartet in its ^{1}H n.m.r. spectrum. This arose from the addition of two molecules of isoprene to one of coumalyl chloride. Two reasons contributed to the formation of (270): the prolonged reaction time (18 hours) and the use of such an excess of isoprene. After extensive experimentation, it was found that the optimum yield of (266) could be attained using a two fold excess of isoprene and heating the mixture in toluene at 120°C in a sealed vessel for 1 hour. Separation of the adducts by dry column flash chromatography[100] proved unsuccessful but 200 MHz ^{1}H n.m.r. spectral analysis indicated a 4:1 mixture of regioisomers.

Treatment of this mixture with Me_2CuLi afforded the conjugate addition product (259) as a single methyl epimer in 55% yield. To determine its relative stereochemistry, a related product (271), was the subject of a n.O.e. experiment [for the preparation of (271) see pages 65 and 81]. Irradiation of the newly introduced methyl group resulted in a 1.9% integrated enhancement of the bridgehead methine proton and a 1.3% integrated enhancement of the methyl ester protons. Similarly irradiation of the bridgehead proton produced a 0.84% reciprocal enhancement of the methyl group under investigation. These results suggest that the methyl is in the α-orientation although they are far from conclusive. By analogy, White and coworkers[92] have indicated that conjugate addition to (272) gives rise to (273); no detail was given of the method used to assign this relative stereochemistry.

In the course of the present synthesis, it was necessary to scale up the conjugate addition reaction. On doing so, increasing







α (277)
β (278)

Scheme (7)

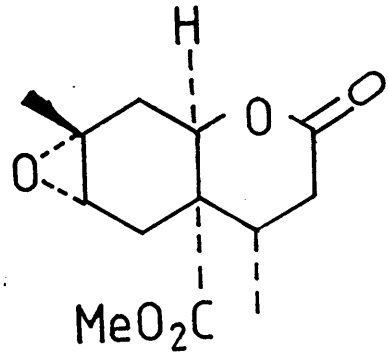
quantities of the diadduct (275), formed *via* Michael addition of the intermediate enolate (274) to (266), were obtained. In order to inhibit formation of (275), the conjugate addition reaction was performed in the presence of chlorotrimethylsilane.[101] This modification proved most useful since not only did it avoid formation of (275) but it also allowed the reaction to be performed at higher concentrations.

Following the proposed pathway[97] (Scheme 7), bromination of the cuprate product (259) and acetolysis of the mixture of *trans*-dibromides (276) gave rise to the corresponding allylic acetates (277) and (278). Acetate saponification and chromatographic separation then provided the desired allylic α-alcohol epimer (279). It was envisaged that this functionality would be protected during the further transformations used to create ring C.

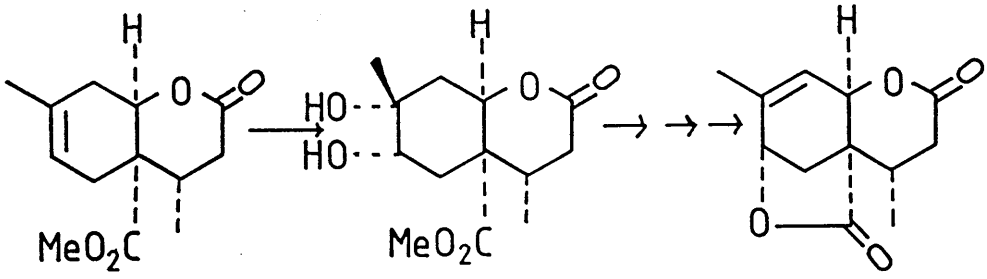
The reported method of acetate cleavage involved stirring a methanolic solution of acetates (277) and (278) over excess K_2CO_3. On repetition, however, it was found that if 5% aqueous MeOH were used the hydrolysis proved non-selective with both lactone and methyl ester functionalities also being cleaved. Using anhydrous MeOH, the desired alcohol (279) could indeed be obtained but in yields less than 25%.

It was at this point that it was deemed necessary to deviate from the proposed pathway. In a multistep total synthesis it is unacceptable to have such low yields near the beginning.

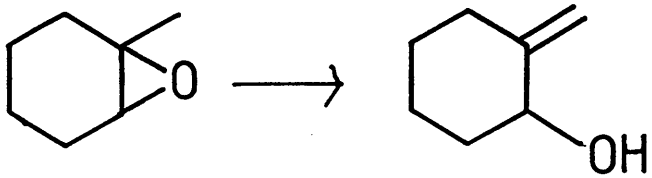
At this time, formation of allylic alcohol (279) remained the primary objective. To this end, epoxide (280) was prepared



(280)



Scheme (8)



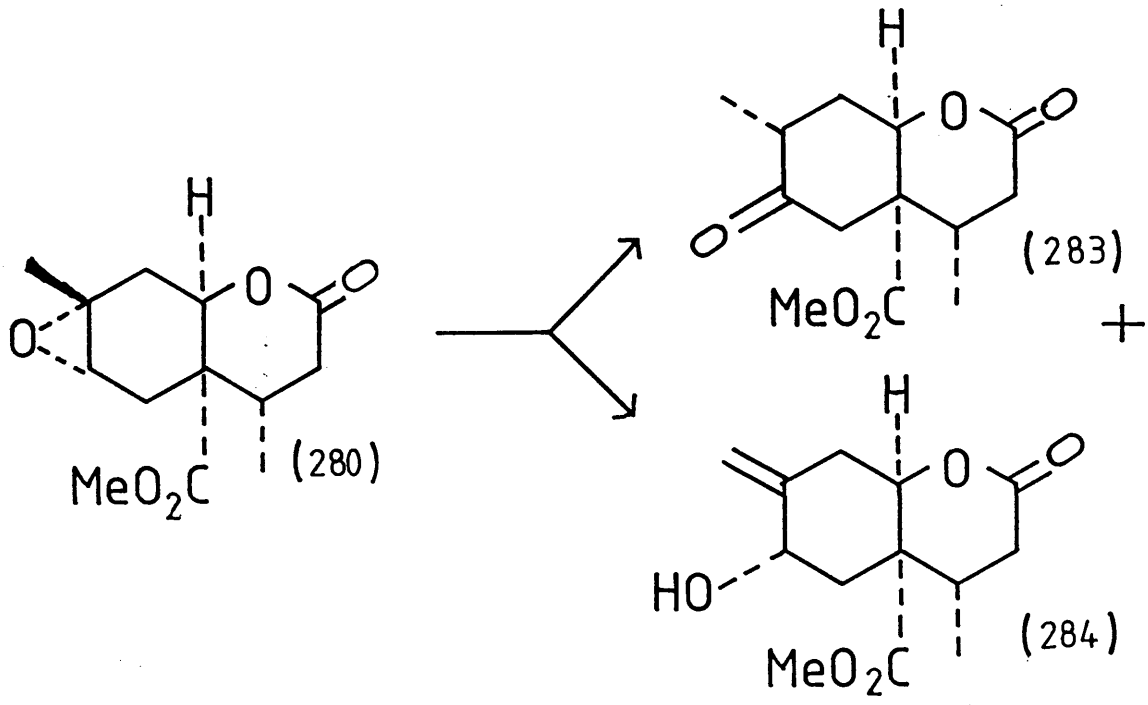
(281) (282)

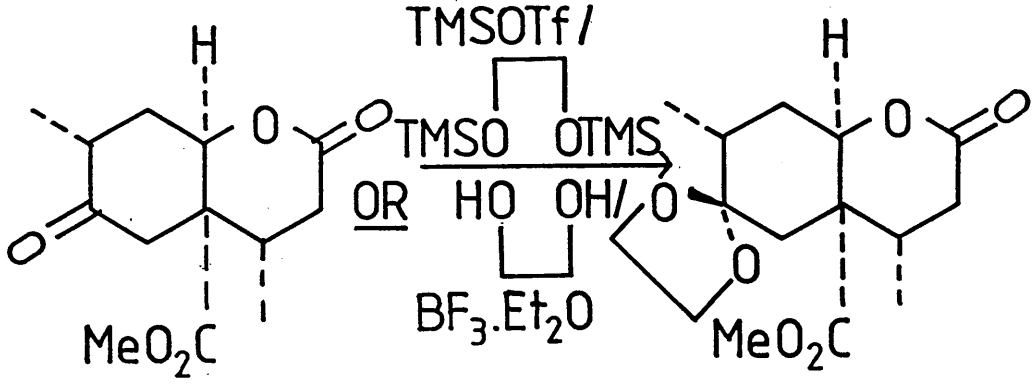
in 81% yield by peracid epoxidation of the corresponding alkene. This reaction gave rise to a single epoxide; although its stereochemistry was unknown it was assumed to be in the α-configuration by analogy with the product obtained from alkene osmylation. The stereochemistry of the osmylated product was unambiguously established[97] by lactone formation (Scheme 8). On this assumption, methods were examined to induce rearrangement of this epoxide to allylic α-alcohol (279).

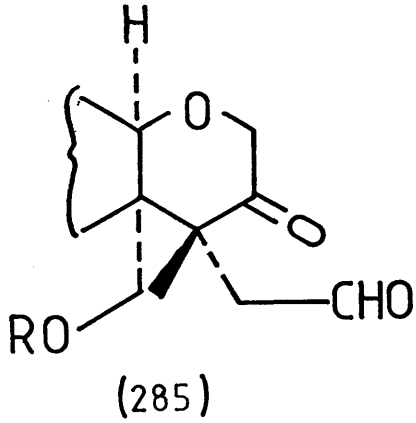
It is well established[102,103,104] that treatment of epoxides with strong non-nucleophilic amide bases can induce their rearrangement to allylic alcohols. Hence (280) was treated with 2.2 equivalents of lithium diethylamide: although all the substrate was consumed, none of the desired product was obtained. Consumption of starting material could be explained by deprotonation of the lactone and intermolecular epoxide ring opening. Indeed, a polymeric substance was obtained from the reaction.

Three other reagents were tested to effect epoxide rearrangement, namely aluminium isopropoxide[105,106,107], lithium perchlorate[108] and trimethylsilyl triflate[109] (TMSOTf). The first two reagents proved unsuccessful, starting material being recovered in each case. The last reagent, however, gave more encouraging results.

Trimethylsilyl triflate has been reported[109] to convert methyl cyclohexene oxide (281) into the corresponding exocyclic allylic alcohol (282). Treatment of (280) with 2.2 equivalents of this reagent gave a 3:1 mixture of (283) and (284). Ketone (283) could function as a useful intermediate en route to T-2 tetraol, but the


H
O
O
MeO2C
(280)
H
O
O
MeO2C
(283)
+
H
O
O
HO
MeO2C
(284)


H
O
O
MeO2C
(283)
TMSOTf /
TMSO OTMS
OR HO OH /
BF3.Et2O
H
O
O
O
O
MeO2C
(258)

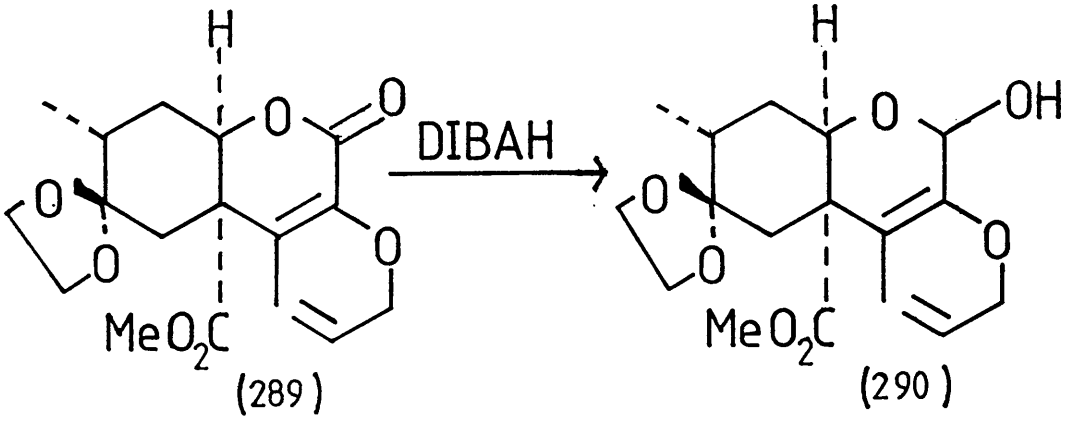

H
O
O
CHO
RO
(285)

use of TMSOTf as a catalyst also produced undesired (284).

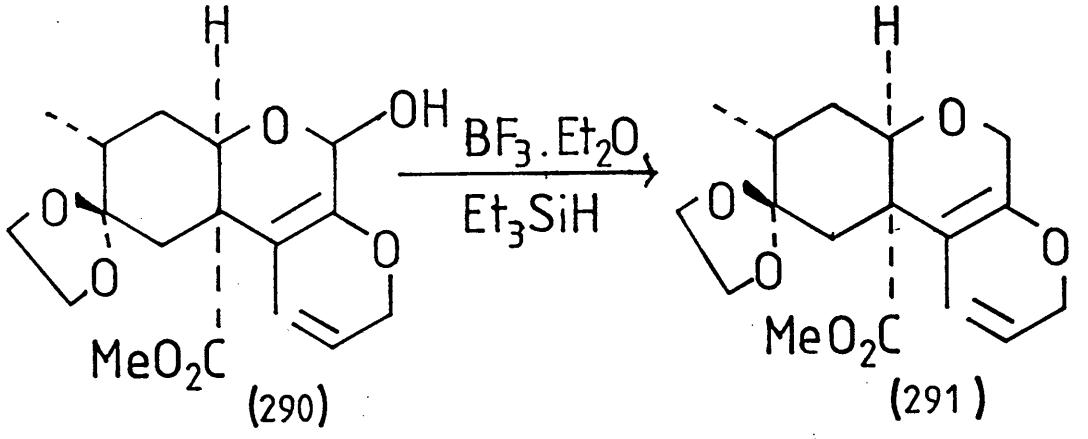
To improve the yield of (283), the use of $BF_3.Et_2O$, a reagent known to convert epoxides into ketones, was investigated. It is known that this reagent can also induce ring contraction in certain cyclic substrates; consequently there was initial hesitancy in employing this Lewis acid. However, a small scale trial experiment indicated that this concern was unfounded; treatment of (280) with $BF_3.Et_2O$ resulted in exclusive formation of (283) in 69% yield.

Conscious of the possibility of transesterification, two methods to convert ketone (283) into ketal (258) were examined. The first was the reaction[110] with 1,2-bistrimethylsilyloxy ethane in the presence of 1 mol % TMSOTf as catalyst. After work-up and purification, ketal (258) was obtained in 49% yield. In the second method, $BF_3.Et_2O$ was used as the Lewis acid catalyst. By simply stirring (283), 1.1 equivalents ethylene glycol and 1.5 equivalents $BF_3.Et_2O$ in CH_2Cl_2 at room temperature overnight, the same ketal (258) was obtained but in a higher yield of 69%. Moreover, using this latter system, epoxide (280) could be transformed directly into ketal (258) in one pot without isolation of the intermediate ketone (283). This procedure proved to be of higher yield overall, typically 60%, and also avoided an additional purification step.

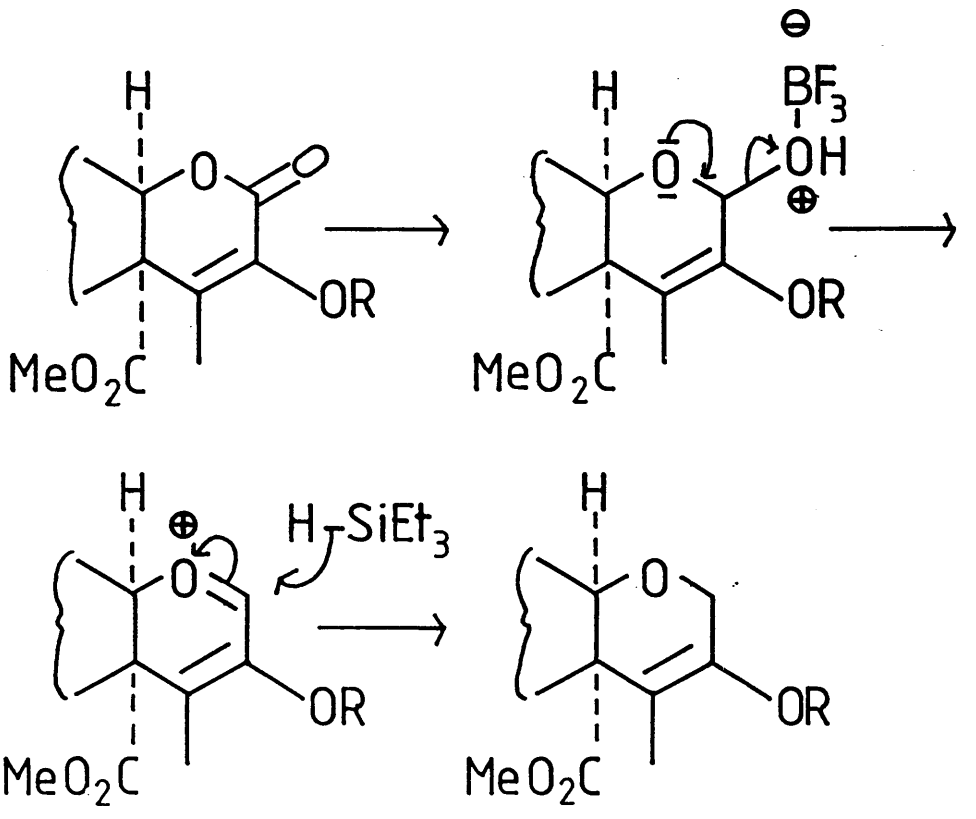
Comparison of the structures (258) and (285) indicates that for (258) to be of further synthetic utility, 1,2-carbonyl transposition must be brought about in ring B. Consultation of the literature did not reveal a simple method of effecting such a transformation.



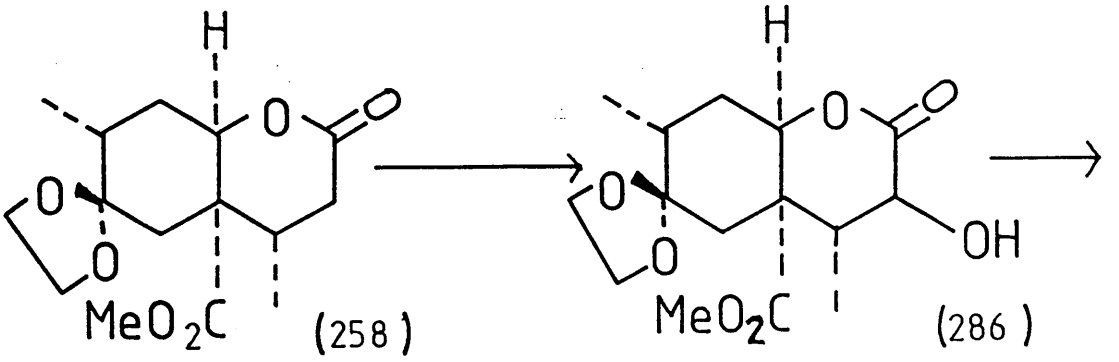
(289) (290)

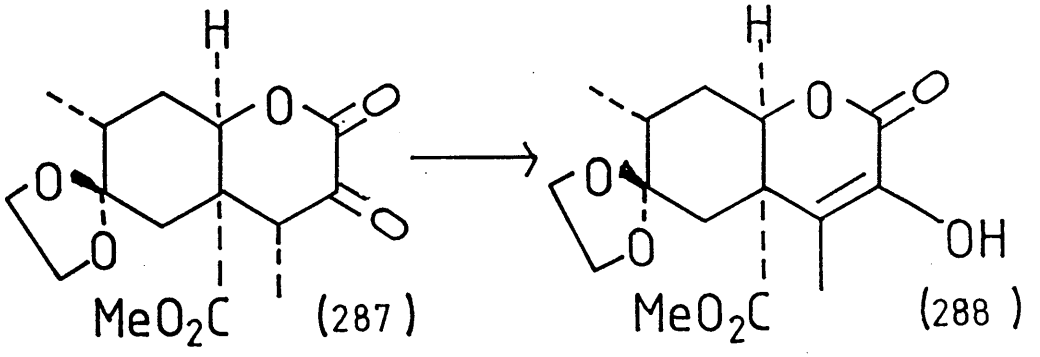


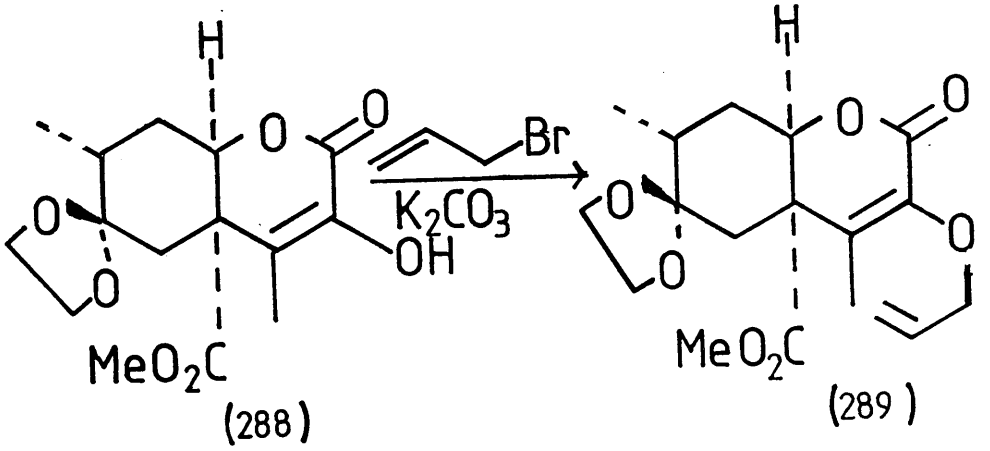
(290) (291)



Scheme (9)


H
O
O
O
O
MeO2C
(258)
H
O
O
O
O
OH
MeO2C
(286)


H
O
O
O
O
MeO2C
(287)
H
O
O
O
O
OH
MeO2C
(288)

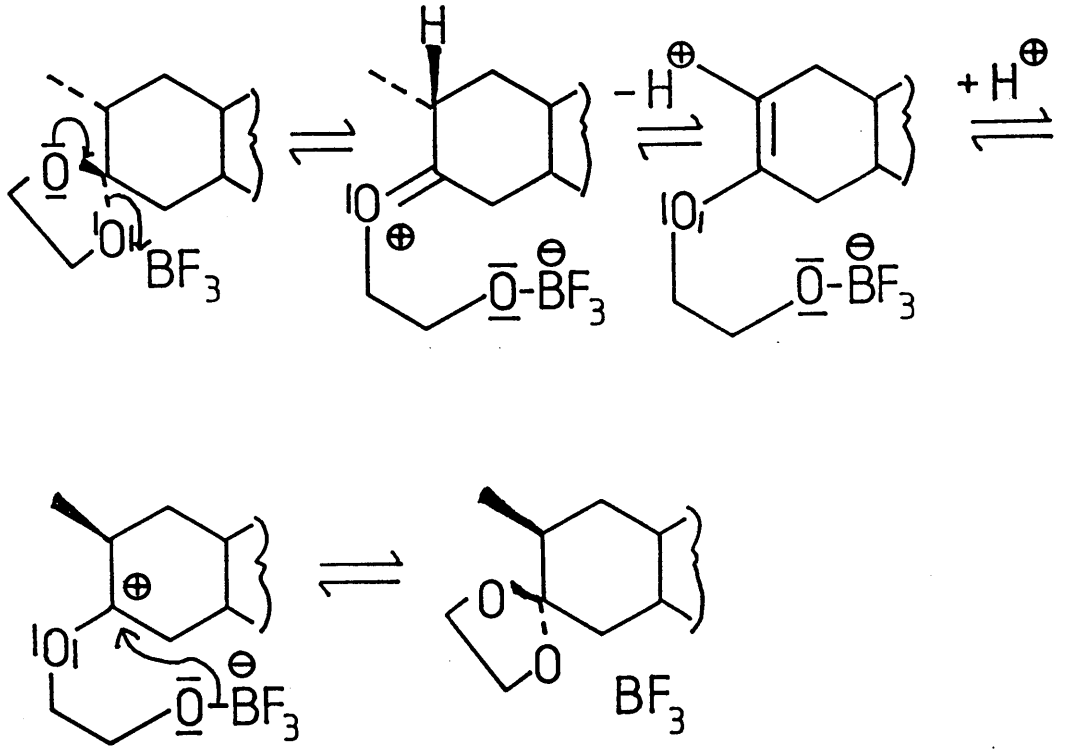

H
O
O
O
O
OH
MeO2C
(288)
Br
K2CO3
H
O
O
O
O
O
MeO2C
(289)

It was therefore proposed to employ Kraus' methodology,[91] that of oxidising α to the lactone to the correct degree of oxidation, protecting the oxidised site and then finally reductively removing the lactonic carbonyl group.

Oxidation of the lactone enolate anion at low temperature with the molybdenum pentoxide reagent of Vedejs[111] produced a 8:1 mixture of diastereoisomeric hydroxylactones in 72% yield. Oxidation of hydroxy lactone (286) by treatment with N-chlorosuccinimide and dimethyl sulphide[112] in CH_2Cl_2 at -25°C followed by the addition of triethylamine produced initially the α-keto lactone (287). On silica gel chromatographic purification, however, (287) tautomerised to the more stable lactone (288) as evidenced by the disappearance of a doublet at 1.15ppm and the appearance of a new singlet at 1.74ppm.

Protection and functionalisation of the enol were accomplished simultaneously by treating (288) with potassium carbonate and excess allyl bromide to give the allyl enol ether (289) in 74% yield. The choice of the protecting group was dictated by future strategy; it was planned to establish the C-5 stereochemistry *via* [3,3] sigmatropic rearrangement following the route pioneered by Fujimoto[60] and furthered by Colvin.[67]

Lactone (289) was converted into the dihydropyran derivative (291) by means of a two step process[62] involving lactone reduction using DIBAH followed by lactol deoxygenation and ionic hydrogenation using $Et_3SiH/BF_3.Et_2O$. A mechanistic representation is shown (Scheme 9). For simple substrates, this two step procedure is efficient. However, complications arose with the DIBAH reduction

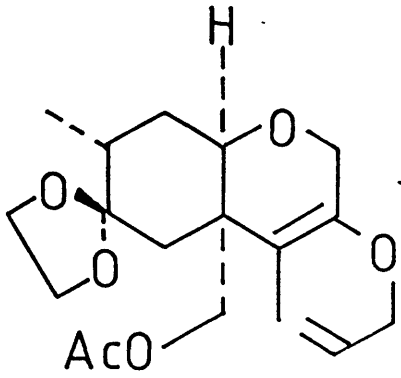


Scheme (10)

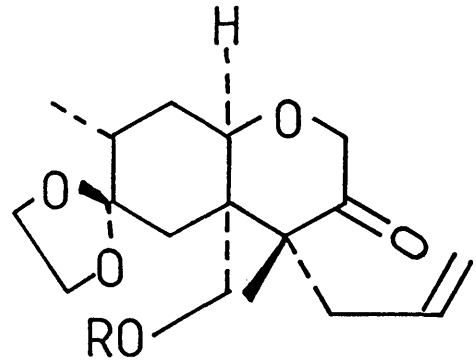
of the heavily functionalised lactone (289). It can be seen that there are two sites at which reduction could occur. Although diisobutyl aluminium hydride is known[113] to reduce esters, the lactone carbonyl should be reduced selectively. These problems were exacerbated by the fact that there is no simple method to determine the molarity of a DIBAH solution. In our hands, prolonged storage resulted in a decrease in molarity and thus, when used in a seemingly stoichiometric amount, reduction was incomplete. To circumvent this problem, an apparent excess of DIBAH had to be used but this resulted in over-reduction of (289). Since it appeared that ester over-reduction was taking place as the reaction mixture was allowed to warm to room temperature, a solution to this problem was achieved by quenching the excess DIBAH with AcOH at low temperature. Using these optimised conditions, reduction of (289) then gave lactol (290) in 81% yield.

At the outset, the lactol deoxygenation step [(290) → (291)] was also problematic. The ring A ketal is acid-sensitive but under strictly anhydrous conditions, no hydrolysis was expected to occur. This proved to be true, but epimerisation to varying extents was observed to take place at the methyl alpha to the ketal, as evidenced by the appearance of a new doublet at 0.93ppm in addition to the doublet at 0.82ppm. This epimerisation is believed to arise by the mechanism illustrated (Scheme 10). Fortunately, it was found that epimerisation could be prevented by quenching the reaction mixture at -78°C with anhydrous K_2CO_3 before allowing the reaction mixture to warm to room temperature.

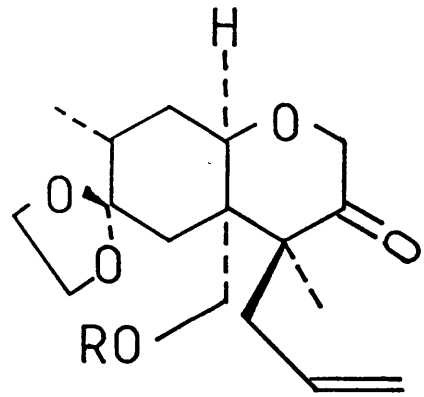
Prior to introduction of a new carbonyl group into the system via Claisen rearrangement, it was deemed prudent to reduce the methyl



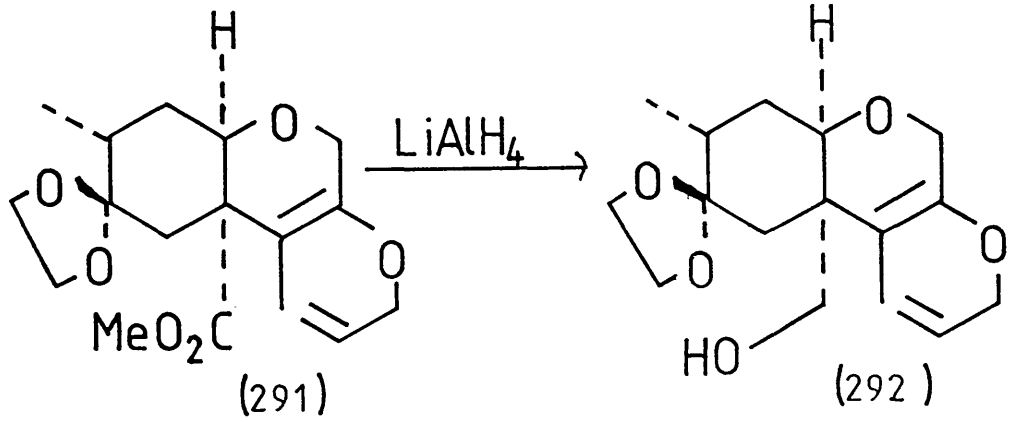
(296)



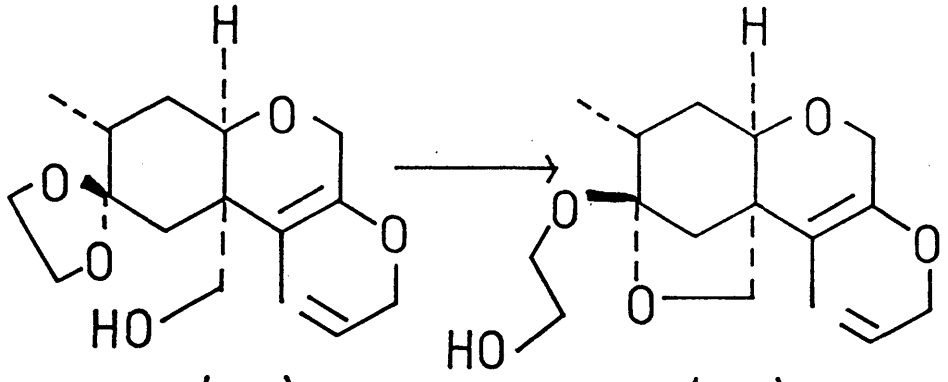
R = H (297)
R = Ac (299)



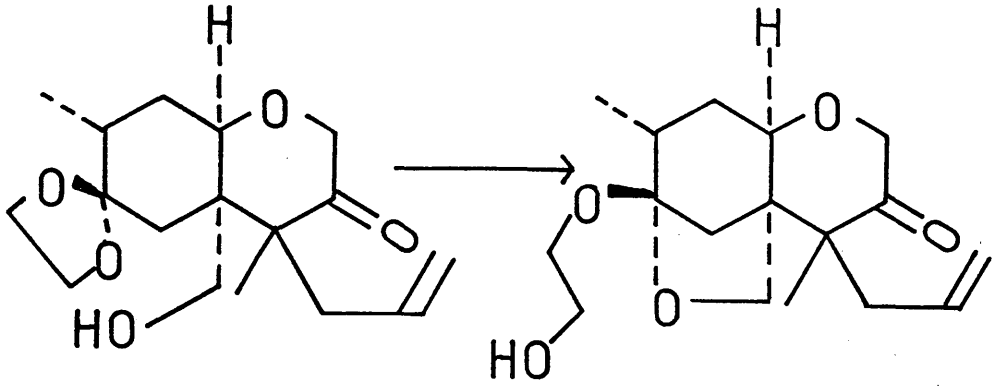
R = H (298)
R = Ac (300)



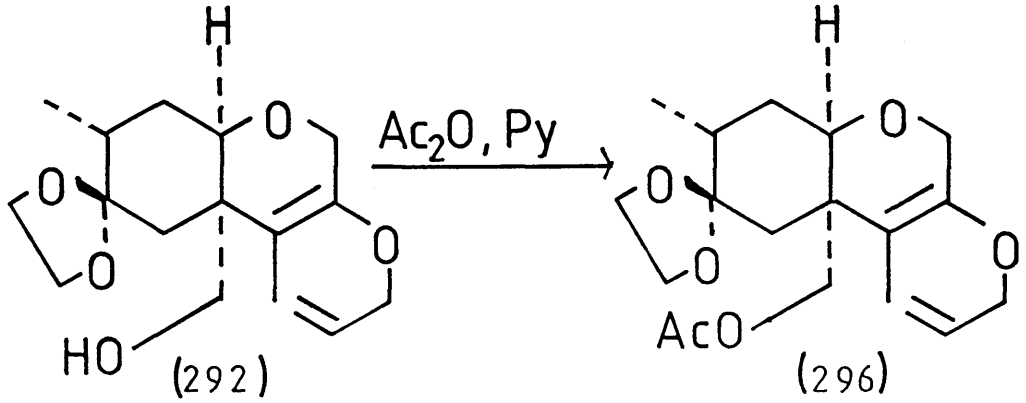
(291) (292)



(292) (293)



(294) (295)



(292) (296)

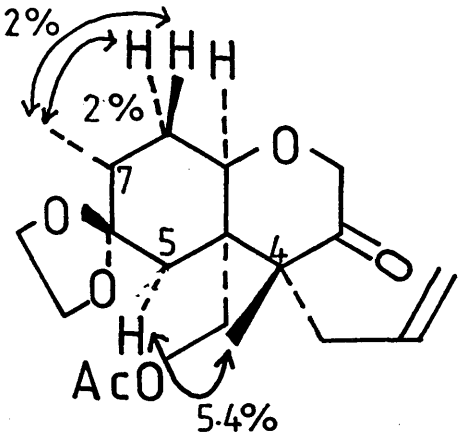
ester to the derived neopentyl alcohol. Lithium aluminium hydride was considered the reductant of choice and the experimental conditions followed the procedure of Kraus,[91] that is, work up by the addition of H_2O and NaOH followed by filtration through Celite. Unfortunately this procedure produced a variety of compounds as judged by t.l.c. analysis. It was decided instead, to use a neutral work-up sequence. Thus, the reaction mixture was quenched by the dropwise addition of saturated aqueous Na_2SO_4 solution followed by excess solid anhydrous Na_2SO_4. ^1H N.m.r. spectroscopic examination of the unpurified product indicated the expected loss of the methyl ester and t.l.c. indicated the formation of one major product. However, after chromatographic purification ^1H n.m.r. spectral analysis indicated that a rearrangement had taken place with the introduction of a new AB quartet. It was believed that this new and more polar product (293) had been formed *via* intramolecular ketal exchange, the AB quartet being attributed to the methylene bearing the oxygen in the new furan ring. Compound (294) also appeared to be unstable, undergoing a similar type of rearrangement (for relevance of this compound see page 47).

To exclude the possibility of such rearrangement occurring, the $LiAlH_4$ product was protected prior to purification as its acetate ester (296). Claisen rearrangement was accomplished in 99% yield by refluxing a solution of acetate (296) in toluene overnight. T.l.c. analysis of the reaction mixture showed only one spot. However, on lowering the polarity of the solvent system an additional spot appeared. From the close-running nature of these components, separation by dry column flash chromatography did not look encouraging. In an attempt to separate the two diastereoisomers by changing their relative

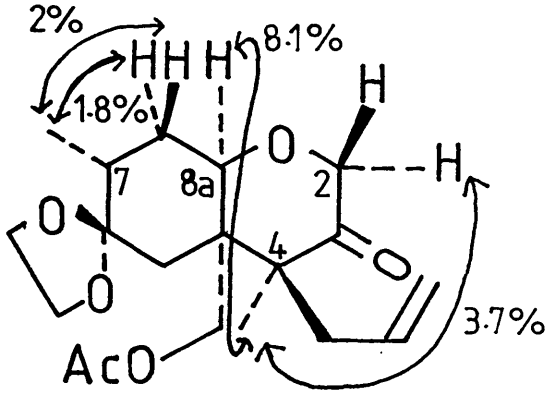
polarity, the acetate protecting group was hydrolysed but t.l.c analysis indicated that there was even less likelihood of separating the free alcohols (297) and (298). However, using positive pressure flash chromatography,[114] milligram quantities of the pure epimeric allyl ketone acetates (299) and (300) were obtained. The individual acetates were then subjected to separate n.O.e. experiments.

The major product (δ1.06ppm, s ,C-4 Me) was assigned the allyl α-stereochemistry (299) on the basis that when the C-4 methyl was irradiated a 5.4% integrated enhancement of the H-5α proton was observed; conformational analysis confirms their close proximity in space.

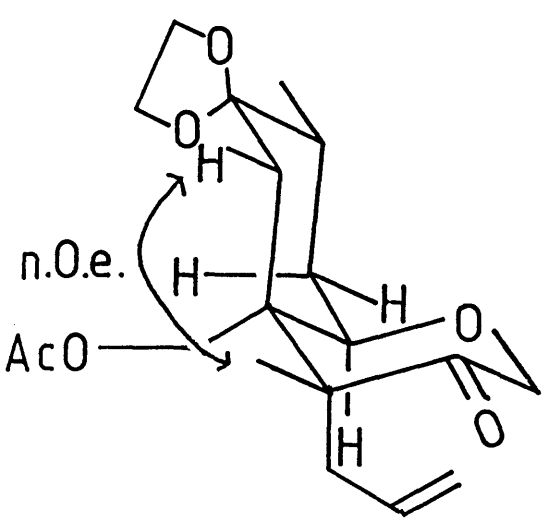
The minor product (δ1.14ppm,s , C-4 Me) was assigned the allyl β-stereochemistry (300) on the basis of two 1,3-diaxial interactions; when the C-4 methyl was irradiated a 8.1% enhancement of H-8a and a 3.7% enhancement of H-2α were both obtained.



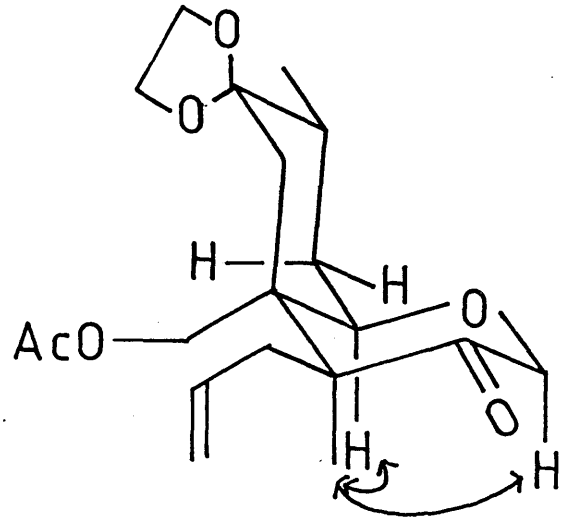
(299)



(300)



(299')

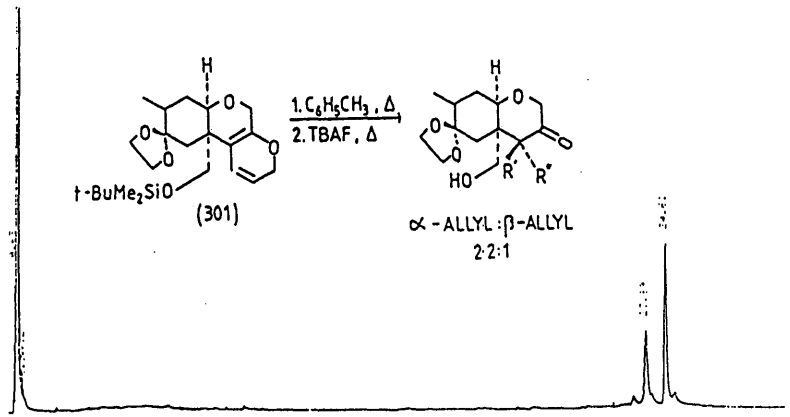


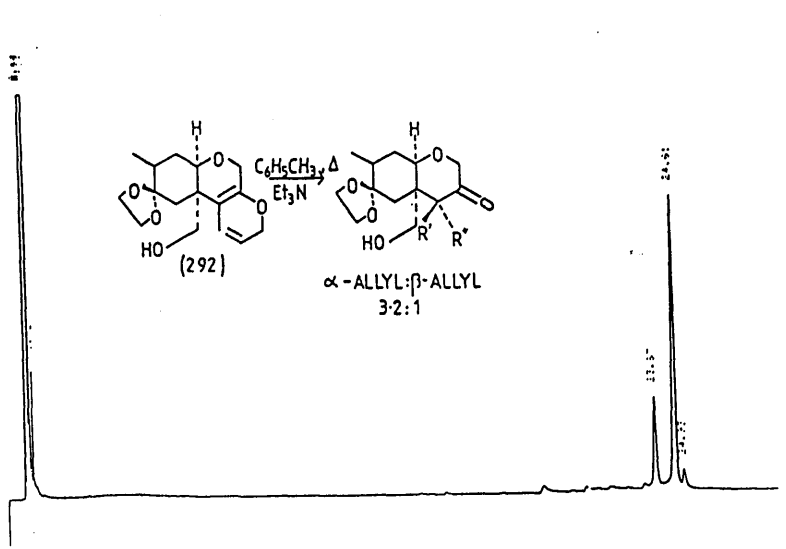
(300') n.O.e.

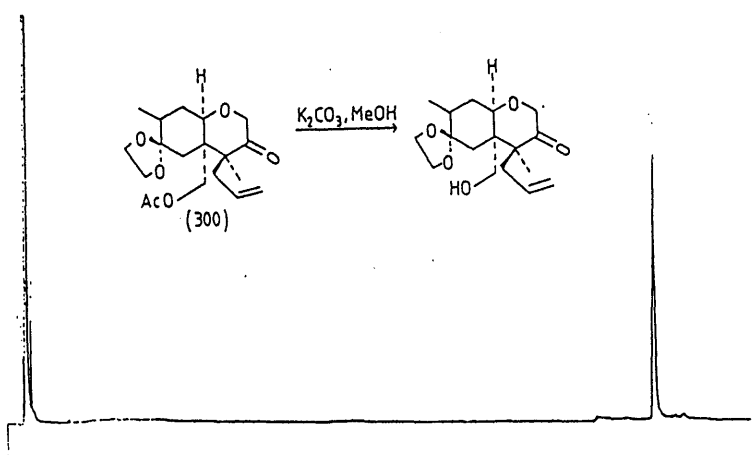
The conformational diagrams (299') and (300') show the respective spatial arrangements more clearly. In both molecules, the C-7 methyl stereochemistry was confirmed as α since on its irradiation there was equal enhancement of both H-8 methylene protons. If the methyl were in the β orientation, differential enhancement of the two protons would be expected.

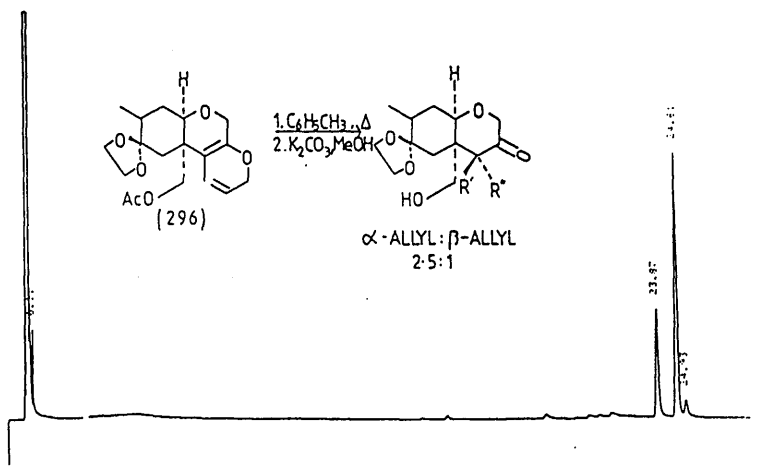
With the relative stereochemistry of the major product now established, a study was undertaken to determine the ratio of the two diastereoisomers and to evaluate whether one could minimise the relative amount of the undesired epimer (300). ^{1}H N.m.r. spectroscopic integration of the C-4 methyl signals gave an approximation of the relative amounts of (299) and (300).

G.l.c. Analysis proved to be of greater utility. By using a Hewlett-Packard 5880A G.C. with a 25m x 0.32mm I.D. fused silica capillary column the alcohols (297) and (298) could be separated,


H
O
O
O
O
t-BuMe2SiO
(301)
1. C6H5CH3 , Δ
2. TBAF , Δ
HO
R'
R"
α - ALLYL : β - ALLYL
2·2:1


H
O
O
O
HO
(292)
C6H5CH3, Δ
Et3N
R'
R"
α - ALLYL : β - ALLYL
3·2:1


H
O
O
O
AcO
(300)
K2CO3, MeOH
HO


H
O
O
O
AcO
(296)
1. C6H5CH3 , Δ
2. K2CO3, MeOH
HO
R'
R"
α - ALLYL : β - ALLYL
2·5:1

although it was not possible to separate acetates (299) and (300). The minor acetate epimer (300) was hydrolysed and the alcohol used as a reference standard.

Claisen rearrangement of acetate (296) followed by acetate cleavage and g.l.c. analysis showed a 2.5:1 epimer ratio with the desired α-epimer predominating.

The effect of a different hydroxyl protecting group was explored. Claisen rearrangement of the t-butyldimethylsilyl ether (301) followed by fluoride ion induced desilylation and g.l.c. analysis indicated a 2.2:1 α:β epimeric ratio.

On the assumption that the rearrangement [(294) → (295), see page 44] was acid catalysed, the free alcohol was heated in toluene made basic by the addition of 5% Et_3N. G.l.c. Analysis of the crude reaction mixture indicated a 3.2:1 α:β epimeric ratio.

From these results it is clearly evident that as the size of the alcohol protecting group is increased, the ratio of desired to undesired product is lowered. This is in full accord with a conformational analysis of the two possible chair transition states (Figures 2 and 3) which indicates that as the protecting group is made larger there is increased steric congestion in transition state (257') forcing the molecule to adopt the alternative transition state (257'').

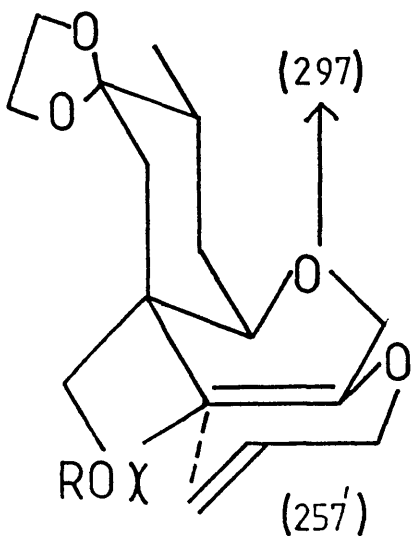


FIGURE 2

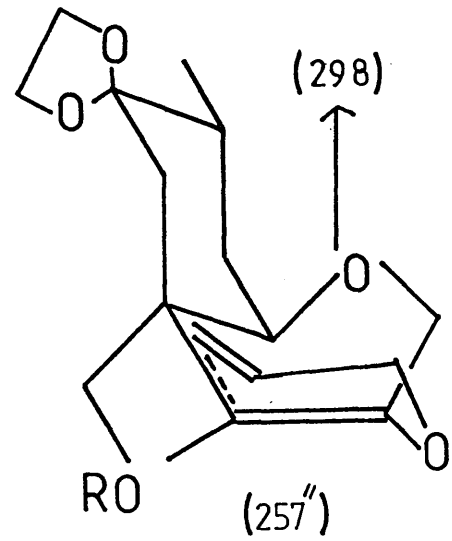
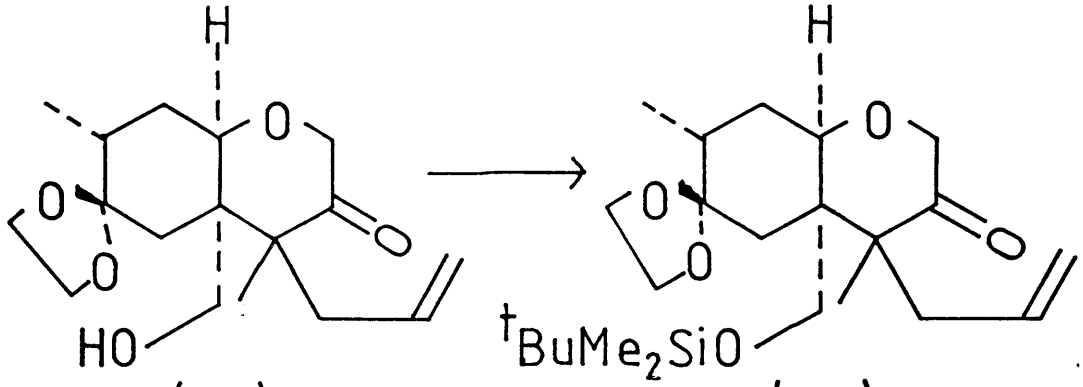


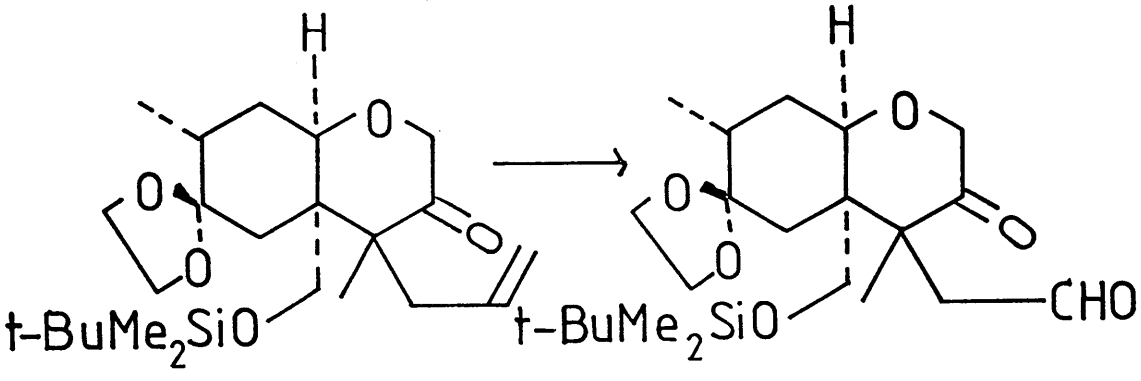
FIGURE 3

As a result of this study it was decided to perform the Claisen rearrangement on the free alcohol (292), and then to protect it prior to subsequent reaction sequences.

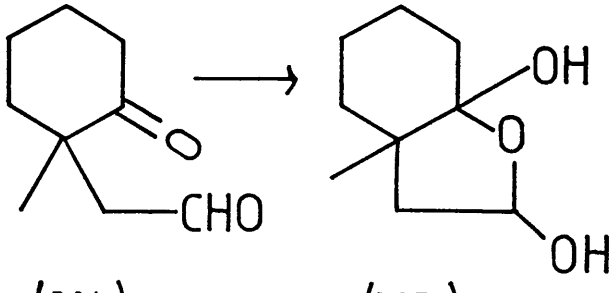
There were several constraints on the choice of a suitable protecting group. It should not require acidic conditions for deprotection, otherwise, on its cleavage the ring A ketal might also be deprotected : this ruled out tetrahydropyranyl and similar acetal-type protecting groups. The base to be used to execute the aldol cyclisation was to be sodium methoxide[60] to which the protecting group would also have to be stable; this eliminated acetate or other simple ester protecting groups. If the cyclisation went smoothly a further hydroxyl group would be introduced at C-3 which would also have to be masked prior to installation of the 12,13-alkene. It was deemed desirable to be able to differentiate between these two hydroxyl groups, i.e., to be able to deprotect them selectively. After much



(294) (302)



(302) (303)

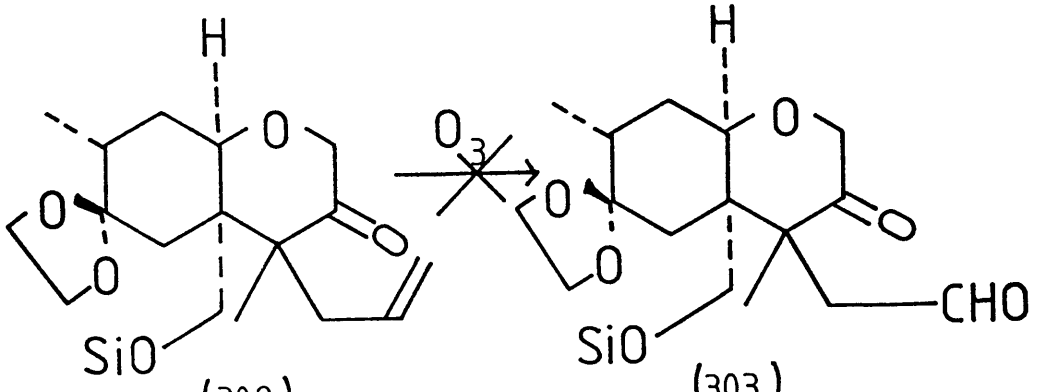


(304) (305)

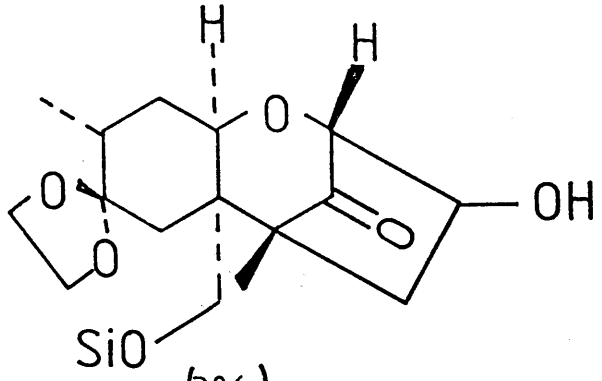
deliberation, the protecting group settled upon for the C-15 hydroxyl group was a tert-butyldimethylsilyl ether, a functionality which is known[49] to be stable to sodium methoxide and one which can be removed[115] specifically using fluoride ion.

Two methods of alcohol silylation[115,116] were examined. The first involved treatment of an ethereal solution of the alcohol with TBDMSCl, triethylamine and 10 mol % of 4,4-dimethylaminopyridine. The second entailed dissolving the alcohol in the minimum quantity of dry DMF and adding TBDMSCl and imidazole. Both procedures proved unsuccessful. From an examination of the molecular models it can be seen that the neopentyl alcohol is relatively hindered. Corey has examined[117] the use of TBDMS triflate as a method of silylating hindered alcohols. The reagent is easily prepared by heating a 1:1 mixture of tert-butyldimethylsilyl chloride and trifluoromethane-sulphonic acid at 60^{o} for a period of 18 hours followed by direct distillation from the reaction vessel. Treatment of (294) with the so-prepared reagent in the presence of 2,6-lutidine resulted in the rapid formation of (302) as monitored by t.l.c analysis.

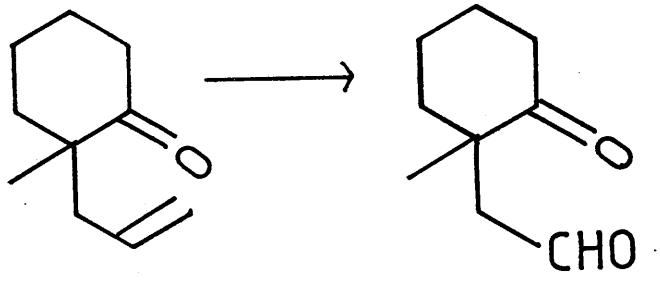
Having thus obtained allyl ketone (302), it remained to cleave the allyl substituent to the ethanal moiety of (303). 1,4-Ketoaldehydes of this type are known[118] to be moisture sensitive. Indeed, it has been reported[119] that the model compound (304) readily takes up the elements of water to form the five-membered cyclic hydrate (305). Cameron has stated[119] that cleavage of this hydrate could not be accomplished by distillation, nor was it a suitable aldol precursor. It was therefore regarded as being imperative to avoid exposure of keto-aldehyde (303) to an aqueous medium.



(302) (303)



(306)



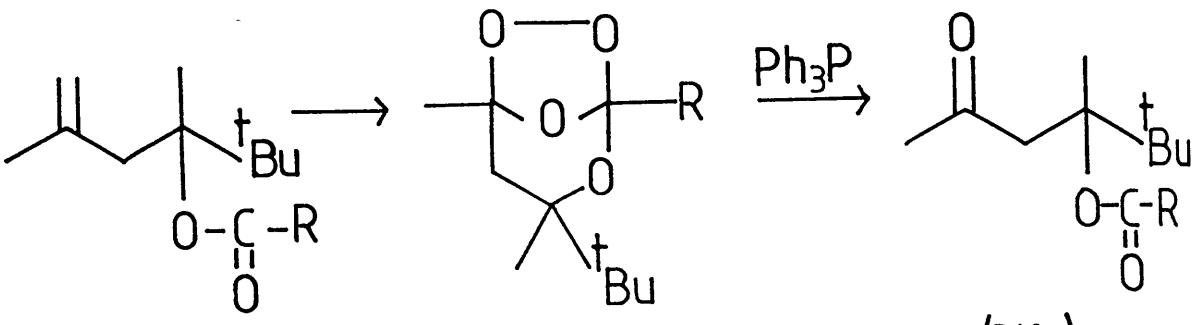
(307) (304)

An excellent method[120] of cleavage of allyl moieties to terminal aldehydes is by catalytic osmylation, with excess of sodium periodate as the co-oxidant. However, this method requires an aqueous or, at best, a two-phase reaction mixture since water is required to solubilise the periodate and to hydrolyse the intermediate osmate ester.

Ozonolysis[121] is a method by which water can be excluded. The correct choice of reagent for reductive cleavage of the ozonide ensures that an aqueous wash is unnecessary. Studies have shown[122] that triethylamine is an effective reducing agent of such systems: final filtration of the reaction mixture through a short column of silica gel removes the triethylamine N-oxide, the keto-aldehyde appearing in the eluate.

Unfortunately, although the reported experimental conditions were strictly adhered to, t.l.c. analysis of the product from [(302) → (303)], showed only streaking. Aldol cyclisation of this crude material did not result in any discrete products. The ozonolysis solvent was varied (CH_2Cl_2, EtOAc, MeOH) to no avail; aldol cyclisation of the oxidation product did not produce the desired tricycle (306). As repeated experimentation at this step was consuming valuable material, a model study was undertaken to investigate alternative methods of forming the bicyclo[3.2.1]octanol ring system (see Model Studies page 58).

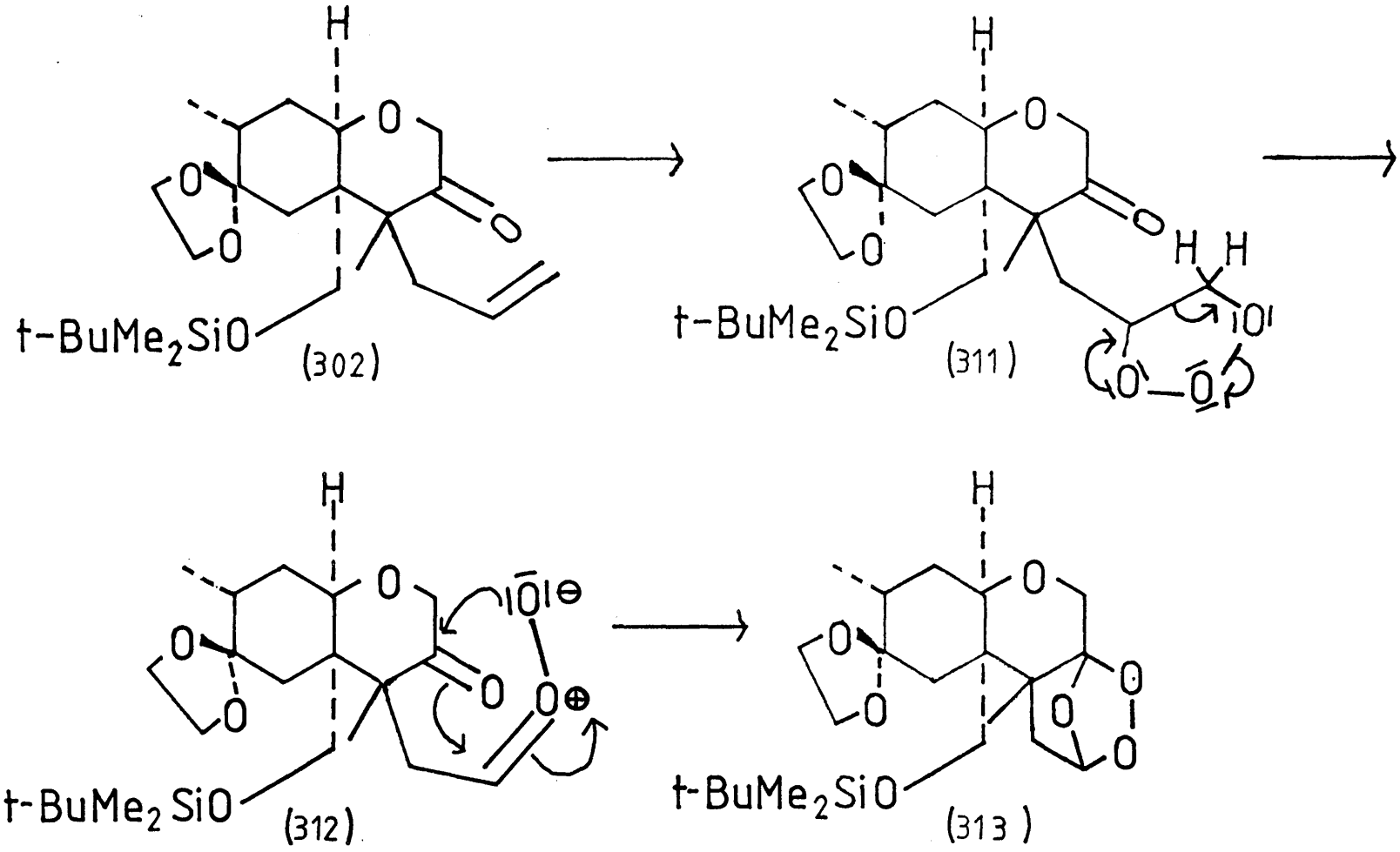
One can postulate why the oxidative cleavage with ozone converted (307) into (304) but did not effect a similar transformation with (302). A proposed mechanism for the ozonolysis of (302) is



(308) (309) (310)

R= p-$NO_2C_6H_4$

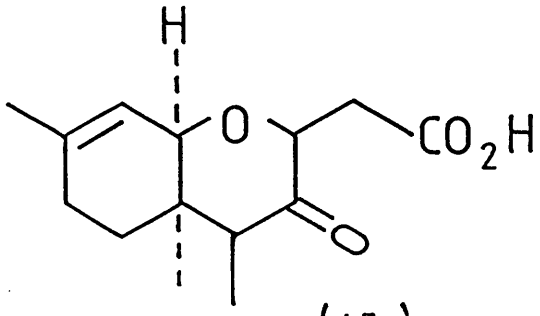
Scheme (11)


H
O
O
O
O
t-BuMe2SiO
(302)
H
O
O
O
H H
O
O
t-BuMe2SiO
(311)
H
O
O
O
O
O⊕
t-BuMe2SiO
(312)
H
O
O
O
O
O
O
t-BuMe2SiO
(313)

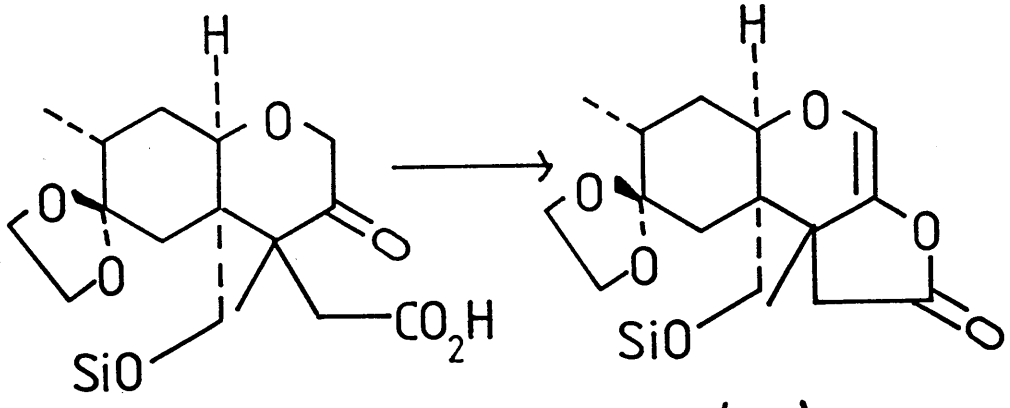
illustrated. Initial [3+2] dipolar cycloaddition of ozone to the terminal alkene will generate the molozonide (311). Normal breakdown of the molozonide will produce the carbonyl oxide (312) and formaldehyde. The usual pathway is for the carbonyl oxide to recombine with the eliminated carbonyl fragment to produce an ozonide. If, however, the carbonyl oxide were to combine with the ketonic carbonyl, it would give rise to (313). This hypothesis is not without precedent[123,124] : Bunnelle and Schlemper have reported the isolation of the crystalline ozonide (309) formed by intramolecular addition of the intermediate carbonyl oxide to the ester side chain (Scheme 11).

The breakdown of an ozonide is believed to originate at the peroxide bridge. With ozonide (313), the peroxide bridge is sterically hindered both by the large tert-butyldimethylsilyl group and by the other rings. On the other hand, the corresponding peroxide bridge is readily accessible in the model compound : this may explain the differing reactivities of the two systems. In an attempt to induce the breakdown of ozonide (313), the stronger reducing agents triphenylphosphine[125] and trimethylphosphite were used. No reaction occurred using Ph_3P and only small amounts of the aldehyde (303) were obtained even after heating a solution of (313) and $(MeO)_3P$ in CH_2Cl_2 under reflux.

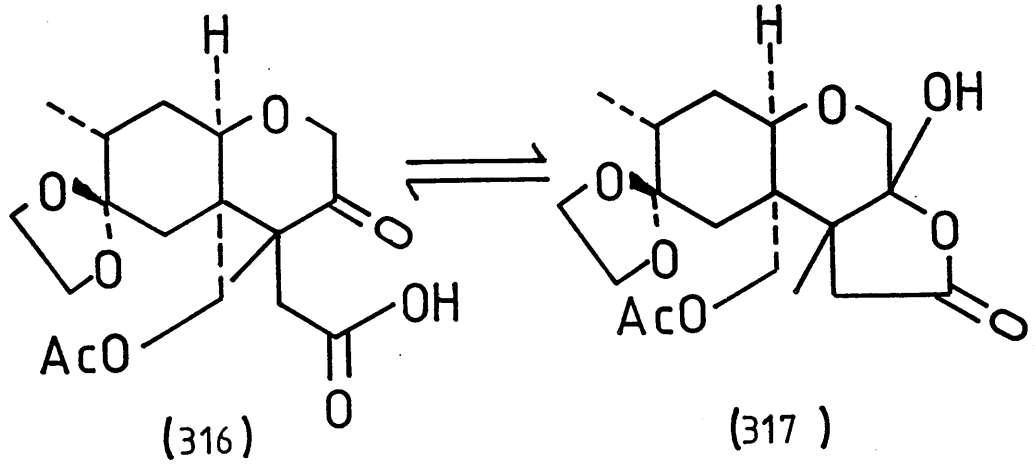
At this time, model studies (Enol-lactone reductive cyclisation page 66) being carried out in parallel were bearing fruit. In the original synthesis of trichodermol[61], an enol-lactone reductive cyclisation step was used to effect the ring closure. A low yield in the C-4, C-5 bond forming reaction was obtained due to non-specific



(45)



(314) (315)



(316) (317)

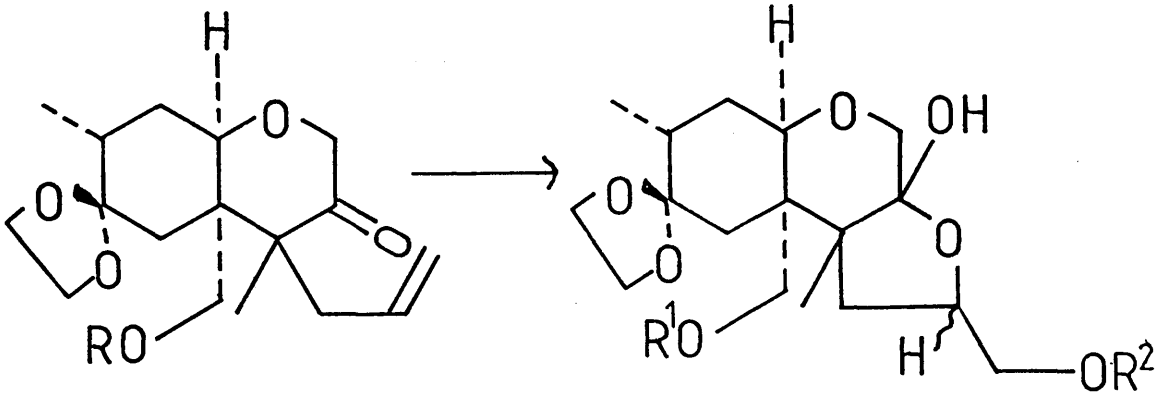
Scheme (12)

enolisation of keto-acid (45). With substrate (314), there is only one possible mode of enol-lactone formation. Hence it was anticipated that reductive cyclisation of (315) should be higher yielding.

To this end, attempts were made to form keto-acid (314).

Sharpless has described[126] an improved procedure for the ruthenium tetroxide catalysed oxidative cleavage of alkenes. Addition of acetonitrile to the conventional CCl_4/H_2O solvent system prevents formation of low valent ruthenium carboxylate complexes and enhances the reliability of the oxidation.

Oxidation of (318) using this method, followed by base-acid extraction, furnished a compound which had no olefinic signals in its ^1H n.m.r. spectrum. The i.r. spectrum showed a broad carbonyl at 1770 cm^{-1} and a sharper carbonyl at 1740 cm^{-1} in addition to hydroxyl stretches at 3400 cm^{-1} and 3600 cm^{-1}. Three signals at 169.61ppm, 172.52ppm and 176.95ppm were observed in its ^{13}C n.m.r. spectrum and a high resolution mass spectrum indicated a parent ion at 370 a.m.u. of composition $C_{18}H_{26}O_8$, which is the correct composition for (316). This data is in agreement with the fact that (316) would be expected to undergo acid-pseudo acid interconversion (Scheme 12) due to the spatial arrangement of hydroxyl and ketonic functionality. However, on treatment with diazomethane, there was no additional methyl signal, as determined by ^1H n.m.r. spectroscopy. To esterify, the acid must be in its open chain form. Accordingly, since the pseudo acid-open chain acid interconversion might be slow, (316) was treated with an ethereal CH_2N_2 solution for 72 hours. Although the excess CH_2N_2



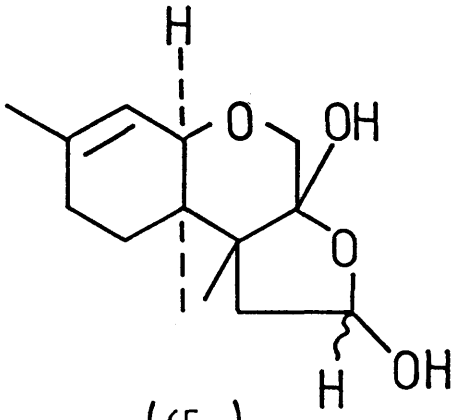
R=Ac (318)
R=Si (302)

R^1=Ac, R^2=H (319)
R^1=Si, R^2=H (320)
R^1=Si, R^2=Ac (321)

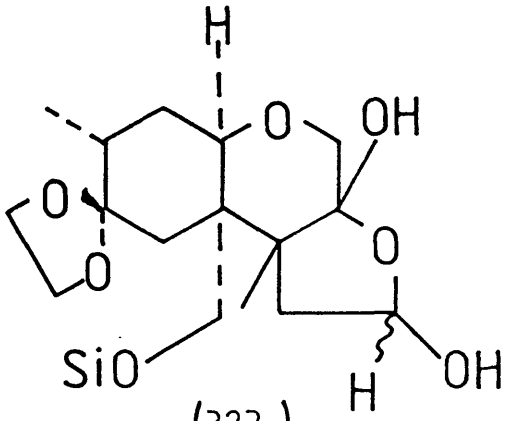
could be seen to polymerise, the starting material was returned unchanged.

Since unequivocal identification of (316) proved impossible, attention was turned to other, milder methods of oxidation. Permanganate ion is also known to convert terminal alkenes into acids. Allyl ketone (318) was treated with a 1:1 $^{t}BuOH : H_2O$ mixture containing 4 equivalents of sodium periodate and a few crystals of $KMnO_4$, made basic with 5% K_2CO_3 solution in order to inhibit ketal cleavage.[127] Instead of obtaining the anticipated acid (316), the diol (319) was formed in 47% yield. Similar treatment of (302) gave diol (320) in which again one of the hydroxyls had added to the ketonic carbonyl. This was apparent from the lack of a carbonyl stretch in its i.r. spectrum. To determine whether the primary or the secondary hydroxyl had added to the carbonyl, (320) was acetylated. The ^{1}H n.m.r. spectrum of this product showed an integrated downfield shift of two protons verifying the formation of tetrahydrofuran (321). This was an unexpected, but useful result. If diol (320) could be cleaved oxidatively under anhydrous conditions, aldehyde (303) would be obtained.

In order to improve the efficiency of this step other methods of diol formation[128] were also examined. Following Fujimoto's method,[60] allyl ketone (302) was oxidised with osmium tetroxide and sodium perchlorate as the co-oxidant. No reaction occurred. The reaction was repeated using fresh sodium perchlorate but again no reaction ensued.



(65)



(323)

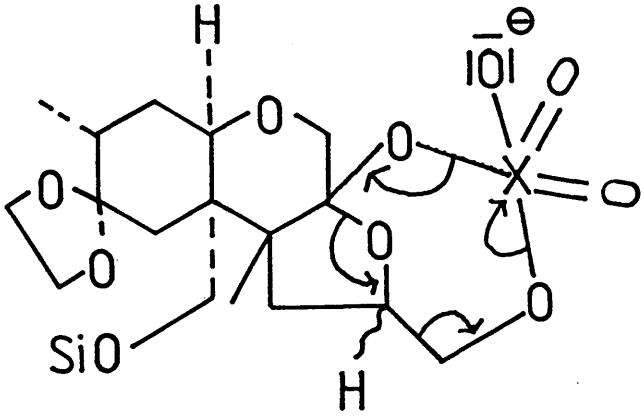
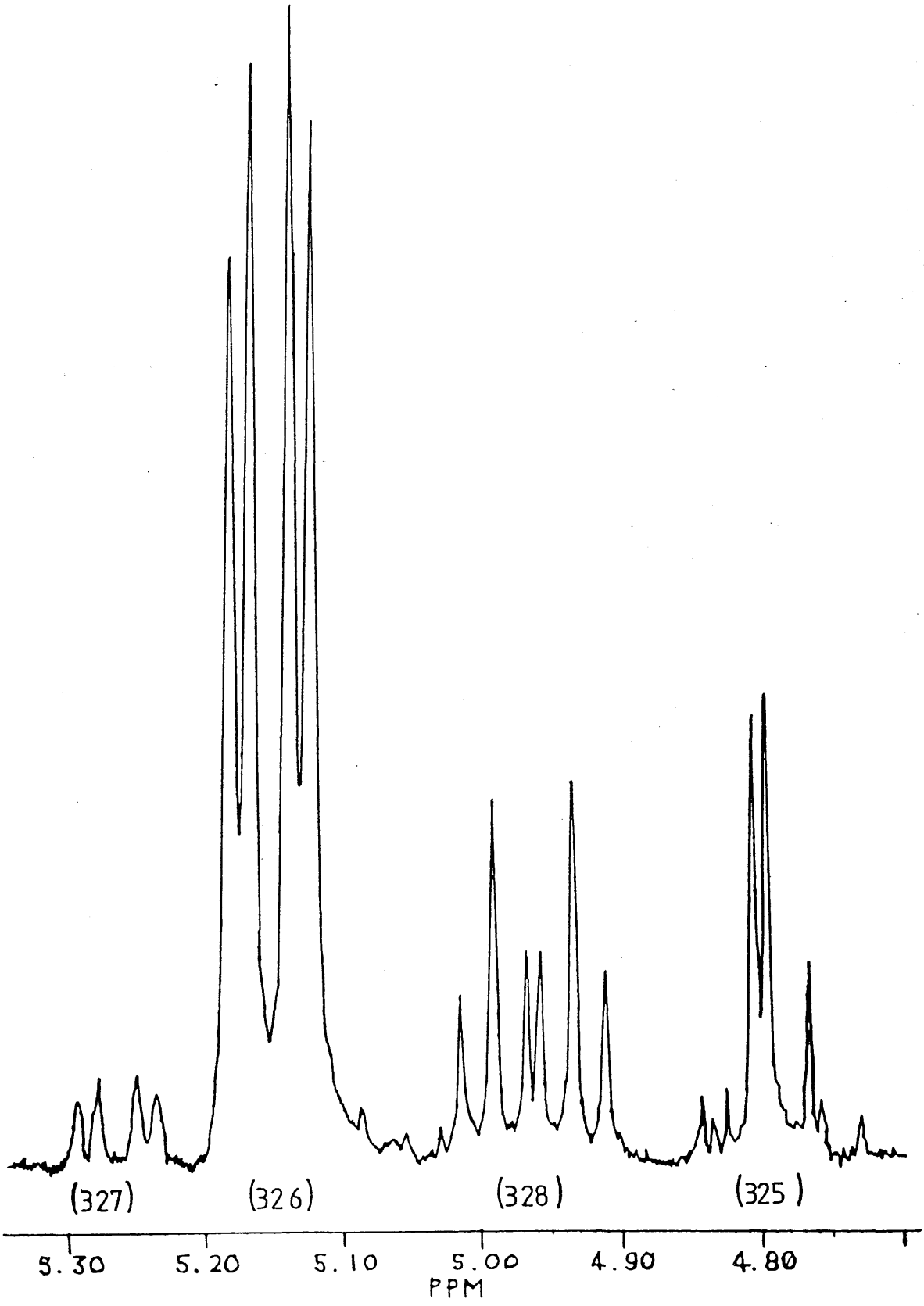


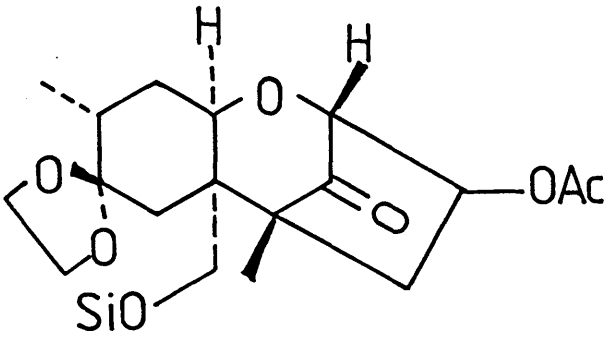
FIGURE 4

Treatment of (302) with catalytic OsO_4 using N-methyl morpholine N-oxide as the co-oxidant[129] gave a compound which by t.l.c. analysis was too non-polar to be diol (320) and which also had a carbonyl in its i.r. spectrum. Although its structure could not be assigned, it was apparent from its ^1H n.m.r. spectrum that it had been oxidised since the olefinic signals, characteristic of the allyl side-chain, had disappeared.

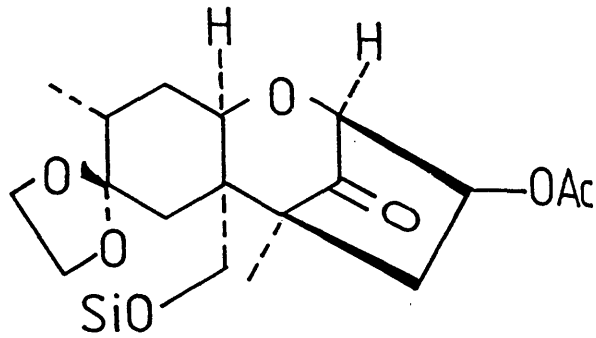
Fujimoto has reported[60] aldol cyclisation of monohydrate (65). With this in mind, the preparation of (323) was attempted. Catalytic osmylation of (302) with 8 equivalents of sodium periodate furnished a compound which by t.l.c. analysis was obviously different from (320). Its i.r. spectrum indicated a strong OH stretch and essentially no carbonyl stretch. From its ^1H n.m.r. spectrum it could be seen that the olefinic signals had disappeared. This compound was recovered unchanged on treatment with sodium methoxide.

Eventually conditions were established to produce (320) in 88% yield using 10 mol % OsO_4 and a heterogeneous 1:1 mixture of ether and water. At the outset, 4 equivalents of sodium periodate were used but for subsequent reactions the ratio was lowered to 1.2 equivalents. It is interesting to note that one of the disadvantages of using sodium periodate as the co-oxidant in a diol-forming reaction is that diol cleavage can occur. With compound (320) no such over-oxidation was observed. Similarly no over-oxidation took place on treatment of (302) with cat.$KMnO_4$ and excess $NaIO_4$. It is postulated that in order to cleave diol (320), the bridging ion (X) would be involved in a 7-membered transition state (Figure 4) : this is known to be unfavourable. Thus this served as a method of protecting the diol

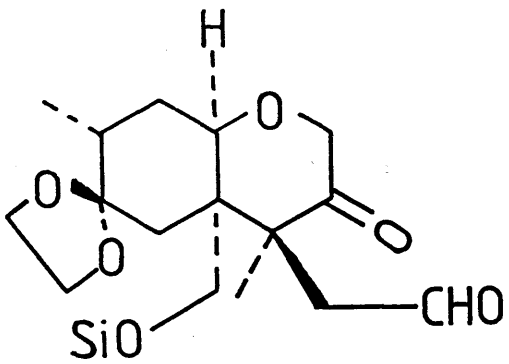

(327)
(326)
(328)
(325)
5.30
5.20
5.10
5.00
4.90
4.80
PPM



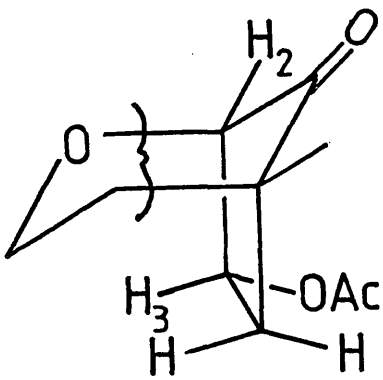
OAc α (325)
OAc β (326)



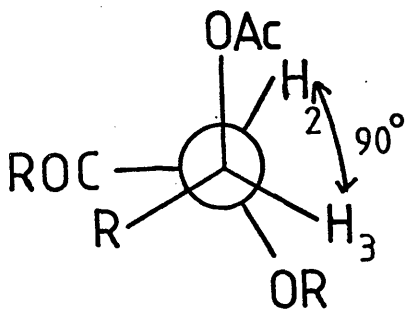
OAc α (327)
OAc β (328)



(329)

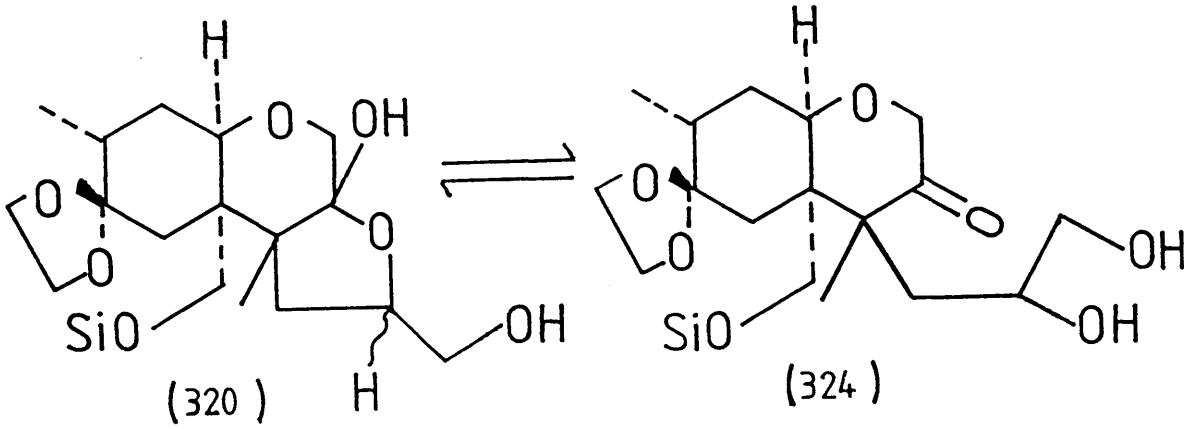


(330)

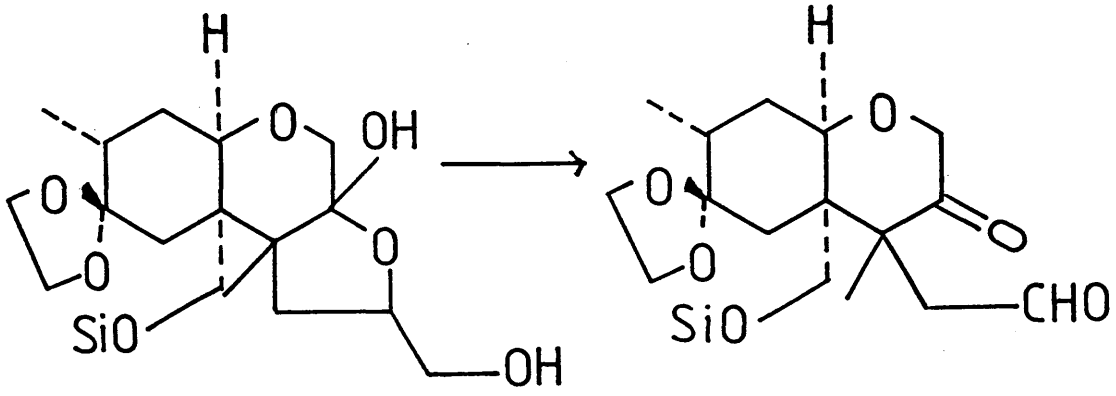


(331)

FIGURES 5 AND 6



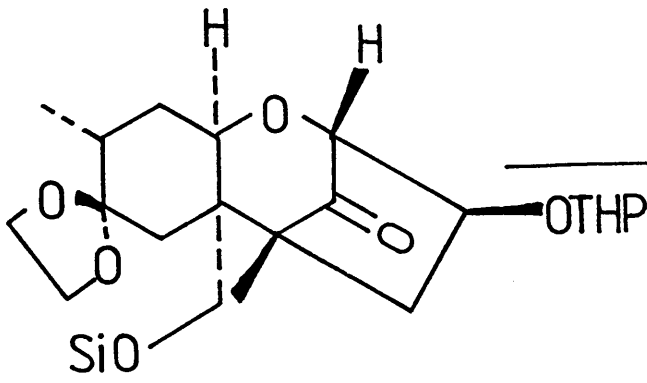
(320) (324)



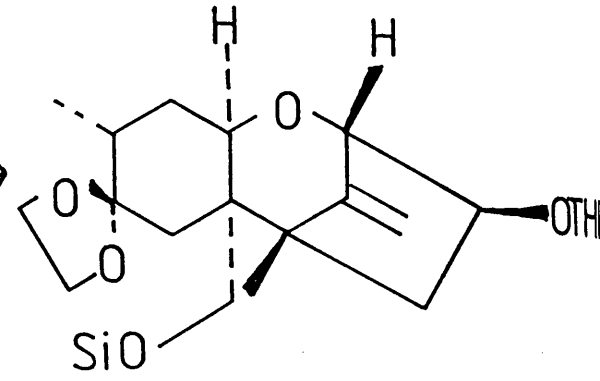
(320) (303)

from over-oxidation.

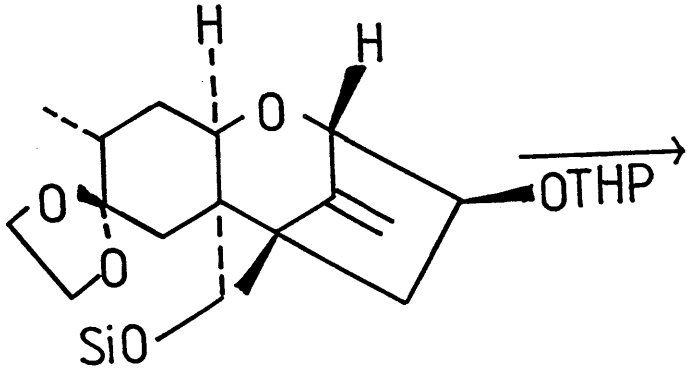
Having established a route to (320), its cleavage under anhydrous conditions was then examined. The first reagent tested was n-tetrabutyl ammonium periodate,[130] but no useful products were obtained from its reaction with (320). Up until this point, both the alkene and the diol oxidation had been carried out in a basic or neutral reaction medium. It was decided to change to an acidic reaction medium to disturb the equilibrium between hemiacetal (320) and open-chain diol (324). As such, the next reagent tested was ethereal periodic acid, which gratifyingly converted (320) into (303). For fear of hydrate formation, aldehyde (303) was immediately subjected to aldol cyclisation conditions and the crude product so obtained was acetylated. The i.r. spectrum of the purified acetate showed two carbonyl absorptions, one at 1760 cm^{-1} characteristic of a cyclic five membered ketone and the other at 1735 cm^{-1}. Expansion of the 200 MHz ^1H n.m.r. spectrum in the region between 4.70 and 5.35ppm indicated a 4.2:1 mixture of (326) to (325). Additionally, it could be seen that the alternative aldehyde (329) had also cyclised, producing (327) and (328) in a ratio of 1:4. A ratio of 3.2:1 for [(325) and (326)] to [(327) and (328)] was obtained; this ratio was determined at the Claisen rearrangement step. The epimers could be distinguished on the basis of the coupling patterns of the CH(OAc) portions in their ^1H n.m.r. spectra - the α-epimer (325) gave the expected ddd pattern at 4.80ppm whereas the β-epimer (326) gave rise to only a doublet of doublets at 5.15ppm, no coupling being observed between H-2 and H-3. From Figures 5 and 6, it can be seen that the dihedral angle between H-2 and H-3 is close to 90° in the β-epimer; the Karplus-Conroy curve



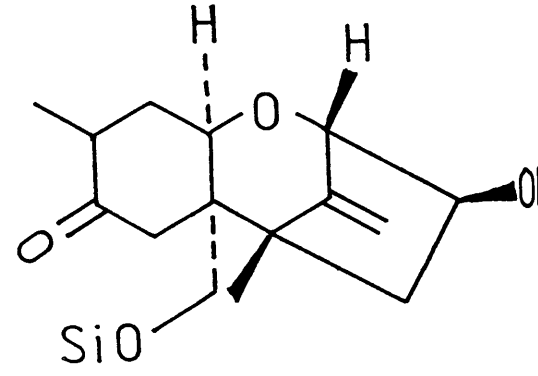
(333)



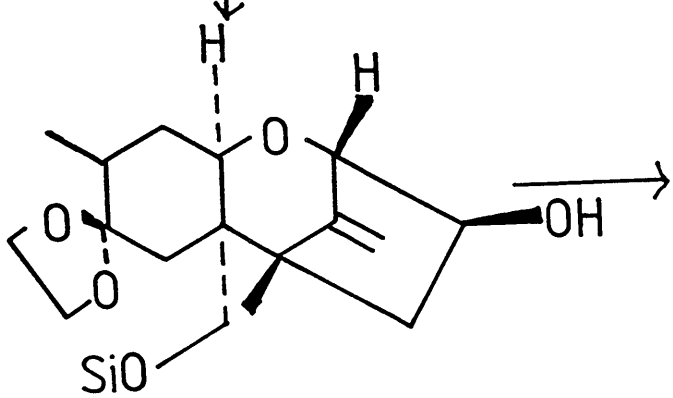
(334)



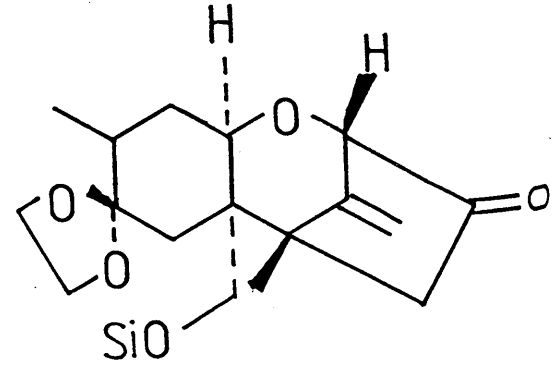
(334)



(335)



(332)



(336)

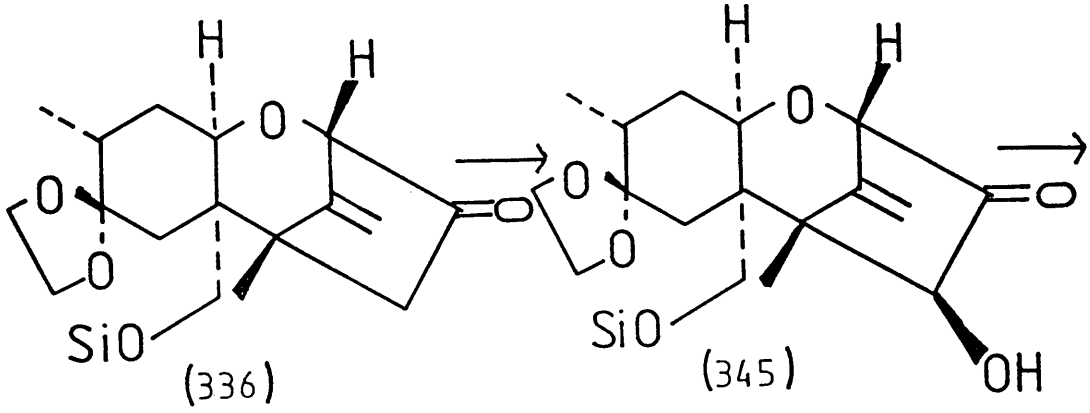
predicts[131] that the coupling in such systems should be zero. Separation of (325)/(326) from (327)/(328) proved impossible.

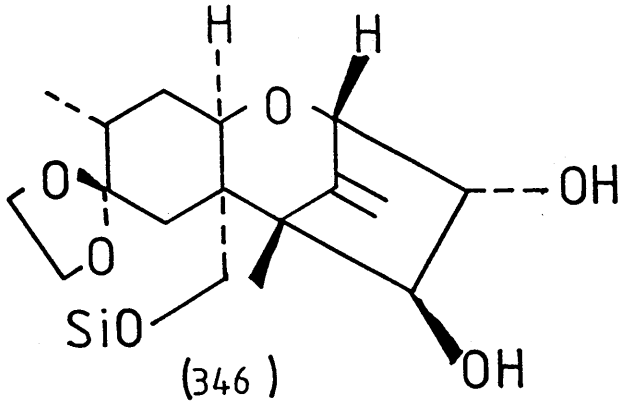
It was planned to introduce the 12,13-alkene by a Wittig reaction. However, treatment of the acetate mixture with an excess of methylenetriphenylphosphorane, generated by treatment of methyltriphenylphosphonium bromide with n-BuLi, did not produce (332). A competitive reaction could be acetate cleavage prior to 12,13-alkene introduction, which would then almost certainly result in a retro-aldol reaction taking place. To prevent this, the purified ketol (306) was therefore quantitatively transformed into its tetrahydropyranyl ether derivative[132] (333). Treatment of (333) with methylenetriphenylphosphorane then furnished the exomethylene alkene (334) without complication.

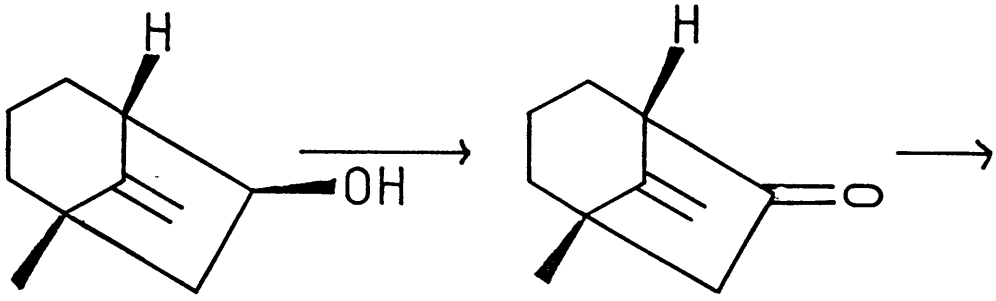
At this point it was considered but a simple matter to deprotect the C-3 hydroxyl and functionalise ring C further.

A good and mild method of cleaving THP ethers involves exchange reaction with methanol in the presence of catalytic PPTS.[132] However under these conditions non-selective cleavage of both the ring A ketal and ring C THP was observed giving rise to ketone (335).

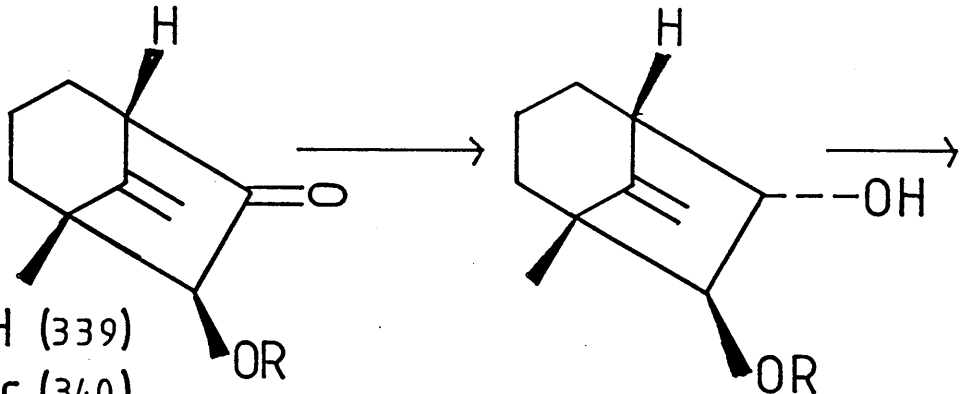
By an ingenious process, the hydroxylic exchange source was switched from methanol to ethylene glycol. Using this protocol, the tetrahydropyranyl ether was selectively removed to give (332). Oxidation of (332) using CrO_3 and 3,5-dimethylpyrazole gave ketone (336) in 79% yield.


H
H
O
O
O
SiO
O
(336)
H
H
O
O
O
SiO
O
OH
(345)


H
H
O
O
O
SiO
OH
OH
(346)

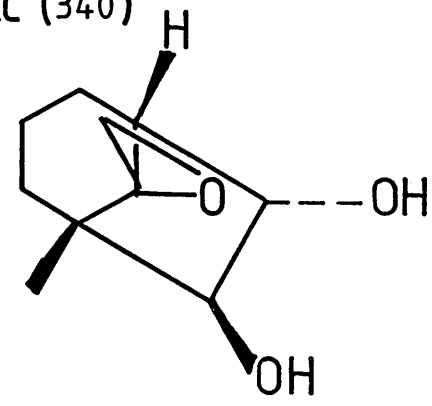


(337) (338)

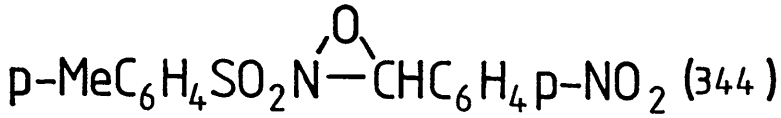


R = H (339)
R = Ac (340)

R = H (341)
R = Ac (342)



(343)

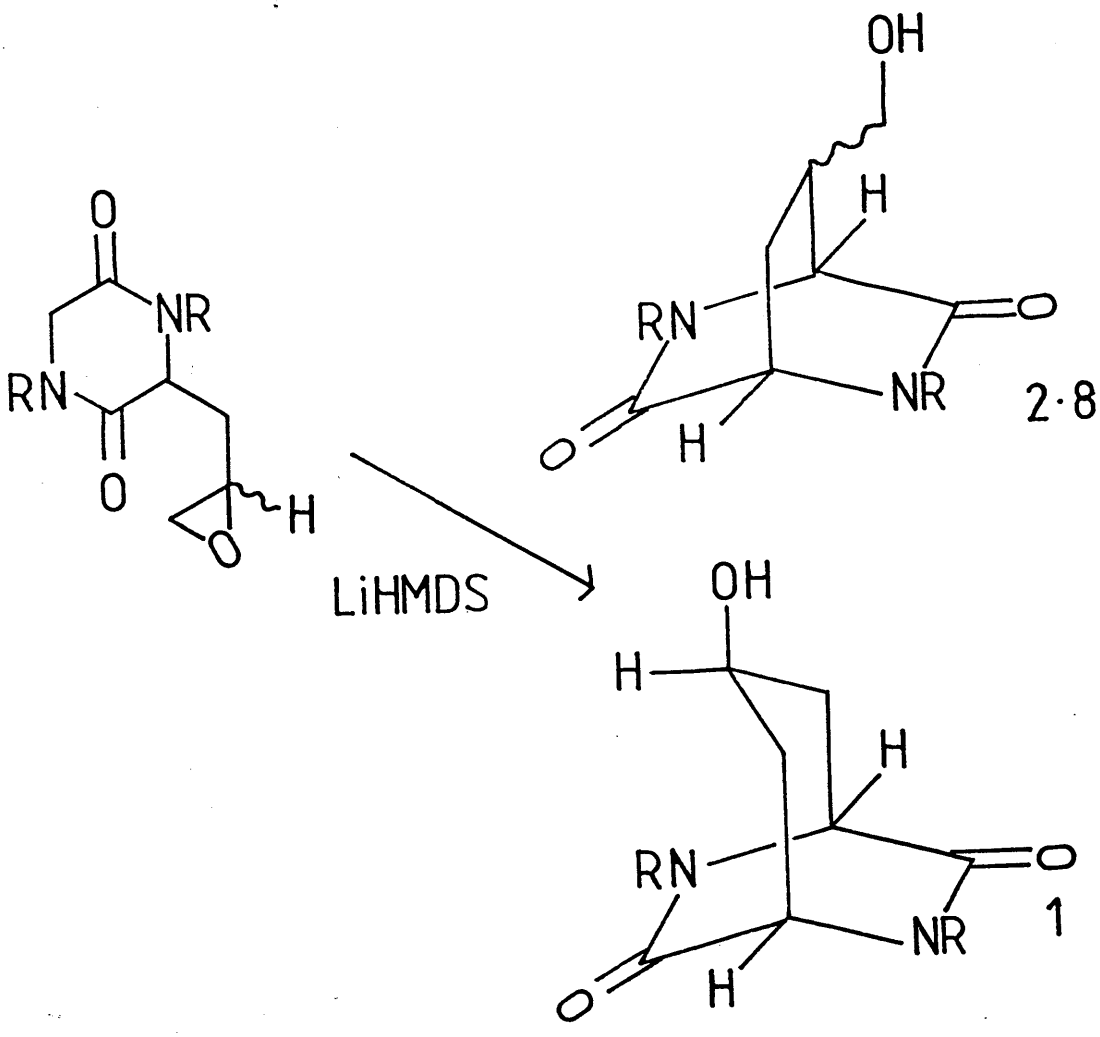


(344)

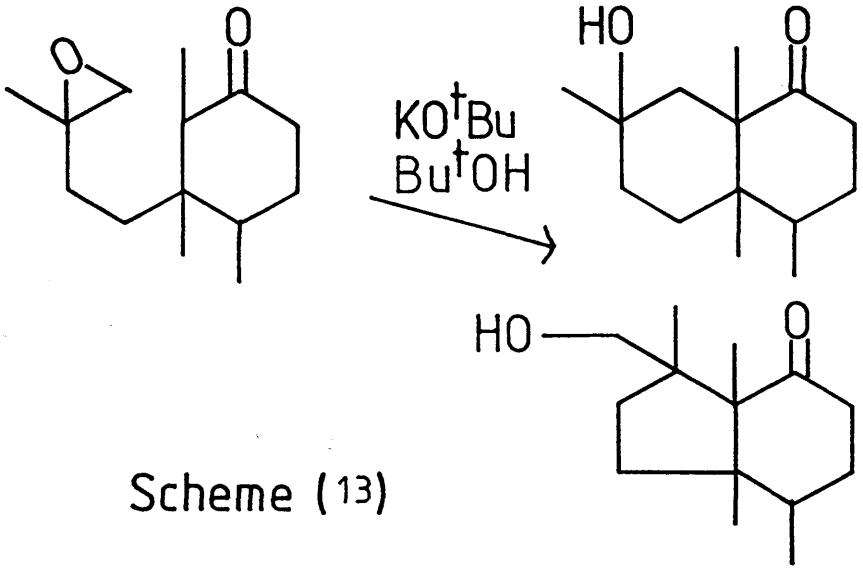
Running concurrently with this project was a study of the best method for stereospecific installation of the ring C trans-3α,4β-diol system. The content of this study will be reported in due course[133] but it is worthy of mention here since it has provided the strategy for and yield optimisation of the reactions currently under investigation. Oxidation of model compound (337)[122] using CrO_3 and 3,5-dimethylpyrazole gave olefin-ketone (338). Alpha hydroxylation of (338) was accomplished by treatment of the potassium enolate of (338) with the sulphonyl oxaziridine[134] (344). Acetylation of the crude α-hydroxyketone gave (340) which was separated from the imine byproduct by means of trituration. Sodium borohydride reduction of (340) gave (342), both the oxidation and reduction taking place from the more accessible exo-face of the bicyclo[3.2.1] octane. Acetate cleavage to diol (341) followed by hydroxyl directed epoxidation furnished epoxydiol (343) and established the correct substituent orientations for ring C of T-2 tetraol.

Extending this methodology to fully functionalised ketone (336), treatment of the potassium enolate of (336) with sulphonyl oxaziridine (344) gave α-hydroxy ketone (345). Purification of this product from the imine byproduct could not be achieved by acetylation and trituration; however, treatment of the crude α-hydroxy ketone with sodium borohydride furnished diol (346) which could be obtained pure by dry column flash chromatography.

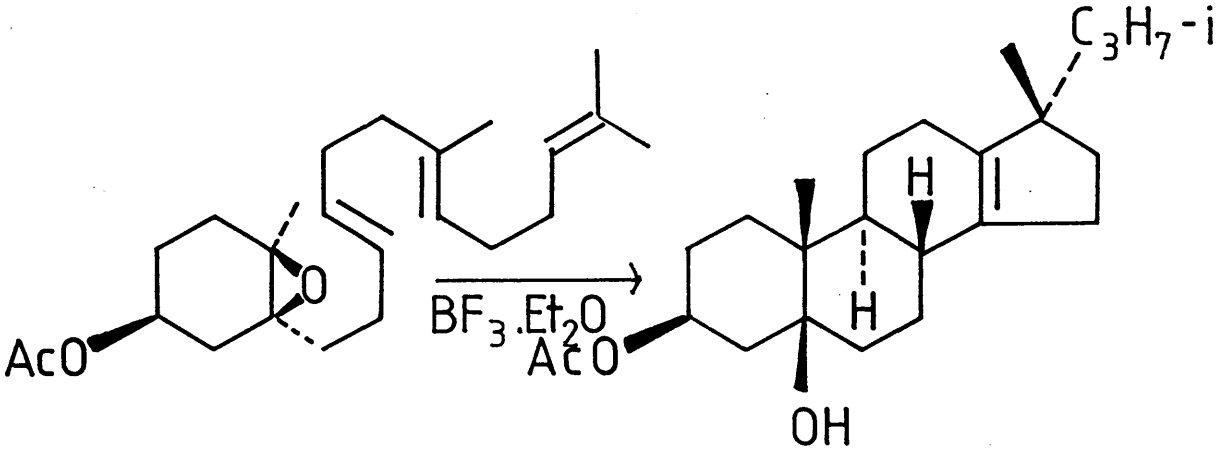
Deketalisation, epoxidation, dehydrogenation, reduction and finally deprotection are necessary operations to complete the synthesis of T-2 tetraol. Information on the progress of these reactions can be found in the Appendix.



Scheme (15)



Scheme (13)



Scheme (14)

MODEL STUDIES

Creation of the C-2, C-3 bond of T-2 tetraol using an aldol approach initially proved problematic since difficulty was encountered in preparing aldehyde (303). Therefore, in order to avoid the consumption of valuable allyl ketone (302), the potential of three alternative methods to form the BC bicyclo[3.2.1] octane subunit was explored.

TERMINAL EPOXIDE ROUTE.

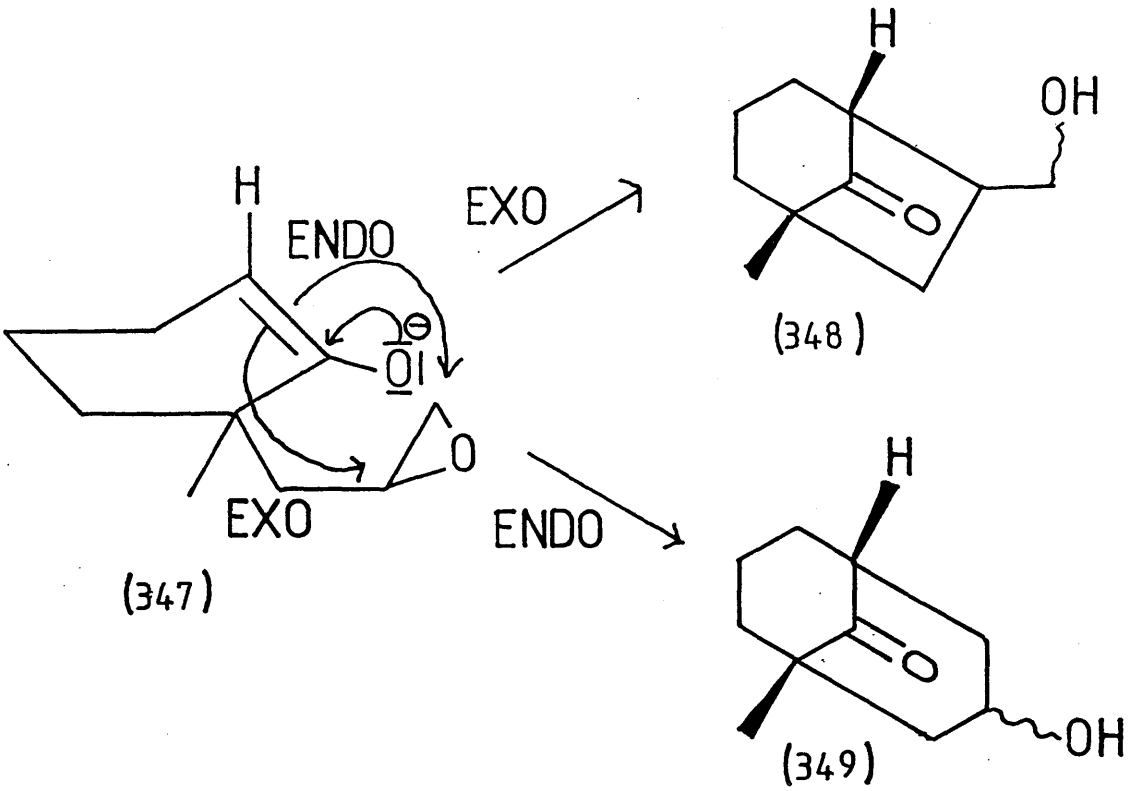
It has been reported[135] that with difunctional molecules which contain both an epoxide and a carbon nucleophile, intramolecular ring opening of the epoxide may occur to generate a carbocycle.

Two general classes of intramolecular cyclisation reactions have been described; those in which the nucleophile is a stabilised carbanion, generated using a strong base (Scheme 13) and those in which the nucleophile is an alkene, this latter reaction usually being carried out in the presence of a Lewis acid to activate the epoxide (Scheme 14).

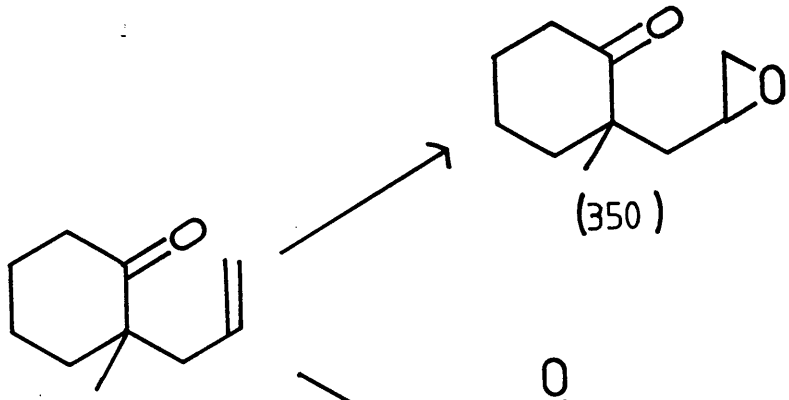
Williams and Maruyama, in the course of the synthesis of a variety of antibiotic analogues, reported[136] the use of the first mentioned class of cyclisation to construct bridged bicyclic systems (Scheme 15). Against this background, attempts were made to construct keto-epoxide (350).

There are two possible intramolecular modes of epoxide ring opening, the exo mode generating the desired bicyclo[3.2.1] octane

system and the endo mode, producing the undesired bicyclo[3.3.1] nonane system.



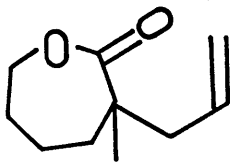
The closure of enolate (347) to form (348) can be analysed geometrically as approximating to a 5-exo-tet ring closure and the closure of (347) to form (349) can be similarly analysed as a 6-endo-tet ring closure. Although, at this stage, the preferred mode of ring closure could not be predicted, Baldwin has noted[137] a general preference for three membered rings to undergo intramolecular ring opening by the exo mode. Here, it was intended to force the ring opening into the exo mode by using the silyl enol ether (351) and



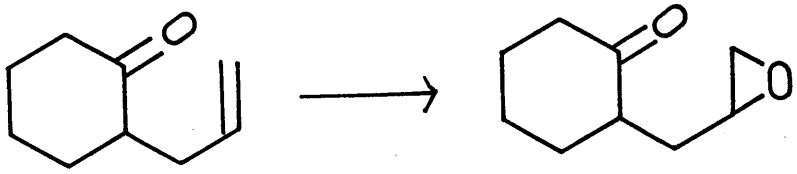
(307)

(350)

(355)

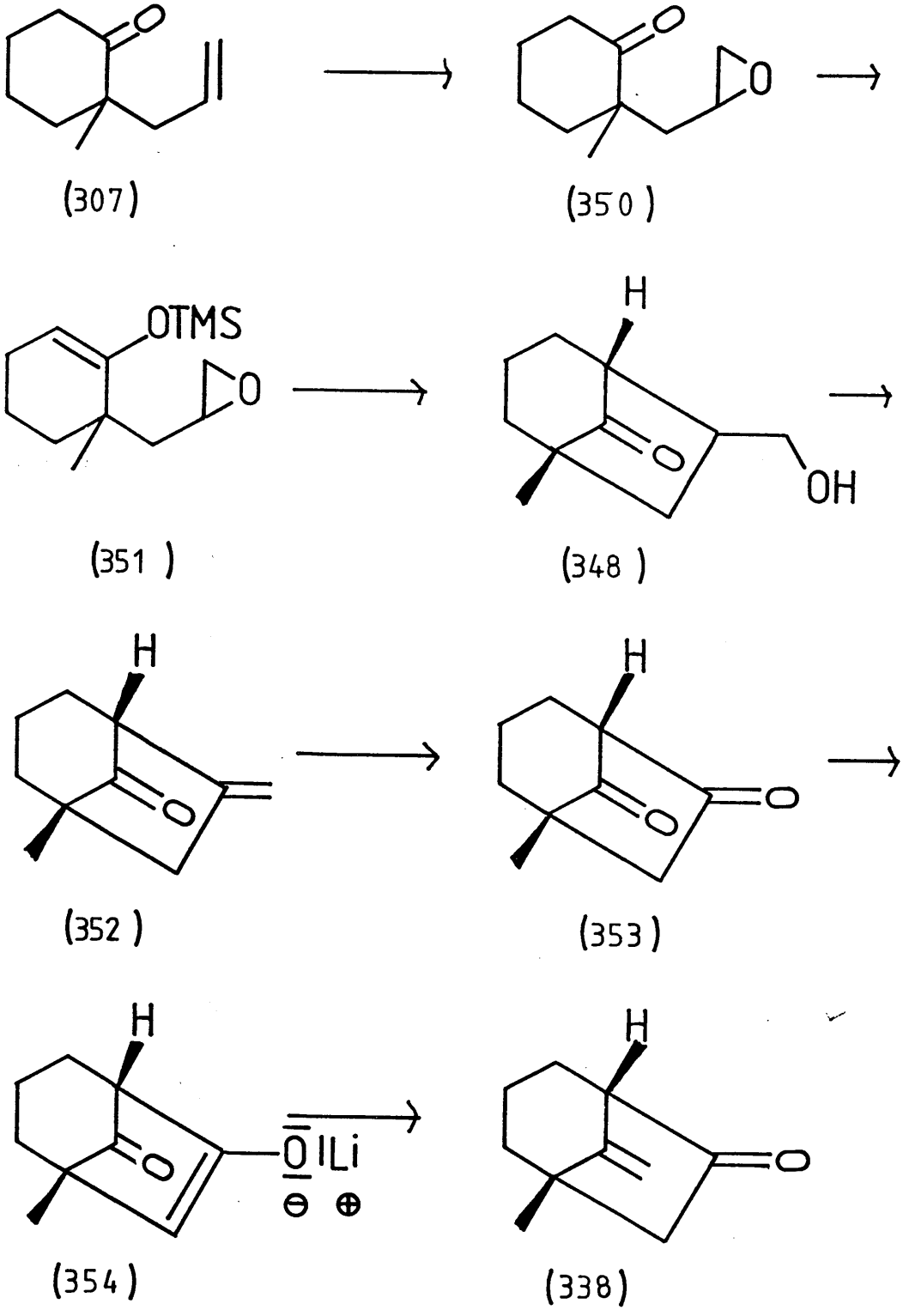


(356)



(357)

(358)



(307) (350)

(351) (348)

(352) (353)

(354) (338)

Scheme (16)

$BF_3.Et_2O$ as Lewis acid catalyst.

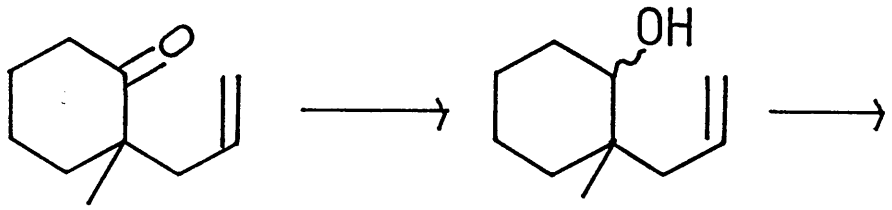
If the cyclisation were to prove successful the primary alcohol (348) would then be dehydrated to alkene (352) using a method[80] which avoids the possibility of bond migration and ring expansion. Straightforward oxidative cleavage of (352) would then lead to (353); selective Wittig olefination would be accomplished by protecting the ketone on the two-carbon bridge as its enolate ion.

On paper scheme 16 seems plausible but in practice, the initial oxidation step to form epoxide (350) presented an insurmountable stumbling block.

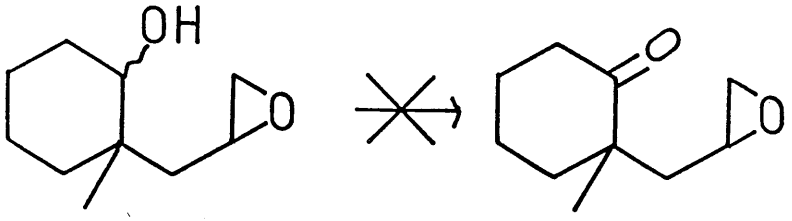
Treatment of (307) with 1.1 equivalents of m-CPBA using Na_2HPO_4 as buffer gave the Baeyer-Villiger product (355). The regioselectivity of oxygen insertion was proven by ^1H n.m.r. spectroscopy which revealed a downfield shift of approximately 0.3ppm for the quaternary methyl. The alternative structure (356) was, in any case considered unlikely. This is in full accord with the migratory aptitudes in Baeyer-Villiger rearrangements.[138] No alkene oxidation was detected.

Payne has reported[139] the conversion of 2-allylcyclohexanone (357) into keto-epoxide (358) using benzonitrile and hydrogen peroxide.

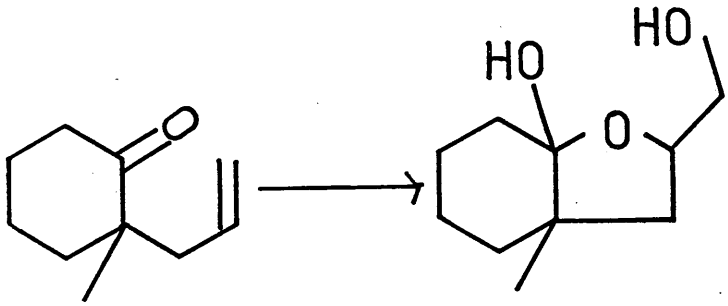
The Baeyer-Villiger reaction, conversion of a ketone into an ester or lactone by the action of a peroxy acid, is generally acid catalysed.[140] The peroxybenzimidic acid oxidation[141] used by Payne is, however, operative under mildly alkaline conditions. It was



(307) (359)



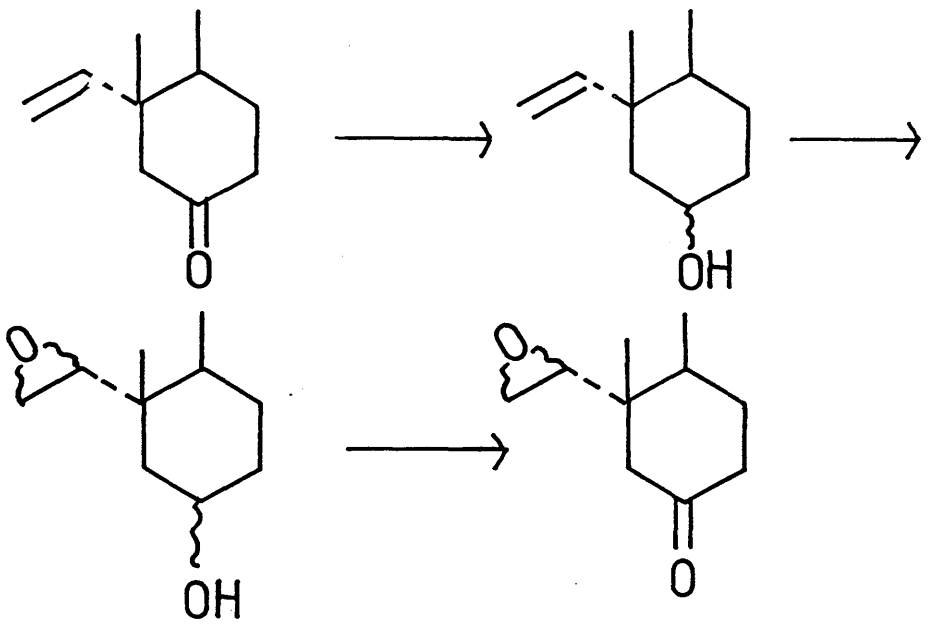
(360) (350)



(307) (361)

predicted, therefore, that oxidation of (307) under basic conditions should lead to epoxy ketone (350) rather than to lactone (355). Unfortunately and inexplicably, treatment of (307) with this epoxidising system resulted in only starting material being recovered.

Ziegler has adopted a reduction-epoxidation-oxidation sequence to exclude the possibility of Baeyer-Villiger oxidation (Scheme 17).



Scheme (17)

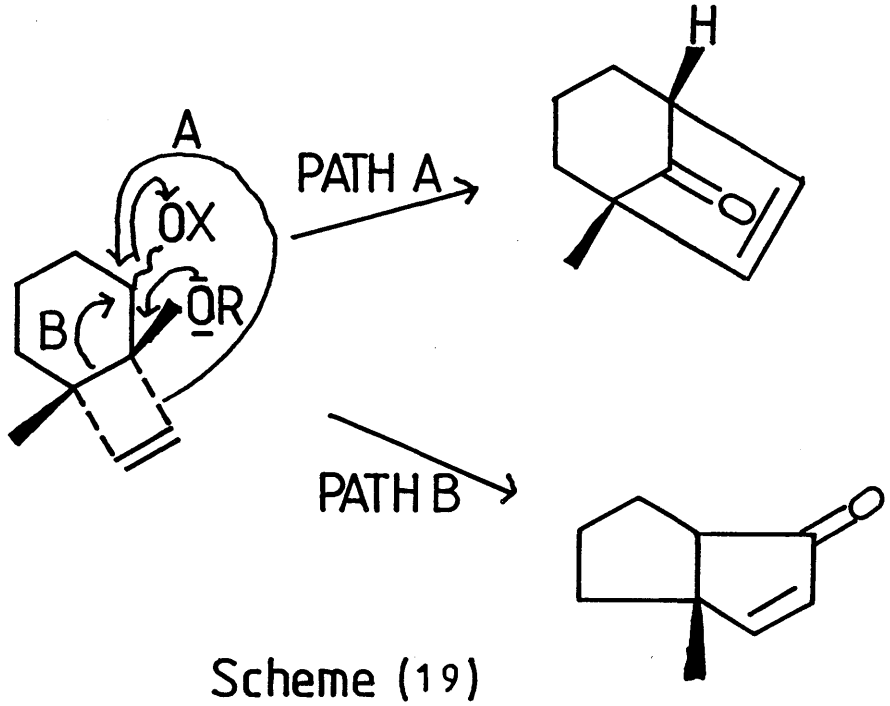
Hydride reduction of (307) proceeded in 97% yield to provide a diastereoisomeric mixture of hydroxy alkenes (359). Epoxidation using buffered m-CPBA proved straightforward giving epoxy-alcohol (360) in 65% yield. Surprisingly, however, all attempts (CrO_3/3,5-dimethylpyrazole,[142] Me_2S/NCS/Et_3N,[112] Jones' reagent) at reoxidising alcohol (360) met with failure, no characterisable products being obtained. The spatial proximity of hydroxyl and epoxy functionality

may be playing a significant part in the failure of this reaction.

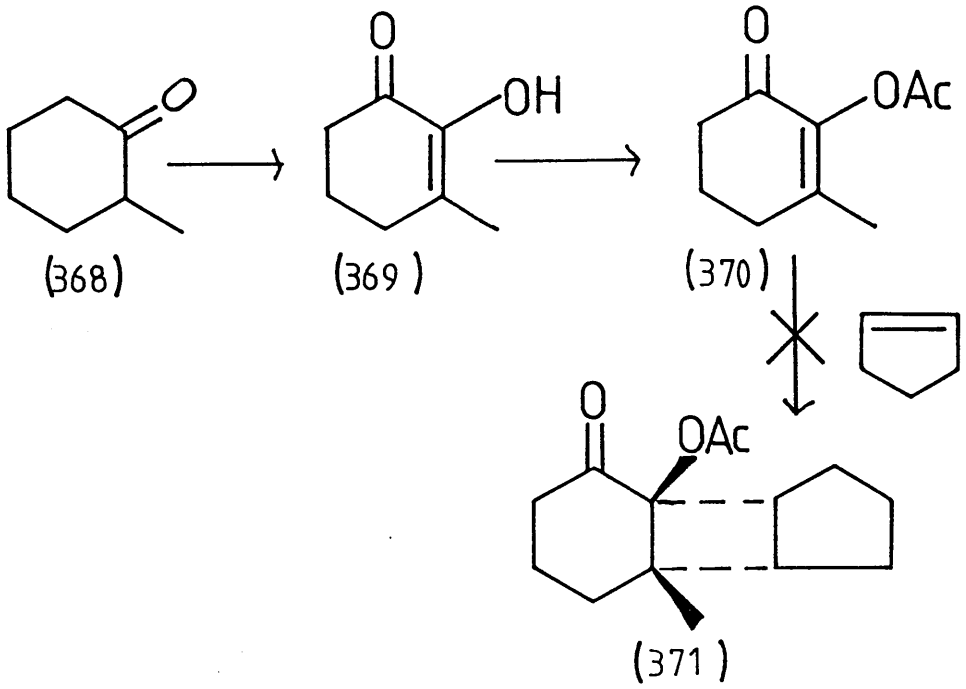
Treatment of (307) with 0.5 mol % OsO_4 using N-Methylmorpholine N-oxide as co-oxidant generated diol (361). It has been reported[143] that small ring oxygen heterocycles can be formed from diol precursors by using a combination of the reagents, triphenylphosphine and diethylazodicarboxylate. Unfortunately, treatment of (361) with these reagents resulted in the degradation of (361). In view of this lack of success the terminal epoxide route was abandoned.

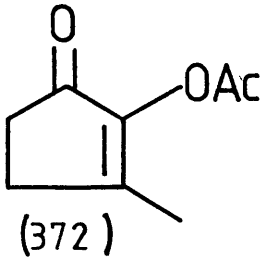
PHOTOCHEMICAL CYCLOADDITION ROUTE.

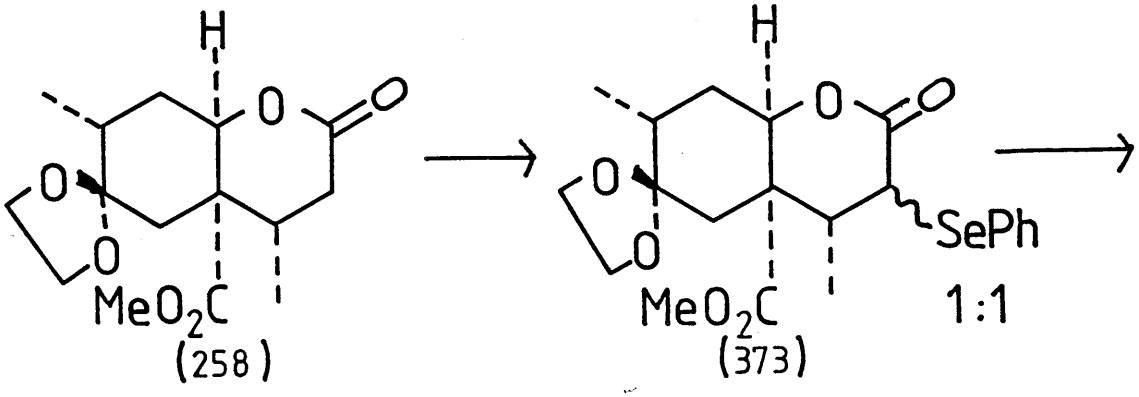
White and coworkers have reported[92] the preparation of (367), an intermediate en route to verrucarol. Photochemical [2+2] cycloaddition of acetylene to α,β-unsaturated lactone (362) gave (363). The key step in this scheme involved Cargill rearrangement[144] of the cyclobutenyl carbinol subunit in (364) to a cyclopenten-4-ol subunit to form (366) (Scheme 18). It appeared attractive to modify this sequence by using lactone (288). Since it was crucial to determine whether the necessary migration (path A, Scheme 19) would occur in this rearrangement, the ring homologation was first explored using model system (369).

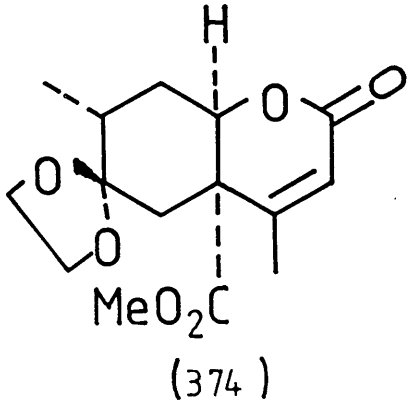


Scheme (19)


O
OH
OAc
(368)
(369)
(370)
OAc
(371)


O
OAc
(372)


H
O
O
O
O
MeO2C
(258)
H
O
O
O
O
SePh
MeO2C
(373)
1:1


H
O
O
O
O
MeO2C
(374)

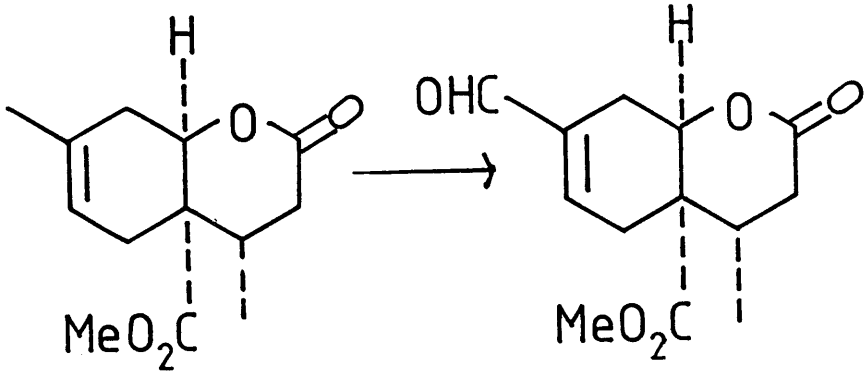
3-Methylcyclohexane-1,2-dione (369) was prepared[145] in 91% yield from 2-methylcyclohexanone by Wallach's method.[146] Acetylation furnished acetate (370) on which the study was to be performed. For ease of experimental procedure, the reaction was carried out using a 100 fold excess of cyclopentene instead of acetylene.

However, irradiation (125-W medium pressure Hanovia lamp, quartz filter, 66 hours) in a variety of solvents (Et_2O, C_6H_6, CH_3CN) did not generate (371); only starting diosphenol acetate (370) and alkene were recovered on solvent evaporation.

An extensive literature study then disclosed[147] that while 2-acetoxypent-2-en-1-one (372) readily undergoes cycloaddition, (370) does not undergo photoaddition under the standard conditions for cyclopentenone derivatives. Moreover, studies have shown[148] that the methyl substituent in 2-methylcyclohexenone greatly diminishes the rate of photoreaction and results in complex reaction mixtures. Presumably this argument could also be extended to 2-acetoxycyclohexenone compounds to explain their lack of reactivity.

White and coworkers have demonstrated that simple α,β-unsaturated lactones do undergo [2+2]photoaddition. For this reason (374) was prepared.

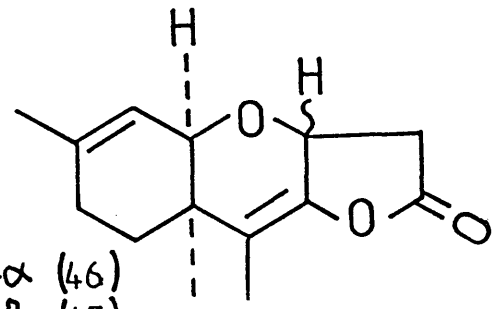
Treatment of the enolate derived from (258) with 1.2 equivalents of phenylselenylchloride[149] gave a 1:1 mixture of α-phenylselenides, selenoxide syn-fragmentation[150] of which gave only low yields of (374) due to the inability of the α-epimer to fragment.



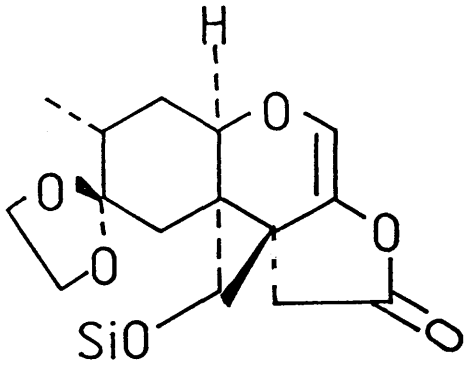
(259) (271)

An alternative method of α-selenylation was examined in an attempt to increase the yield of (374). Lactone (259) was heated under reflux in chlorobenzene with 1 equivalent benzeneseleninic anhydride[151,152] for 18 hours. However, the product, formed in 42% yield, proved to be the α,β-unsaturated aldehyde (271) (see page 38) and not the desired α,β-unsaturated lactone (374).

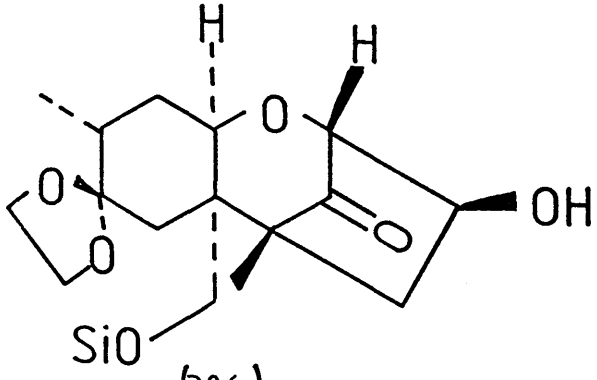
To exclude the possibility of allylic oxidation, ketal (258) was subjected to similar treatment; this gave rise to a complex reaction mixture from which no useful products could be obtained. At this stage, exploration of the [2+2]photoaddition route ceased.



H-α (46)
H-β (47)
ENEDIOL(48)



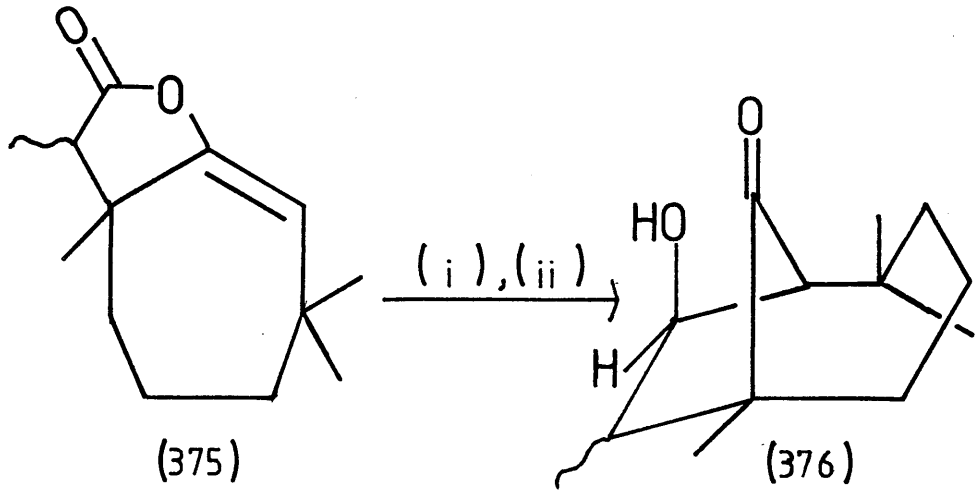
(315)



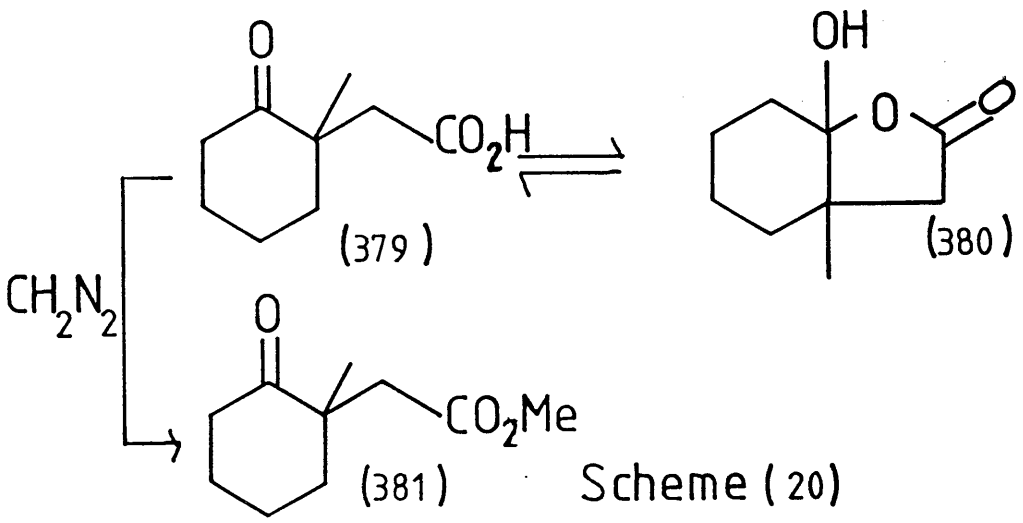
(306)

ENOL-LACTONE REDUCTIVE CYCLISATION ROUTE

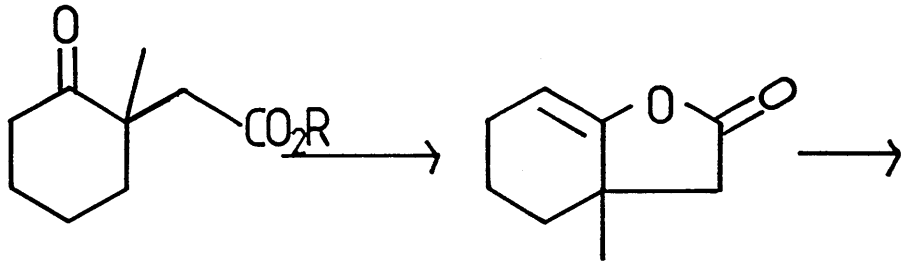
As discussed earlier, an enol-lactone reductive cyclisation step using $LiAl(O^tBu)_3H$ was used to create ring C in the original synthesis of trichodermol. A low yield was obtained because of non-selective enolisation of keto-acid (45); only enol-lactone (47) led to the desired tricyclic product. Welch and Walters, in the course of a total synthesis of (±)-longicyclene, reported[153] the high yielding reductive cyclisation of lactone (375) using DIBAH. It was anticipated, therefore, that reductive cyclisation of (315) should lead to (306).



To this end model enol-lactone (383) was synthesised for further study. Two methods were used to prepare keto-acid (379). Alkylation of (377)[154] with ethyl bromoacetate gave keto-ester (378), hydrolysis of which led to (379) [82% yield from (377)]. Alkylation of (377) with allyl bromide gave allyl ketone (307) in 87% yield,

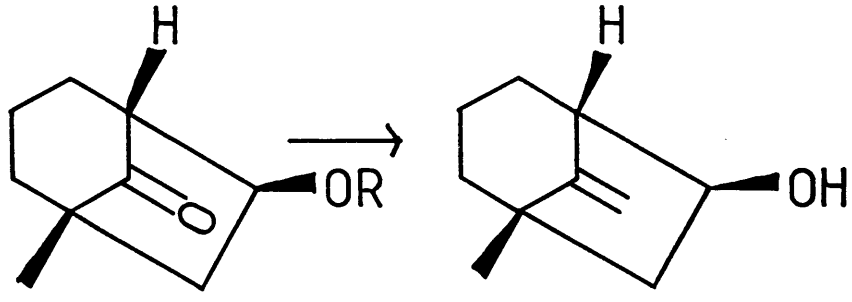


Scheme (20)



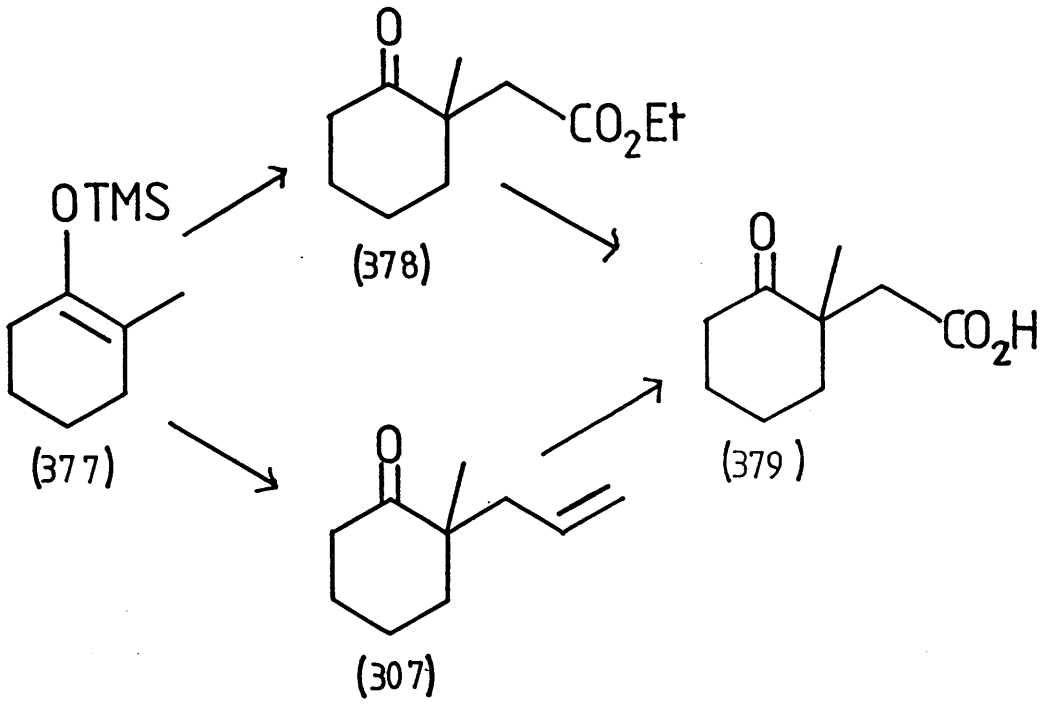
R = H (379)
R = Ac (382)

(383)



(386)

R = H (384)
R = Ac (385)


OTMS
O
CO2Et
(377)
(378)
(307)
(379)
O
CO2H

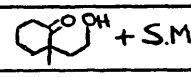
the vinyl group of which could be oxidatively cleaved using either cat. RuO_2 [126] [63% yield from (377)] or cat. $KMnO_4$ [127] [51% yield from (377)] with $NaIO_4$ as co-oxidant in both cases. The ^{13}C n.m.r. spectrum of (379) was broad and indecipherable, presumably due to acid-pseudoacid interconversion (Scheme 20), so for characterisation purposes it was converted into its methyl ester (381), (for comparison, see page 52).

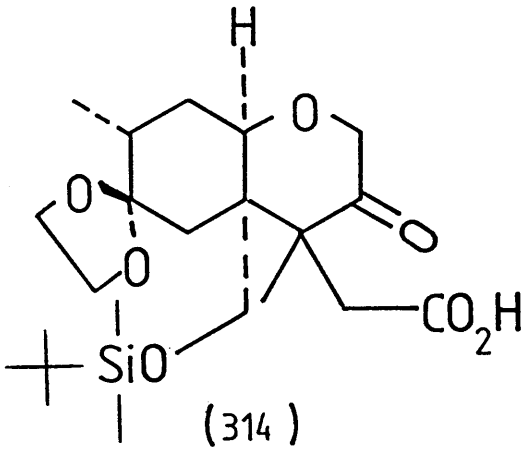
Treatment of keto-acid (379) with acetic anhydride and a catalytic amount of perchloric acid in ethyl acetate[155] produced mixed anhydride (382) and not enol-lactone (383). However, on refluxing keto-acid (379) in acetic anhydride with a catalytic amount of freshly fused sodium acetate, enol-lactone (383) was formed in 68% yield.

Enol-lactone (383) was subjected to an extensive reductive cyclisation study by varying solvent, temperature, time of reaction and hydride source (Table 1). The best results were obtained using DIBAH as the hydride source and Et_2O as solvent. Using CH_2Cl_2 as the solvent resulted in coagulation of the inorganic aluminates on work-up with resulting colloidal solutions.

Only β-ketol (384) was obtained from the reaction. Its exclusive formation is believed[156] to arise from the interaction of the carbonyl lone pair with the chelating alkoxy aluminate in a thermodynamically favoured 6-membered system (Figure 7).

TABLE 1.

HYDRIDE SOURCE	SOLVENT	PERIOD OF TIME	YIELD OF KETOL	TEMPERATURE
DIBAH	CH_2Cl_2	18 hrs	Starting material	-78°C
"	"	2 hrs	17%	-25°C
"	"	18 hrs	30%	-25°C
"	Et_2O	18 hrs	22%	-78°C → RT
"	"	"	35%:isolated as acetate	-25°C → RT
$LiAl(O^tBu)_3^{85}H$	THF	18 hrs	starting material	-78°C → RT
"	DME	4 hrs	"	"
"	"	18 hrs	complex reaction mixture	-40°C → RT
"	"	"	"	-10°C → RT
"	"	4 hrs	 + S.M.	-78°C→ REFLUX
" Inverse addition	"	18 hrs	complex reaction mixture	-25°C → RT



(314)

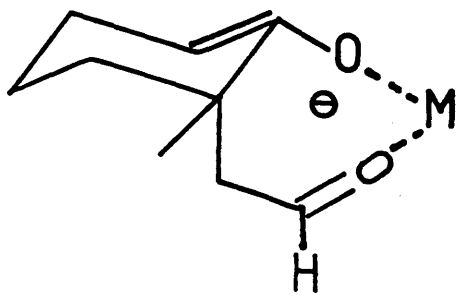


FIGURE 7

The assignment of the stereochemistry at the ketol hydroxyl was carried out on the basis of ^{1}H n.m.r. coupling constants; these have been described on page 55 .

Ketol (384) was acetylated to give keto-acetate (385) in 87% yield. Olefin introduction using 2.5 equivalents of methylene triphenylphosphorane took place with accompanying acetate cleavage to give alkene (386) in 45% yield.

Although modestly successful, this route was not used in the synthesis of T-2 tetraol since difficulty was encountered in preparing fully functionalised keto-acid (314).

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, or on a Bruker AM 200 spectrometer, both operating at 200 MHz. ^{13}C n.m.r spectra were recorded on a Varian XL100 spectrometer operating at 25 MHz or on a Bruker WP 200 SY spectrometer operating at 50 MHz, or on a Bruker AM 200 spectrometer operating at 25 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00ppm), using Me_4Si or the 7.25ppm residual chloroform peak and the 77.0ppm $CDCl_3$ peak as internal references for ^{1}H and ^{13}C n.m.r. spectra respectively. ^{1}H n.m.r. data are reported using the following convention: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The multiplicities of the 50 MHz ^{13}C spectral resonances were determined by the use of DEPT spectra[86] with pulse angles, $\theta = 90^{o}$ and 135^{o}. The multiplicities of the 25 MHz ^{13}C spectral resonances were determined by the use of ^{13}C-^{1}H couplings in the off-resonance spectra. 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 nitrogen. All solvents and reagents used were analytical grade

where possible. Anhydrous magnesium sulphate was used to dry reaction mixtures after work-up. Tetrahydrofuran, dimethoxyethane and ether were distilled freshly from sodium/benzophenoneketyl. All the following reagents/solvents were stored, after purification, over 4 Å molecular sieves. N,N-Dimethyl formamide was distilled from blue silica gel. Dichloromethane was distilled from CaH_2. Toluene was either distilled from CaH_2 or it was distilled from P_2O_5 and filtered through Grade 1 basic alumina. Allyl bromide was distilled from anhydrous $CaCl_2$. Both pyridine and diisopropylamine were distilled from KOH. Petroleum ether refers to that fraction boiling between 40° and 60°C. All compounds made are racemic in form. Dry column flash chromatography[100] and positive pressure flash chromatography[114] refer to techniques already described.

NUMBERING SYSTEM

The numbering system of intermediates, particularly tricyclic follows the conventional trichothecene numbering system (Figure 8). Correspondingly, the direct Diels-Alder adducts, and bicyclic intermediates resulting from synthetic transformations on these adducts, are numbered as benzopyranone derivatives (Figure 9). The model bicyclic compounds are numbered as illustrated (Figure 10).

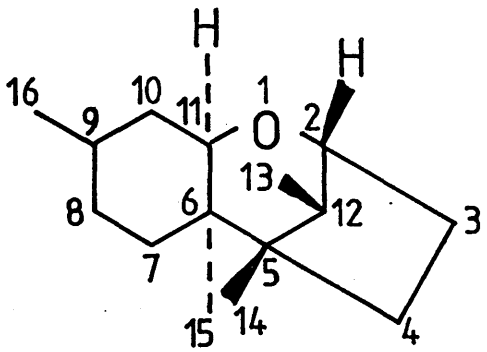


FIGURE 8

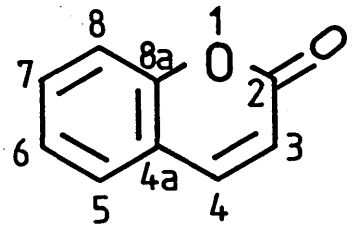


FIGURE 9

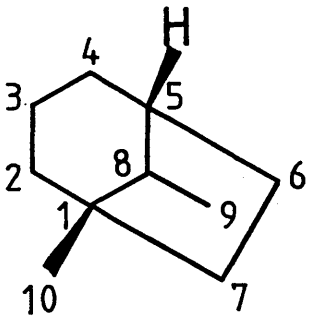
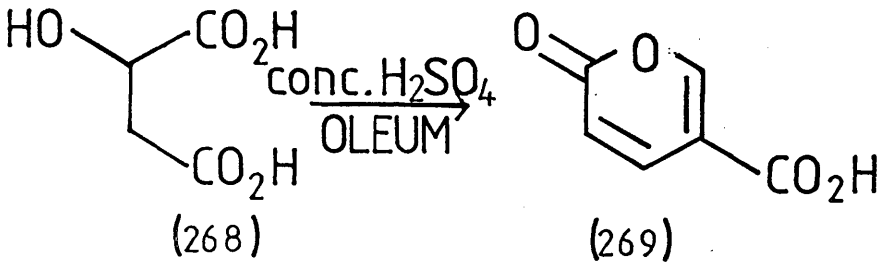


FIGURE 10

COUMALIC ACID (269).

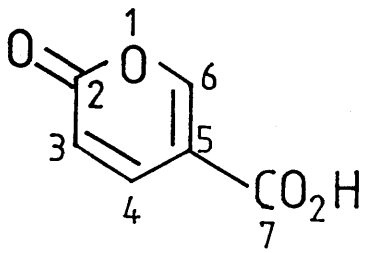


(268) (269)

(Prepared by the method of Wiley and Smith[98] but incorporating minor alterations).

In a 3l 3-necked r.b. flask was placed malic acid (400g, 2.98 mole) and conc. H_2SO_4 (340ml) and the heavy suspension stirred mechanically. To this was added three aliquots of fuming H_2SO_4 (3 x 100ml) at 45 minute intervals. After the evolution of gas had slackened the solution was stirred and heated with a water bath for 2 hours. The reaction mixture was then cooled and poured slowly on to 1.5kg of crushed ice with stirring. After standing overnight, the acid was filtered on a Buchner funnel using glass filter paper, washed with ice-cold water and dried in a vacuum desiccator over P_2O_5 until constant weight.

One half of the crude product was dissolved in five times its weight of hot methanol and the solution was heated with 3g of decolourising carbon. The solution was filtered while hot and then cooled in an ice-bath. The crystals so obtained were removed by filtration. The remaining crude material was recrystallised from the mother liquors, to give, after drying, coumalic acid (90.9g, 44%) as bright yellow crystals, m.p. 204-210°C. Lit.[98] m.p. 203-205°C (dec).

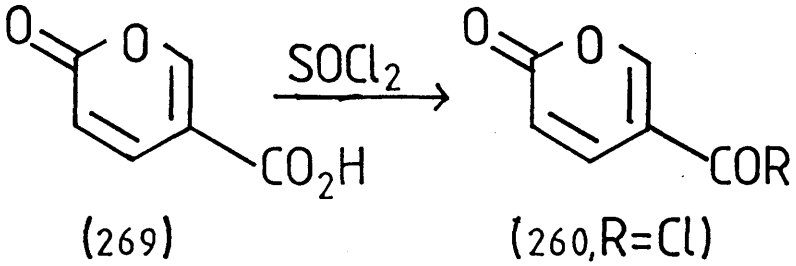


PROTON NUMBER	δppm ^{1}H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^{1}H	MULTIPLICITY ^{13}C	J(Hz) ^{1}H
-	-	C-2	162.17	-	s	-
H-3	6.36	C-3	115.82	dd	d	1.15, 9.8
H-4	7.86	C-4	143.71	dd	d	2.62, 9.8
-	-	C-5	113.79	-	s	-
H-6	8.42	C-6	159.83	dd	d	1.14, 2.60
-	-	C-7	165.81	-	s	-

i.r. (KBr Disc): 3090(broad), 1725, 1705, 1680, 1630, 1540, 1410, 1230, 1100 cm^{-1}.

M.S: 140.0090 (M^{+}); calc. for $C_6H_4O_4$:140.0110.

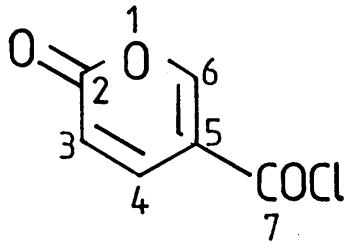
COUMALYL CHLORIDE (260, R = Cl).



(269) (260, R=Cl)

Coumalic acid (10g, 71.43 mmol) was heated under reflux in thionyl chloride (49.2g, 30ml, 413 mmol) overnight. Removal of the excess thionyl chloride under reduced pressure afforded a dark red-brown residue which solidified on cooling. Overnight extraction of the residue using a Soxhlet extractor with anhydrous petroleum ether (b.p. 60-80°C) and concentration of the resulting extract under reduced pressure afforded the acid chloride (260, R=Cl) (8.91g, 79%) as white crystals, m.p. 71-74°C. lit[99] m.p. 74-75°C.

(Note: Care had to be exercised when handling this material since it caused skin sensitivity).

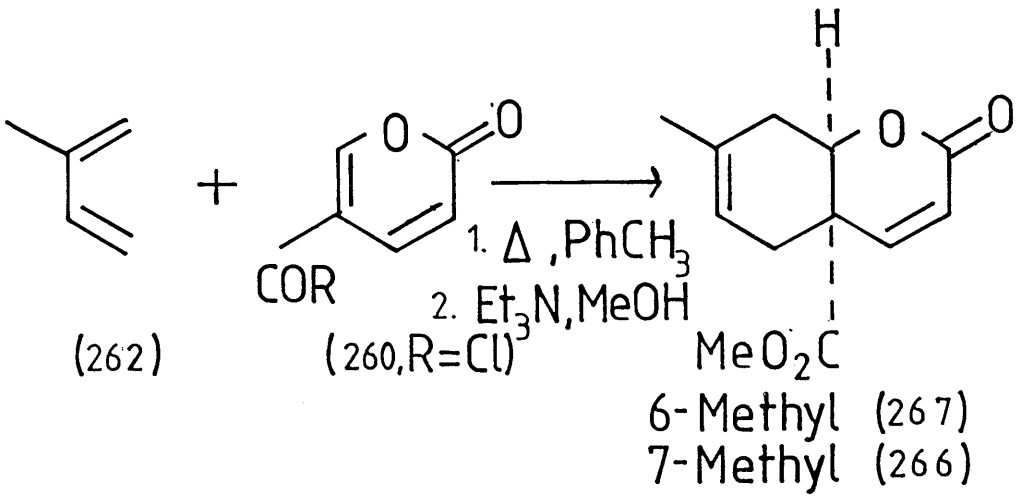


PROTON NUMBER	δppm ^{1}H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY J(Hz) ^{1}H	^{13}C	^{1}H
-	-	C-2	158.09	-	s	-
H-3	6.34	C-3	115.06	dd	d	1.05, 9.95
H-4	7.72	C-4	140.08	dd	d	2.80, 9.95
-	-	C-5	116.29	-	s	-
H-6	8.54	C-6	162.84	dd	d	1.06, 2.80
-	-	C-7	162.56	-	s	-

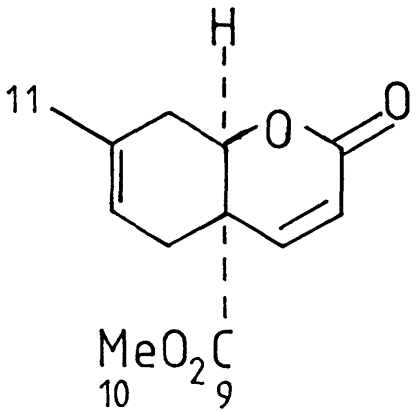
i.r. (CCl_4) : 1780, 1765, 1735, 1250, 1230, 855 cm^{-1}

M.S: 158 (M^+), 123 (M^+-Cl, 100%), 95 (M^+-COCl).

(±)-(4aα,8aα)-4a-Carbomethoxy-4a,5,8,8a-tetrahydro-7-methyl-2H-1-benzopyran-2-one (266) and its 6-methyl regioisomer (267).



A mixture of coumalyl chloride (3.5g, 22.1 mmol) in dry toluene (60 ml), a few crystals of hydroquinone and freshly distilled isoprene (3.0g, 4.4 ml, 44 mmol) was heated at 120°C for 1 hour in a sealed tube. On cooling to room temperature, the mixture was transferred to a round bottom flask and cooled to 0°C in an ice-bath. With stirring, triethylamine (4.4g, 6.12 ml, 44 mmol) was added in one portion at this temperature, followed by methanol (1.42g, 1.8ml, 44 mmol); stirring was continued for 40 minutes. The resulting slurry was diluted with EtOAc (250 ml) and washed sequentially with saturated aqueous $NaHCO_3$ solution (100 ml), cold water (100 ml) and saturated brine (100 ml). After drying and concentration of the organic layer, purification of the crude residue by dry column flash chromatography afforded the Diels-Alder adducts (266) and (267) (2.03g, 41.4%) as an inseparable viscous yellow oil in a regioisomeric ratio of 4:1 as determined by 200 MHz ^1H n.m.r. spectral integration of the olefinic methine signals. Tabulated spectroscopic data refer to the major component (266).

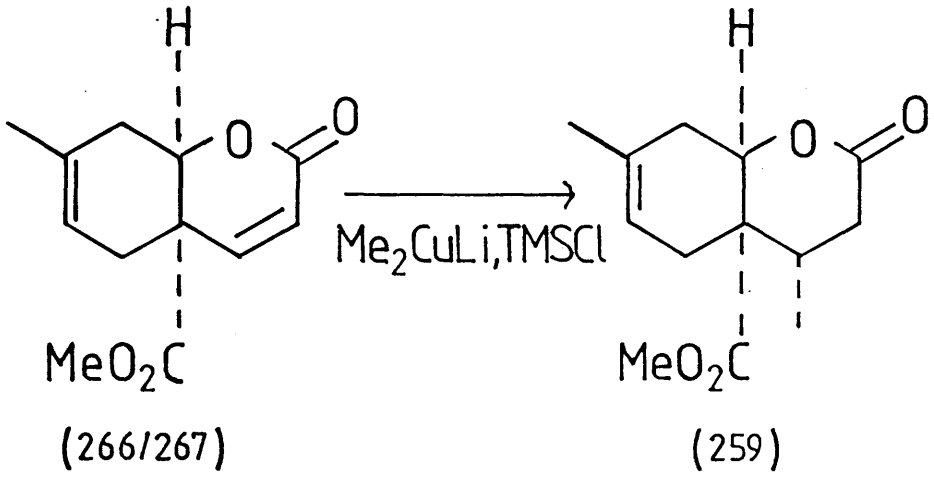


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY J(Hz) ^1H	^{13}C	^1H
-	-	C-2	163.33	-	s	-
H-3	6.04	C-3	120.82	d	d	9.66
H-4	6.93	C-4	149.64	d	d	9.65
-	-	C-4a	45.67	-	s	-
H-5(2H)	2.05-	C-5	33.59/	m	t	-
H-8(2H)	2.85	C-8	31.05	m	t	-
H-6	5.44	C-6	117.61	m	d	-
-	-	C-7	131.12	-	s	-
H-8a	4.99	C-8a	75.92	m	d	-
-	-	C-9	171.78	-	s	-
H-10(3H)	3.76	C-10	52.90	s	q	-
H-11(3H)	1.68	C-11	22.85	bs	q	-

i.r. ($CHCl_3$): 3010, 1715, 1630, 1240 cm^{-1}

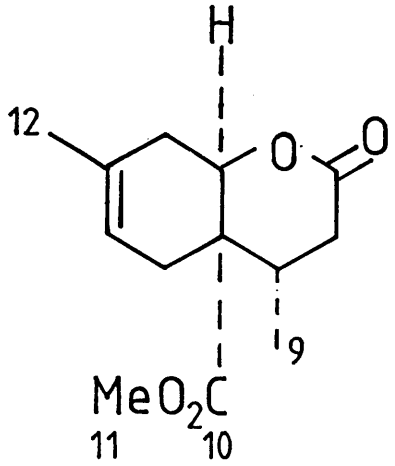
M.S: 222.0896 (M^+); calc. for $C_{12}H_{14}O_4$:222.0900

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,8,8a-hexahydro-4α,7-dimethyl-2H-1-benzopyran-2-one (259).



(266/267) (259)

To a suspension of CuI (5.86g, 30.8 mmol) in dry Et_2O (150 ml) at 0°C under N_2 was added MeLi (1.5M in Et_2O) until the initially formed yellow precipitate had just disappeared. The reaction mixture was cooled to -78°C, then trimethylsilyl chloride (3.35g, 3.9 ml, 30.8 mmol) and the regioisomeric Diels-Alder mixture (5.7g, 25.7 mmol) in dry Et_2O (15 ml) were successively added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over a period of 2.5 hours during which a yellow precipitate appeared. The reaction mixture was poured into cold saturated NH_4Cl solution (200 ml) and filtered through a pad of Celite. The blue aqueous layer was extracted with Et_2O (3 x 100 ml) and the combined ethereal extracts washed with brine (100 ml). After drying and concentration of the organic layer, purification of the crude residue by dry column flash chromatography gave the cuprate product (259) (3.3g, 55%) as white needles, m.p. 79-81°C (Et_2O/petroleum ether).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	171.34	-	s	-
H-3(2H)	1.85-	C-3	29.96/	-	t	-
H-5(2H)		C-5	34.02/	-	t	-
H-8(2H)		C-8	35.70	-	t	-
H-4	2.95	C-4	32.91	-	d	-
-	-	C-4a	47.64	-	s	-
H-6	5.30	C-6	118.58	m	d	-
-	-	C-7	130.70	-	s	-
H-8a	4.85	C-8a	74.04	dd	d	-
H-9(3H)	0.97	C-9	17.80	d	q	9
-	-	C-10	173.20	-	s	-
H-11(3H)	3.65	C-11	51.76	s	q	-
H-12(3H)	1.60	C-12	22.80	bs	q	-

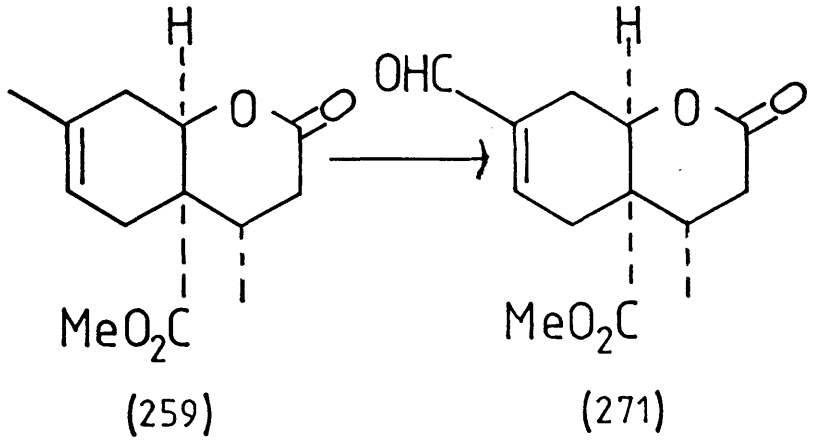
i.r. (KBr Disc): 2950, 1750, 1728, 1445, 1200 cm^{-1}

M.S: 238.1208 (M^+); calc. for $C_{13}H_{18}O_4$:238.1200.

$C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%

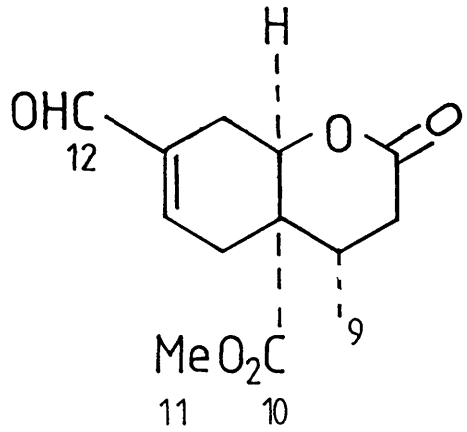
Found: C, 65.48; H, 7.60%.

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,8,8a-hexahydro-4α-methyl-7-formyl-2H-1-benzopyran-2-one (271).



(259) (271)

Benzeneseleninic anhydride (332 mg, 0.90 mmol) was added to a solution of the cuprate product (259) (213 mg, 0.90 mmol) in dry chlorobenzene (25 ml) and the reaction mixture was heated under reflux for 18 hours. The solvent was removed in vacuo by repeated azeotropic distillation with toluene. Purification of the crude residue by dry column flash chromatography gave the aldehyde (271) (95 mg, 42%) and recovered cuprate product (259) (97 mg, 45%).

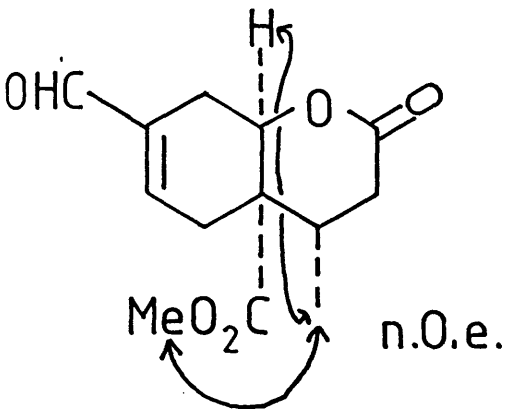


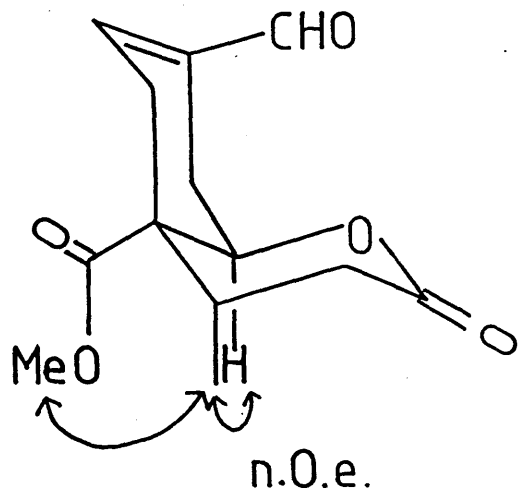
PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	^{13}C	J(Hz) ^1H
-	-	C-2	172.04	-	s	-
H-3α H-3β	2.66 2.31	C-3	31.00	dd dd	t	7.07, 16.45 8.78, 16.44
H-4	1.95- 2.15	C-4	33.81	d/ quintets	d	-
-	-	C-4a	48.28	-	s	-
H-5α H-5β	3.01 2.27	C-5	35.54	dd dd	t	5.34, 19.48 2.56, 19.48
H-6	6.70	C-6	146.08	m	d	-
-	-	C-7	137.30	-	s	-
H-8(2H)	2.59	C-8	25.71	-	t	-
H-8a	4.94	C-8a	72.19	t	d	3.19
H-9(3H)	0.98	C-9	17.93	d	q	6.91
-	-	C-10	170.92	-	s	-
H-11(3H)	3.64	C-11	52.12	s	q	-
H-12	9.36	C-12	192.62	s	d	-

i.r. ($CHCl_3$): 3020, 1725, 1680, 1640, 1180, 1025 cm^{-1}

M.S : 252.0979 (M^+); calc. for $C_{13}H_{16}O_5$:252.0998.

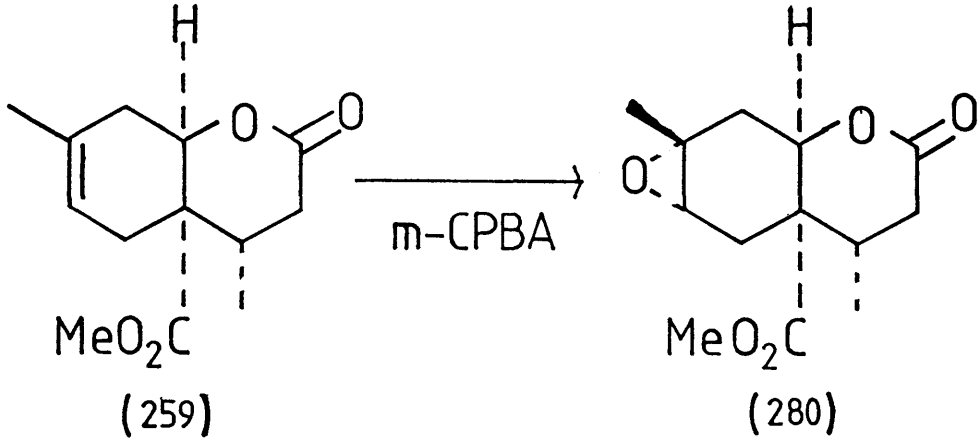
n.O.e. Results.



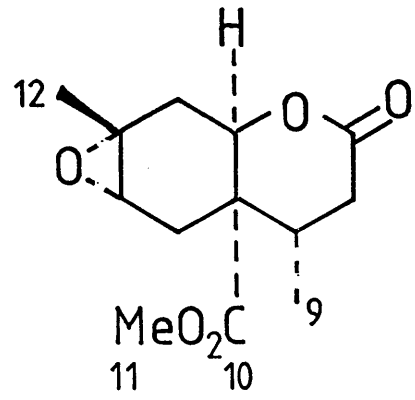


Irradiate	% enhancement
H-9	1.9% H-8a
H-9	1.3% H-11
H-8a	0.84% H-9

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,6,7,8,8a-octahydro-4α,7β-dimethyl-6,7-epoxy-2H-1-benzopyran-2-one (280).



To a solution of the cuprate product (259) (5.9g, 24.8 mmol) in dry CH_2Cl_2 (150 ml) was added Na_2HPO_4 (10 g, 70 mmol) and m-CPBA (6.4 g, 37.2 mmol). The reaction mixture was stirred at 0°C for 2.5 hours and then filtered, poured into H_2O (100 ml) and extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (100 ml). After drying and concentration of the organic extracts, purification by dry column flash chromatography gave the epoxide (280) (5.08 g, 80.6%) as white crystals, m.p. 117-119°C, (EtOAc/petroleum ether).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	171.49	-	s	-
H-3(2H)		C-3	29.62/	-	t	-
H-5(2H)	1.8-	C-5	32.28/	-	t	-
H-8(2H)	2.8	C-8	35.65	-	t	-
H-4		C-4	33.33	-	d	-
-	-	C-4a	44.91	-	s	-
H-6	3.01	C-6	58.92	m	d	-
-	-	C-7	54.50	-	s	-
H-8a	4.62	C-8a	71.97	bd	d	4.5
H-9(3H)	0.93	C-9	17.86	d	q	6.93
-	-	C-10	172.35	-	s	-
H-11(3H)	3.69	C-11	51.62	s	q	-
H-12(3H)	1.29	C-12	23.68	s	q	-

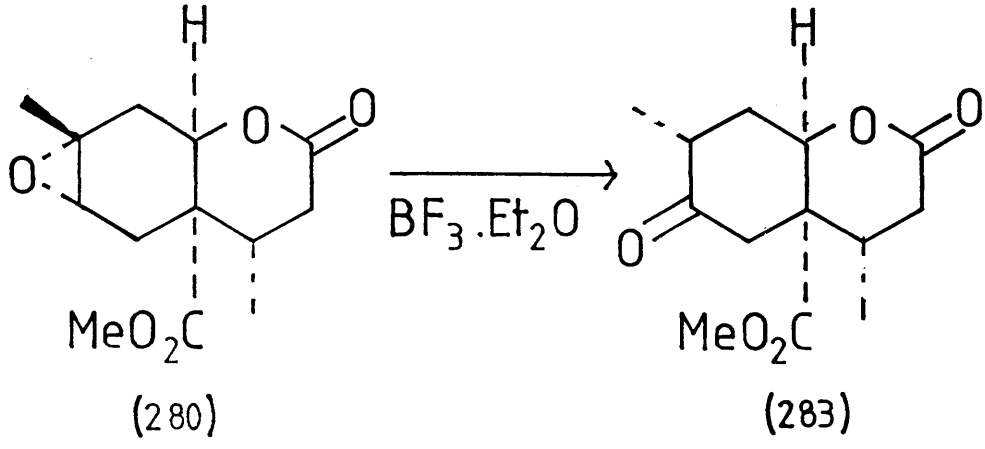
i.r. ($CHCl_3$) : 3020, 1730, 1230 cm^{-1}

M.S : 254.1161 (M^+); calc. for $C_{13}H_{18}O_5$:254.1149

$C_{13}H_{18}O_5$ requires C, 61.41; H, 7.14%

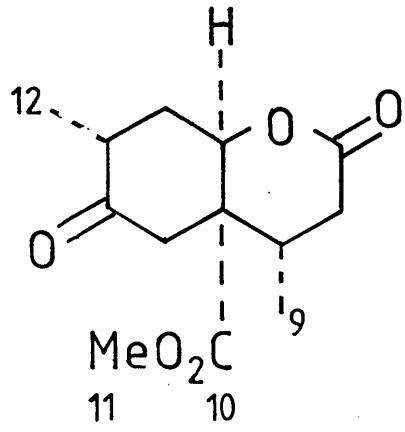
Found: C, 61.57; H, 7.18%.

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,6,7,8,8a-octahydro-4α,7α-dimethyl-6-oxo-2H-1-benzopyran-2-one (283).



(280) (283)

To a solution of the epoxide (280) (4.68 g, 18.4 mmol) in dry CH_2Cl_2 (100 ml) under N_2 and at room temperature was added dropwise, with stirring, $BF_3.Et_2O$ (2.88 g, 2.5 ml, 20.3 mmol). The reaction mixture was stirred for 10 minutes then poured into saturated aqueous $NaHCO_3$ solution (50 ml). After the effervescence had subsided the aqueous layer was extracted with EtOAc (3 x 50 ml). The organic extracts were dried and the solvent removed in vacuo. Purification of the crude residue by dry column flash chromatography gave the ketone (283) (3.26 g, 69.6%) as white crystals, m.p. 127 - 129°C (EtOAc/petroleum ether).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	171.02	-	s	-
H-3(2H)	1.60-1.85	C-3	35.09/	-	t	-
H-8(2H)	2.30-	C-8	36.45	-	t	-
H-5(2H)	2.95	C-5	44.96	-	t	-
H-4	1.98	C-4	35.84	m	d	-
-	-	C-4a	53.75	-	s	-
-	-	C-6	207.89	-	s	-
H-7	2.72	C-7	38.48	m	d	-
H-8a	4.92	C-8a	74.64	m	d	-
H-9(3H)	0.97	C-9	13.51	d	q	6.56
-	-	C-10	171.78	-	s	-
H-11(3H)	3.70	C-11	52.47	s	q	-
H-12(3H)	1.01	C-12	17.20	d	q	7.06

i.r. ($CHCl_3$) : 3020, 1720, 1230 cm^{-1}

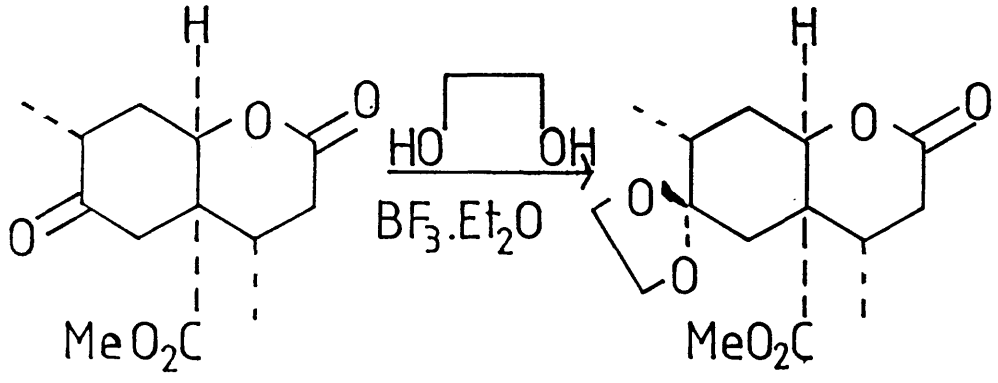
M.S : 254.1155 (M^+); calc. for $C_{13}H_{18}O_5$:254.1149

$C_{13}H_{18}O_5$ requires C, 61.41; H, 7.14%

Found: C, 61.31; H, 6.93%

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,6,7,8,8a-octahydro-4α,7α-dimethyl-6-oxo-2H-1-benzopyran-2-one ethylene ketal (258).

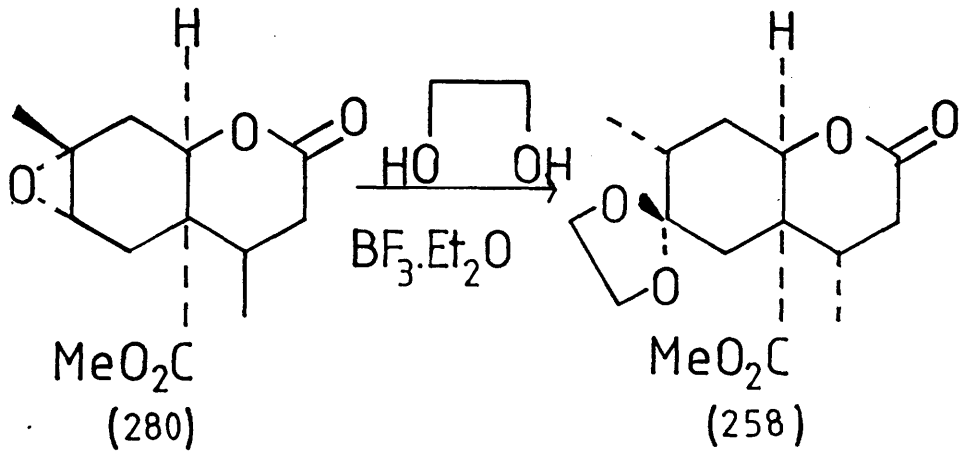
METHOD 1.



(283) (258)

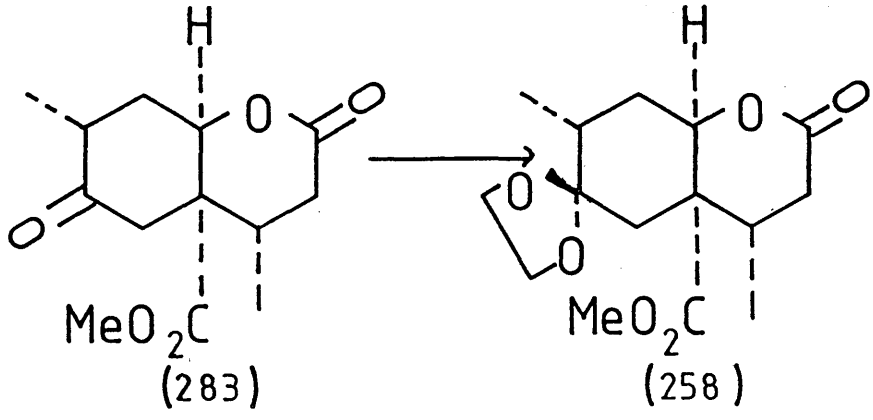
To a solution of the ketone (283) (752 mg, 2.96 mmol) in dry CH_2Cl_2 (50 ml) under N_2 was added successively ethylene glycol (222 mg, 200 µl, 3.55 mmol) and $BF_3.Et_2O$ (504 mg, 437 µl, 3.55 mmol). Stirring was continued at room temperature for 18 hours. The reaction mixture was diluted with saturated $NaHCO_3$ solution (25 ml) and extracted with CH_2Cl_2 (3 x 50 ml). After drying and concentration of the combined organic extracts, purification by dry column flash chromatography gave the ketal (258) (609 mg, 69%) as white needles, m.p. 130-132°C (EtOAc/petroleum ether).

METHOD 2.

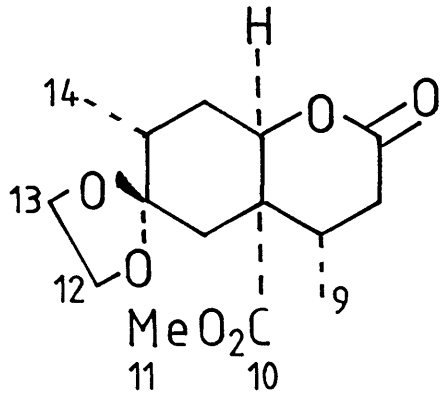


To a solution of the epoxide (280) (7.8 g, 30.6 mmol) in dry CH_2Cl_2 (150 ml) under N_2 was added successively $BF_3.Et_2O$ (6.56 g, 5.7 ml, 46 mmol) and ethylene glycol (2.1 g, 1.89 ml, 34 mmol). Stirring was continued at room temperature for 18 hours. The reaction mixture was diluted with saturated $NaHCO_3$ solution (100 ml) and extracted with CH_2Cl_2 (3 x 75 ml). The combined organic extracts were washed with brine (100 ml). After drying and concentration, purification of the crude residue by dry column flash chromatography gave the ketal (258) (5.58 g, 61%).

METHOD 3.



To a stirred solution of trimethylsilyl triflate[88] (0.873 mg, 4.5 x 10^{-3} mmol, 1 mol %) in dry CH_2Cl_2 (1 ml) under N_2 and at -78°C was successively added ketone (283) (115 mg, 0.45 mmol) in CH_2Cl_2 (2 ml) and 1,2-bistrimethylsilyloxy ethane (103 mg, 0.5 mmol). The mixture was stirred at -78°C for 24 hours then quenched by the addition of dry pyridine (250 µl). The reaction mixture was poured on to saturated aqueous $NaHCO_3$ solution (10 ml) and then extracted with Et_2O (3 x 15 ml). After drying and concentration, purification by dry column flash chromatography gave the ketal (258) (66 mg, 49%).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	170.32	-	s	-
H-3(2H)	1.65— 2.83	C-3	33.03/	-	t	-
H-8(2H)		C-8	34.07	-	t	-
H-4		C-4	34.47	-	d	-
H-5(2H)		C-5	48.32	-	t	-
H-7		C-7	37.42	-	d	-
-	-	C-4a	52.00	-	s	-
-	-	C-6	108.97	-	s	-
H-8a	4.90	C-8a	74.94	m	d	-
H-9(3H)	0.84	C-9	12.61	d	q	6.06
-	-	C-10	173.42	-	s	-
H-11(3H)	3.72	C-11	51.76	s	q	-
H-12(2H)	3.75-	C-12	64.66/	-	t	-
H-13(2H)	4.10	C-13	65.44	-	t	-
H-14(3H)	0.98	C-14	17.47	d	q	7.06

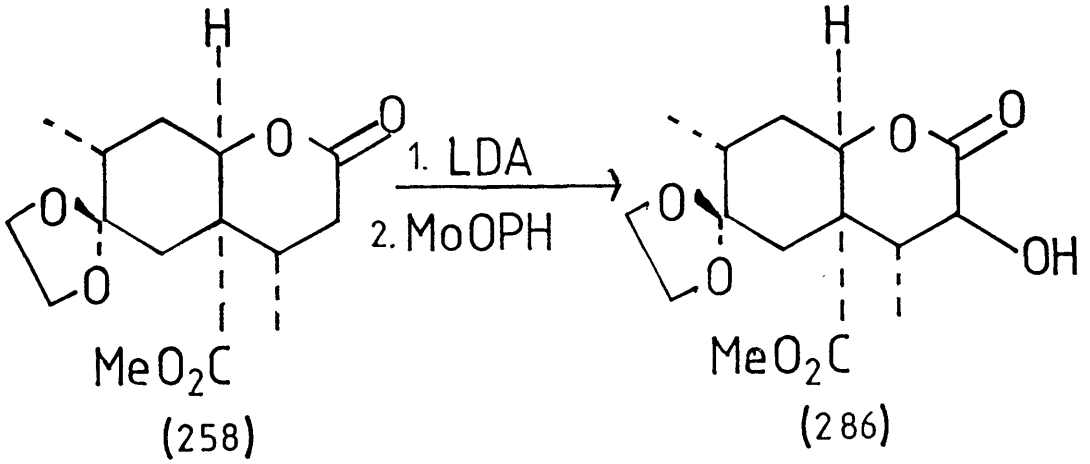
i.r. ($CHCl_3$): 3010, 2960, 1725, 1260, 1090 cm^{-1}

M.S : 298.1415 (M^+); calc. for $C_{15}H_{22}O_6$:298.1416

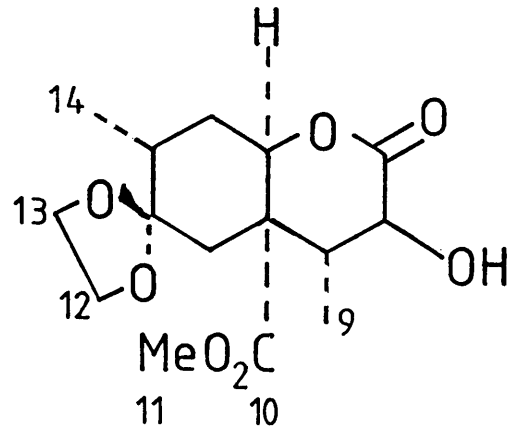
$C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43%

Found : C, 60.42; H, 7.44%

(±)-(4aα,8aα)-4a-Carbomethoxy-3,4,4a,5,6,7,8,8a-octahydro-3-hydroxy-4α,7α-dimethyl-6-oxo-2H-1-benzopyran-2-one ethylene ketal (286).



To a solution of diisopropylamine (632 mg, 876 µl, 6.25 mmol) in THF (15 ml) at 0°C was added n-BuLi (2.6M in hexane, 2.4 ml, 6.25 mmol). After 15 minutes the solution was cooled to -78°C and the lactone (258) (1.49 g, 5 mmol) in THF (10 ml) added dropwise. After stirring at -78°C for 30 minutes the MoO_5 complex (2.82 g, 6.5 mmol) was added in one portion and stirring continued for 4 hours at -78°C. The mixture was then allowed to warm to 0°C over 30 minutes. Saturated NH_4Cl solution was added, followed by Et_2O and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine. After drying and concentration, purification of the crude residue by dry column flash chromatography gave the α-hydroxylactone (286) (1.14g, 72.6%) as an oily mixture of diastereoisomers. Tabulated spectroscopic data refer to the major component.

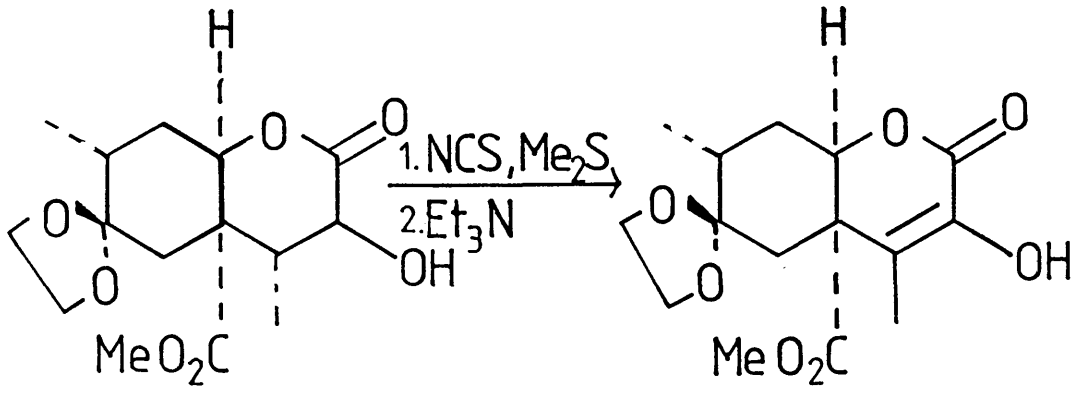


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	175.00	-	s	-
H-3	4.02	C-3	68.91	d	d	-
H-4	1.3 - 2.6	C-4	43.72	-	d	-
H-5(2H)		C-5	39.40	-	t	-
H-7		C-7	32.72	-	d	-
H-8(2H)		C-8	33.76	-	t	-
-	-	C-4a	50.56	-	s	-
-	-	C-6	108.26	-	s	-
H-8a	4.89	C-8a	73.91	m	d	-
H-9(3H)	1.13	C-9	14.83	d	q	6.95
-	-	C-10	172.08	-	s	-
H-11(3H)	3.73	C-11	51.38	s	q	-
H-12(2H)	3.80 -	C-12	64.28/	-	t	-
H-13(2H)	4.00	C-13	65.34	-	t	-
H-14(3H)	0.89	C-14	12.49	d	q	6.53

i.r. ($CHCl_3$) : 3520, 3020, 2980, 1730, 1100 cm^{-1}

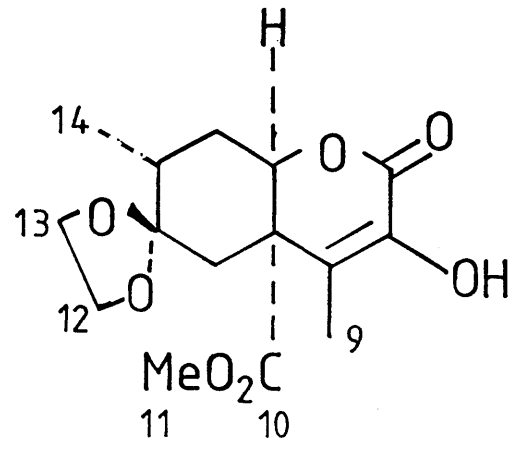
M.S. : 314.1356 (M^+); calc. for $C_{15}H_{22}O_7$:314.1366

(±)-(4aα,8aα)-4a-Carbomethoxy-4a,5,6,7,8,8a-hexahydro-3-hydroxy-4,7α-dimethyl-6-oxo-2H-1-benzopyran-2-one ethylene ketal (288).



(286) (288)

To a solution of N-chlorosuccinimide (721 mg, 5.4 mmol) in dry CH_2Cl_2 (40 ml) was added Me_2S (444 mg, 524 µl, 7.15 mmol) with stirring at 0°C. The mixture was stirred at 0°C for 20 minutes, then cooled to -25°C. The α-hydroxylactone (286) (1.12 g, 3.57 mmol) in CH_2Cl_2 (10 ml) was added dropwise, and the mixture was stirred at -25°C for 2 hours. Triethylamine (546 g, 753 µl, 5.4 mmol) in CH_2Cl_2 (1 ml) was added slowly, the cooling bath was removed, the mixture stirred for 1 hour, then it was poured into Et_2O. This solution was washed once with 1M HCl, water and brine then concentrated in vacuo. The crude oil, consisting of α-keto lactone and its enol tautomer, was dissolved in acetone and stirred over anhydrous K_2CO_3 for 10 minutes. After filtration and concentration, purification by dry column flash chromatography yielded the enol (288) (785 mg, 70.5%) as a yellow oil.

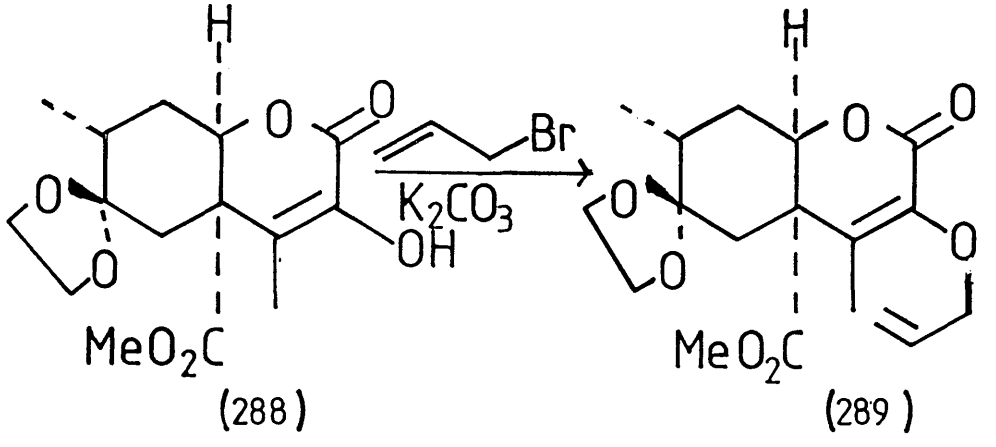


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	163.37	-	s	-
-	-	C-3	135.93	-	s	-
-	-	C-4	125.34	-	s	-
-	-	C-4a	50.77	-	s	-
H-5(2H)	1.30 -	C-5	36.77	-	t	-
H-7		C-7	32.67	-	d	-
H-8(2H)	2.70	C-8	33.92	-	t	-
-	-	C-6	107.85	-	s	-
H-8a	4.92	C-8a	76.55	bm	d	-
H-9(3H)	1.74	C-9	11.90/	s	q	-
H-14(3H)	0.80	C-14	12.53	d	q	6.56
-	-	C-10	170.52	-	s	-
H-11(3H)	3.71	C-11	52.05	s	q	-
H-12(2H)	3.75 -	C-12	64.13/	-	t	-
H-13(2H)	4.10	C-13	65.23	-	t	-

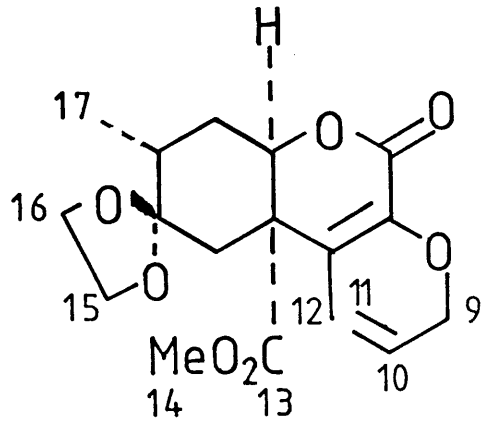
i.r. ($CHCl_3$): 3500 (s), 3020, 1730, 1710, 1190 cm^{-1}

M.S: 312.1202 (M^+); calc. for $C_{15}H_{20}O_7$:312.1209

(±)-(4aα,8aα)-4a-Carbomethoxy-4a,5,6,7,8,8a-hexahydro-3-allyloxy-4,7α-dimethyl-6-oxo-2H-1-benzopyran-2-one ethylene ketal (289).



A mixture of the enol (288) (785 mg, 2.52 mmol), anhydrous K_2CO_3 (435 mg, 3.15 mmol) and allyl bromide (3.05 g, 2.18 ml, 25.2 mmol) in acetone (50 ml) was heated under reflux for 24 hours. On cooling the mixture was poured into Et_2O, filtered through Celite, and concentrated in vacuo. Purification by dry column flash chromatography gave the allyl enol ether (289) (656mg, 74%) as an oil.

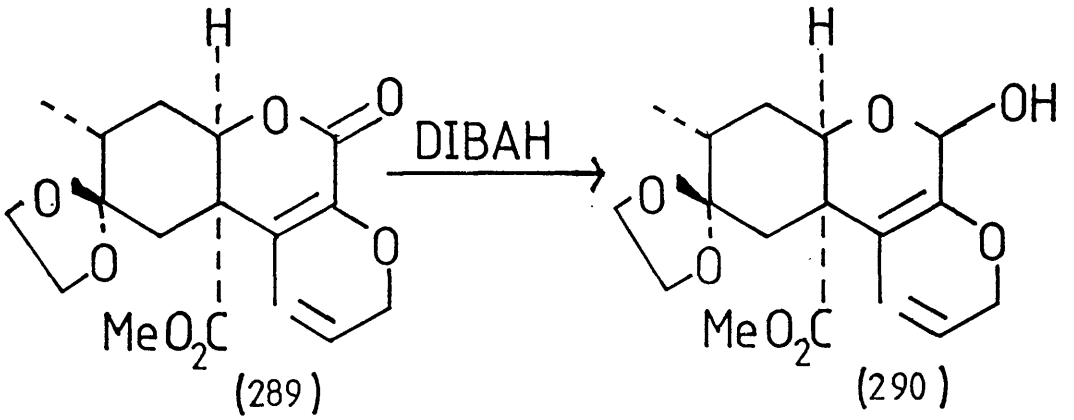


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	160.72	-	s	-
-	-	C-3	139.87/	-	s	-
-	-	C-4	140.68	-	s	-
-	-	C-4a	51.56	-	s	-
H-5(2H)	1.40 - 2.70	C-5	33.94/	-	t	-
H-8(2H)		C-8	36.55	-	t	-
H-7		C-7	32.64	-	d	-
-	-	C-6	107.96	-	s	-
H-8a	4.88	C-8a	75.10	bm	d	-
H-9(2H)	4.25 - 4.60	C-9	72.99	m	t	-
H-10	5.78 - 6.02	C-10	133.14	m	d	-
H-11(2H)	5.12 - 5.35	C-11	118.70	m	t	-
H-12(3H)	1.79	C-12	12.56/	s	q	-
H-17(3H)	0.81	C-17	12.95	d	q	6.6
-	-	C-13	170.44	-	s	-
H-14(3H)	3.73	C-14	52.12	s	q	-
H-15(2H)	3.60 -	C-15	64.16/	m	t	-
H-16(2H)	4.10	C-16	65.28	m	t	-

i.r. ($CHCl_3$) : 3020, 2960, 2900, 1720, 1175 cm^{-1}

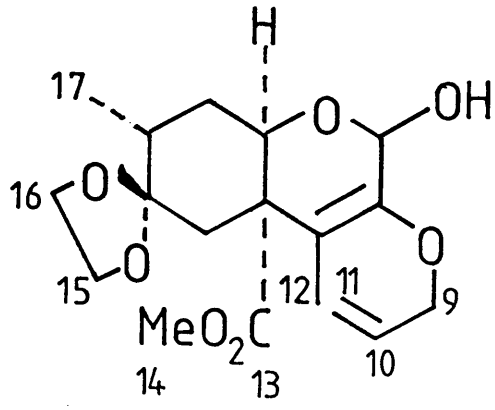
M.S : 352.1521 (M^+); calc. for $C_{18}H_{24}O_7$: 352.1522

(±)-(4aα,8aα)-4a-Carbomethoxy-4a,5,6,7,8,8a-hexahydro-2-hydroxy-3-allyloxy-4,7α-dimethyl-6-oxo-2H-1-benzopyran ethylene ketal (290).



(289) (290)

To a solution of the lactone (289) (420 mg, 1.19 mmol) in dry CH_2Cl_2 (50 ml) was added DIBAH (1M in CH_2Cl_2, 1.55 ml, 1.55 mmol) at -78°C with stirring. Stirring was continued for 2 hours at -78°C whereupon acetic acid (1 ml) was added and the cooling bath removed. The mixture was allowed to warm to room temperature over a period of 30 minutes, then diluted with Et_2O (100 ml) and washed with 1M HCl and brine. After drying and concentration, purification of the crude residue by dry column flash chromatography yielded the lactol (290) (340 mg, 81%) as an oily mixture of alcohol epimers. The doubling of peaks in the ^{13}C n.m.r. spectrum reflects this epimeric mixture.

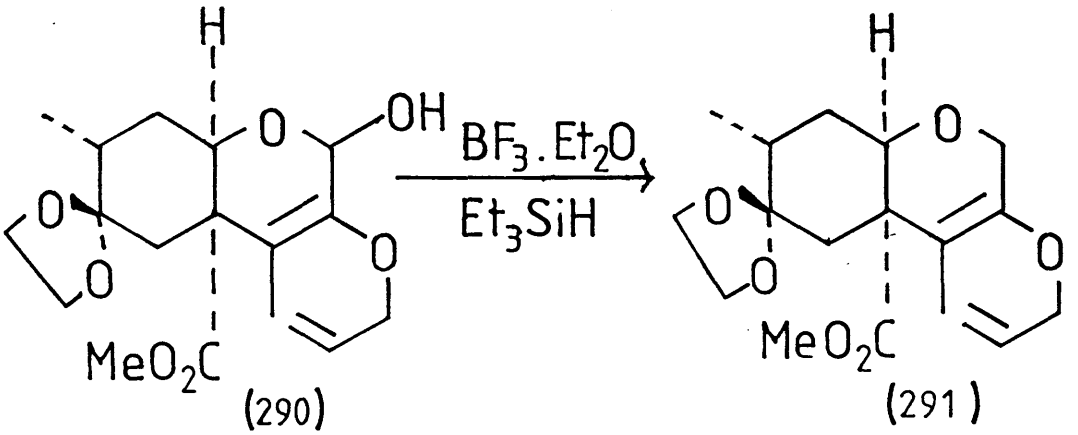


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	-	C-2	88.72 91.35	-	d	-
-	-	C-3	147.02 147.69	-	s	-
-	-	C-4	120.41 122.01	-	s	-
-	-	C-4a	51.24	-	s	-
H-5α	2.60	C-5	34.85	d	t	13
H-5β	1.5-2.4			-	t	-
-	-	C-6	109.29	-	s	-
H-7	1.5 - 2.4	C-7	36.51 37.37	-	d	-
H-8(2H)		C-8	32.90	-	t	-
H-8a	3.8-4.2	C-8a	70.50	-	d	-
H-9(2H)	4.2-4.4	C-9	71.34 71.75	m	t	-
H-10	5.65-6.25	C-10	133.90 134.06	m	d	-
H-11(2H)	5.10-5.60	C-11	117.05 117.60	m	t	-
H-12(3H)	1.61	C-12	12.90	s	q	-
-	-	C-13	172.55	-	s	-
H-14(3H)	3.72	C-14	51.57	s	q	-
H-15(2H)	3.80-	C-15	64.11/	m	t	-
H-16(2H)	4.20	C-16	65.14		t	-
H-17(3H)	0.81	C-17	10.93/ 11.26	d	q	7

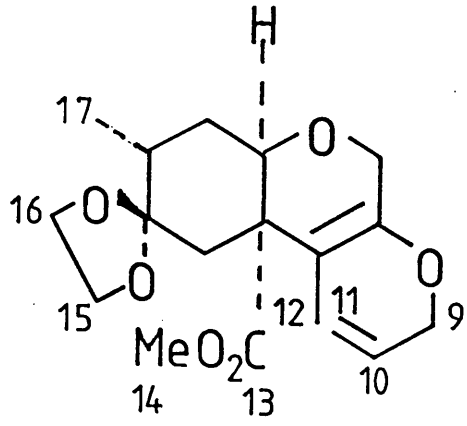
i.r ($CHCl_3$): 3600, 2960, 1725, 1670, 1080 cm^{-1}

M.S: 354.1668 (M^+); calc. for $C_{18}H_{26}O_7$: 354.1678

(±)-(4aα,8aα)-4a-Carbomethoxy-4a,5,6,7,8,8a-hexahydro-3-allyloxy-4,7α-dimethyl-6-oxo-2H-1-benzopyran ethylene ketal (291)



To a solution of the lactol (290) (1.13 g, 3.2 mmol) and Et_3SiH (558 mg, 767 µl, 4.8 mmol) in CH_2Cl_2 (50 ml) was added $BF_3.Et_2O$ (454 mg, 394 µl, 3.2 mmol) with stirring at -78°C. Stirring was continued at -78°C for 30 minutes, when excess solid anhydrous K_2CO_3 was added. The mixture was stirred at this temperature for 30 minutes before being warmed to room temperature. On reaching room temperature saturated aqueous $NaHCO_3$ solution (10 ml) was added. The mixture was diluted with CH_2Cl_2 (20 ml), washed once with saturated aqueous $NaHCO_3$ solution, dried and concentrated in vacuo. Purification by dry column flash chromatography gave the pyran (291) (950 mg, 88%) as a viscous oil.

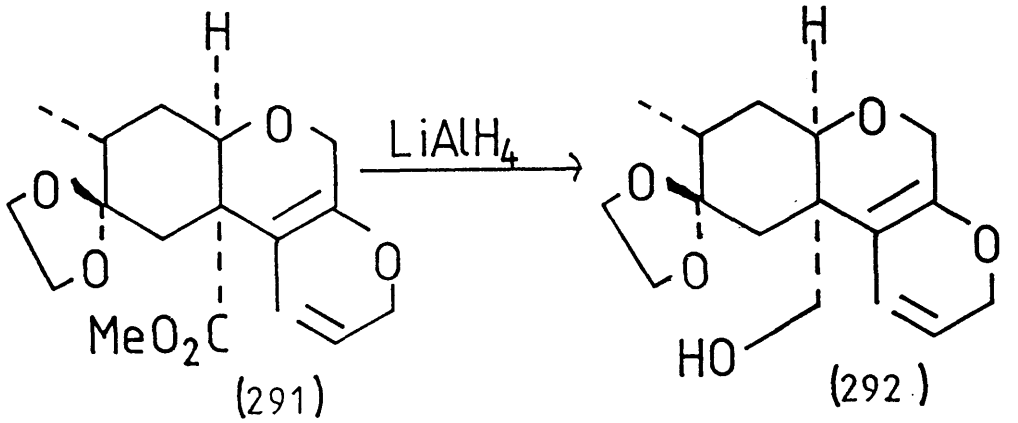


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2(2H)	4.13 - 4.16	C-2	70.82	—	t	—
-	-	C-3	147.23	-	s	-
-	-	C-4	116.56	-	s	-
-	-	C-4a	50.90	-	s	-
H-5β	1.70-1.90	C-5	37.10	-	t	-
H-5α	2.58			dd		13.66, 1.36w
-	-	C-6	109.34	-	s	-
H-7	2.00-2.23	C-7	32.97	m	d	-
H-8(2H)	1.70-1.90	C-8	35.14	m	t	-
H-8a	4.06	C-8a	73.36	m	d	-
H-9(2H)	3.63 -	C-9	64.07/		t	-
H-15(2H)		C-15	64.93/	m	t	-
H-16(2H)	4.25	C-16	65.13		t	-
H-10	5.75-5.99	C-10	133.80	m	d	-
H-11(2H)	5.10-5.37	C-11	117.36	m	t	-
H-12(3H)	1.57	C-12	12.93	t	q	1.93
-	-	C-13	172.93	-	s	-
H-14(3H)	3.67	C-14	51.35	s	q	-
H-17(3H)	0.80	C-17	10.70	d	q	6.6

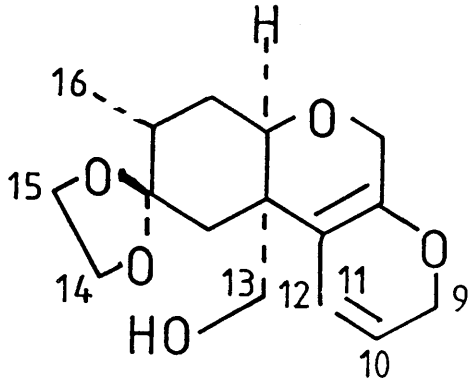
i.r. ($CHCl_3$) : 3010, 2960, 1725, 1680, 1115 cm^{-1}

M.S : 338.1717 (M^+); calc. for $C_{18}H_{26}O_6$: 338.1729

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-3-allyloxy-4,7α-dimethyl-4a-hydromethyl-6-oxo-2H-1-benzopyran ethylene ketal (292).



To a suspension of $LiAlH_4$ (60 mg, 1.54 mmol) in Et_2O (2 ml) was added the ester (291) (130 mg, 0.385 mmol) in Et_2O (3 ml). The mixture was stirred at 0°C for 30 min, then saturated aqueous Na_2SO_4 solution added dropwise followed by excess solid anhydrous Na_2SO_4. The mixture was filtered through Celite and the pad copiously washed with Et_2O. Concentration and purification of the residue by dry column flash chromatography using neutral alumina afforded the alcohol (292) (112 mg, 94%) as a viscous oil.

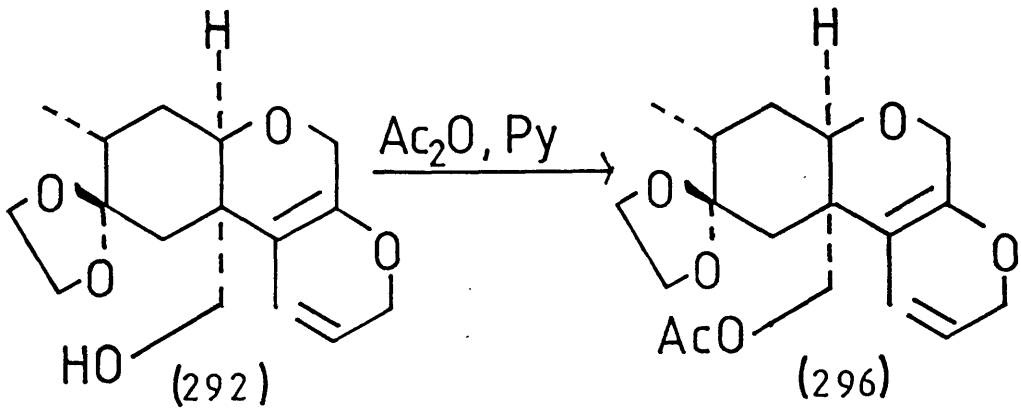


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2(2H)	4.07-4.14	C-2	70.81	q	t	1.87
-	-	C-3	147.28	-	s	-
-	-	C-4	118.35	-	s	-
-	-	C-4a	44.29	-	s	-
H-5(2H)	1.7-2.0	C-5	38.70	-	t	-
-	-	C-6	110.40	-	s	-
H-7	2.02-2.25	C-7	33.68	m	d	-
H-8(2H)	1.7-2.0	C-8	34.40	-	t	-
H-8a	3.57	C-8a	73.46	m	d	-
H-9(2H)	4.14 - 4.23	C-9	64.49/	m	t	5.55, 1.48
H-13(2H)	3.73 -	C-13	64.92/	-	t	-
H-14(2H)	4.0	C-14	65.54	-	t	-
H-15(2H)		C-15	65.66	-	t	-
H-10	5.80 - 6.02	C-10	134.02	m	d	-
H-11(2H)	5.10 - 5.40	C-11	117.49	m	t	-
H-12(3H)	1.63	C-12	13.44	t	q	1.92
H-16(3H)	0.85	C-16	8.90	d	q	6.56

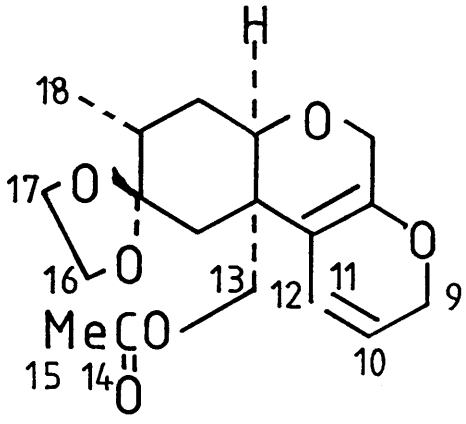
i.r. ($CHCl_3$): 3500, 2915, 1680, 1110 cm^{-1}

M.S: 310.1768 (M^+); calc. for $C_{17}H_{26}O_5$: 310.1780

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-3-allyloxy-4,7α-dimethyl-4a-acetoxymethyl-6-oxo-2H-1-benzopyran ethylene ketal (296)



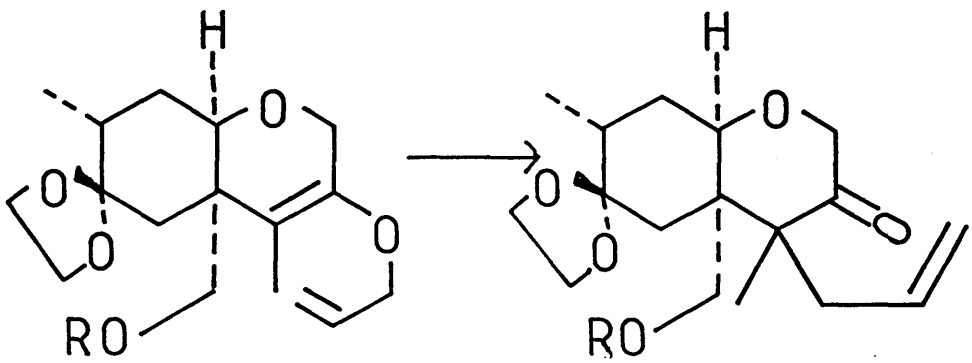
To the alcohol (292) (343 mg, 1.1 mmol) in Et_2O (3 ml) was added a preformed mixture of Ac_2O (2 ml) and pyridine (1 ml). The mixture was stirred at room temperature overnight then concentrated in vacuo, the Ac_2O and pyridine being removed by repeated azeotropic distillation with toluene. Purification of the crude residue by dry column flash chromatography gave the acetate (296) (348 mg, 90%) as a colourless oil.



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	^{13}C	J(Hz) ^1H
H-2(2H)	3.75-4.33	C-2	71.10	-	t	-
-	-	C-3	146.42	-	s	-
-	-	C-4	119.02	-	s	-
-	-	C-4a	42.51	-	s	-
H-5(2H)	1.70 - 1.90	C-5	38.77	-	t	-
-	-	C-6	109.87	-	s	-
H-7	-	C-7	33.55	-	d	-
H-8(2H)	1.70-1.90	C-8	33.79	-	t	-
H-8a	3.55	C-8a	72.65	t	d	2.96
H-9(2H)	3.75-4.33	C-9	64.54/	-	t	-
H-13(2H)	4.01 + 4.45	C-13	64.92/	AB quartet	t	12.24
H-16(2H)	3.75-	C-16	65.44	-	t	-
H-17(2H)	4.33	C-17	65.56	-	t	-
H-10	5.80 - 6.05	C-10	134.11	m	d	-
H-11(2H)	5.10-5.37	C-11	117.37	m	t	-
H-12(3H)	1.56	C-12	13.33	t	q	1.96
-	-	C-14	170.94	-	s	-
H-15(3H)	1.99	C-15	20.89	s	q	-
H-18(3H)	0.83	C-18	8.98	d	q	6.62

i.r. ($CHCl_3$) : 3015, 1735, 1690, 1115 cm^{-1}

M.S: 352.1904 (M^+); calc. for $C_{19}H_{28}O_6$: 352.1886



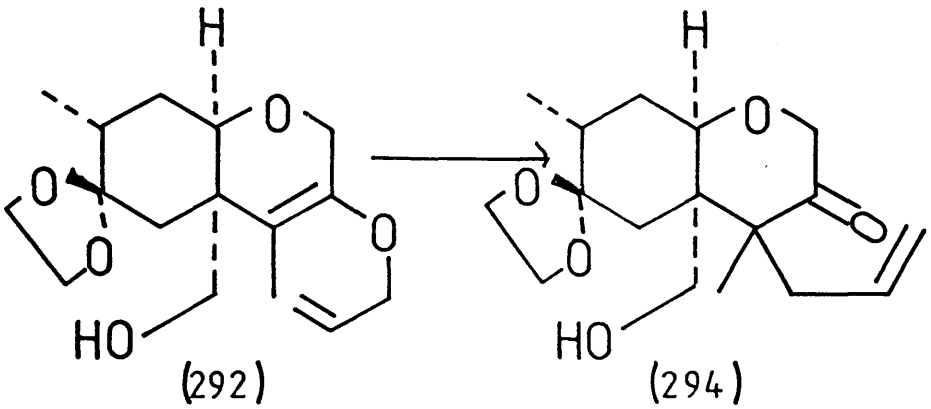
R	α-allyl : β-allyl ratio
H	3.2 : 1
Ac	2.5 : 1
t-BuMe$_2$Si	2.2 : 1

Capillary column G.L.C. was performed with a Hewlett-Packard 5880A gas chromatograph equipped with SE-54 and CP Sil 5 CB fused-silica capillary columns (25m x 0.32mm ID) and Grob-type injectors operated in split mode (50:1). Both columns were temperature programmed to operate at 230^{o}C; the helium carrier and make-up gas flow rates were 3ml/min and 25ml/min for both columns respectively.

The respective retention times for the allyl α-epimer on these columns were 24.61 min and 18.05 min.

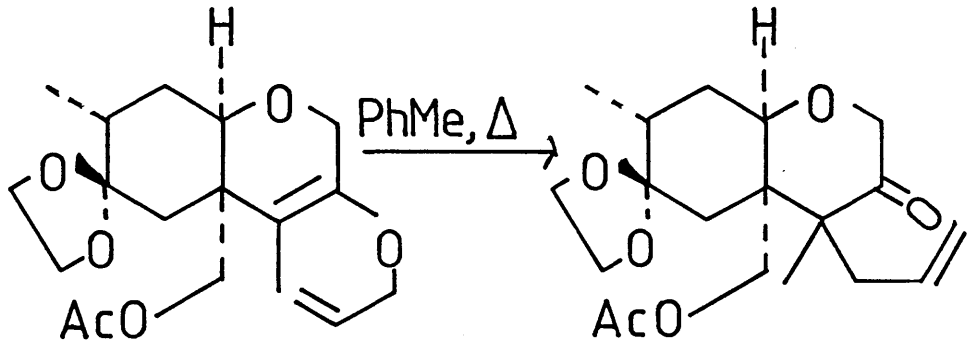
The respective retention times for the allyl β-epimer on these columns were 23.87 min and 17.46 min.

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-4-allyl-4,7α-dimethyl-4a-hydroxymethyl-6-(oxo-ethylene ketal)-2H-1-benzopyran-3(4H)-one (294)



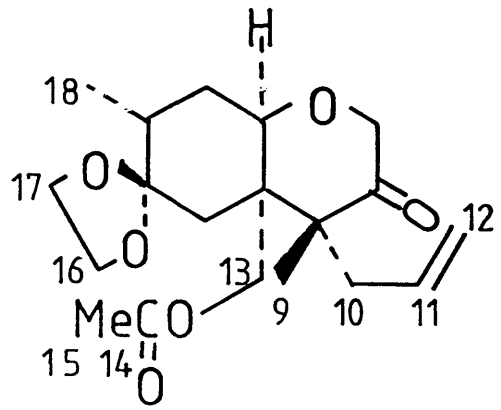
A solution of the allyl enol ether (292) (653 mg, 2.1 mmol) in toluene (35 ml) made basic by the addition of Et_3N (1 ml) was heated under reflux for 24 hours. Concentration in vacuo and purification by dry column flash chromatography using neutral alumina afforded the allyl ketone (294) (581 mg, 89%) as an inseparable 3.2:1 mixture of α-allyl:β-allyl epimers. This compound was fully characterised as acetate (318).

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-4-allyl-4,7α-dimethyl-4a-acetoxymethyl-6-(oxo-ethylene ketal)-2H-1-benzopyran-3(4H)-one (318).



(296) (318)

A solution of the allyl enol ether (296) (353 mg, 1 mmol) in toluene (50 ml) was heated under reflux for 24 hours. Concentration in vacuo and purification by dry column flash chromatography yielded the allyl ketone (318) (350 mg, 99%) as an oily 2.5:1 mixture of α-allyl:β-allyl epimers which were partially separated by positive pressure flash chromatography.

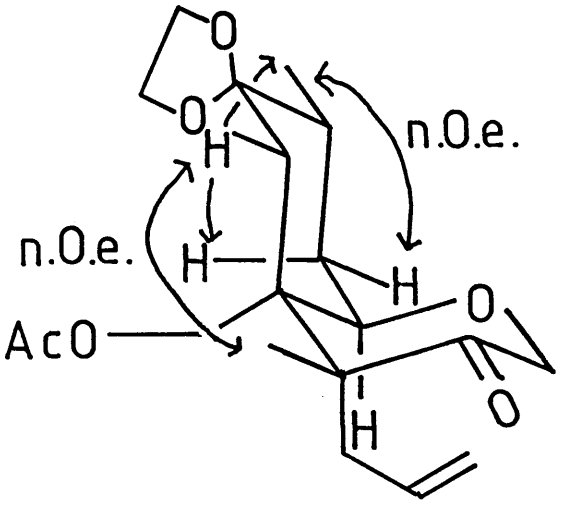


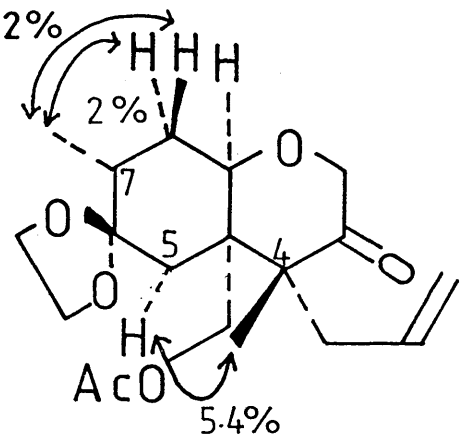
PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	^{13}C	J(Hz) ^1H
H-2(2H)	4.29 + 4.45	C-2	71.58	AB quartet	t	15.72
-	-	C-3	208.05	-	s	-
-	-	C-4	54.50	-	s	-
-	-	C-4a	47.56	-	s	-
H-5(2H)	1.30 - 1.95	C-5	33.89/	-	t	-
H-8(2H)	2.72-2.87	C-8	35.03	-	t	-
-	-	C-6	109.89	-	s	-
-	-	C-7	32.45	-	d	-
H-8a	4.23	C-8a	71.05	m	d	-
H-9(3H)	1.06	C-9	14.75	s	q	-
H-10(2H)	1.95-2.30	C-10	38.70	-	t	-
H-11	5.32-5.55	C-11	132.38	m	d	-
H-12(2H)	4.95-5.10	C-12	118.63	m	t	-
H-13(2H)	3.89 + 4.08	C-13	64.00/	AB quartet	t	14.03
H-16(2H)	3.78-	C-16	64.72/	m	t	-
H-17(2H)	4.00	C-17	65.81	m	t	-
-	-	C-14	170.37	-	s	-
H-15(3H)	2.07	C-15	21.05	s	q	-
H-18(3H)	0.82	C-18	13.05	d	q	6.7

i.r. ($CHCl_3$): 3020, 2980, 1740, 1730, 1640, 1240, 1090 cm^{-1}

M.S: 352.1890 (M^+); calc. for $C_{19}H_{28}O_6$: 352.1886

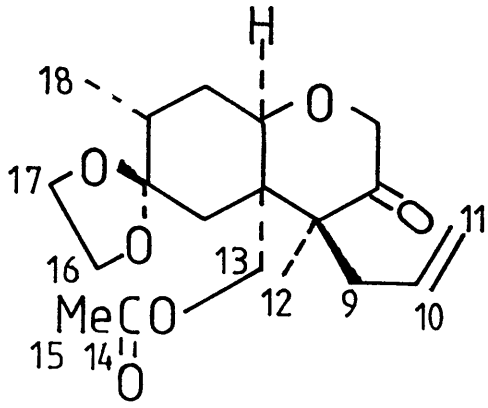
n.O.e. Results.





(299)

Irradiate	% enhancement
H-9	5.4% H-5α
H-18	2.0% H-8α
H-18	2.0% H-8β

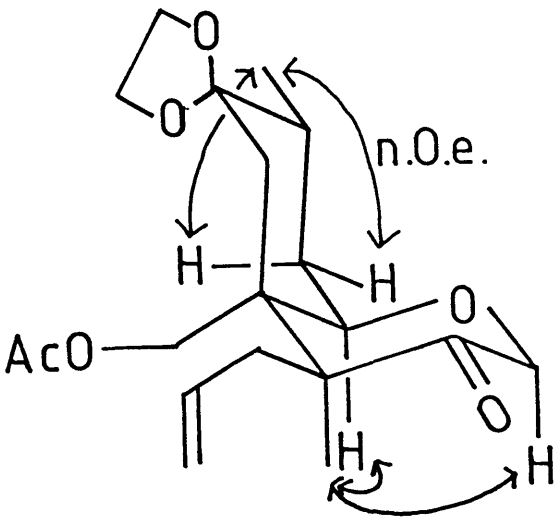


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	^{13}C	J(Hz) ^1H
H-2(2H)	4.23 + 4.45	C-2	71.65	AB quartet	t	12.50
-	-	C-3	210.46	-	s	-
-	-	C-4	52.60	-	s	-
-	-	C-4a	47.85	-	s	-
H-5(2H)	1.54-1.91	C-5	33.94/	-	t	-
H-8(2H)	2.57-2.73	C-8	34.89	-	t	-
-	-	C-6	109.87	-	s	-
H-7	-	C-7	32.78	-	d	-
H-8a	4.06	C-8a	72.37	m	d	-
H-9(2H)	2.00-2.30	C-9	37.42	-	t	-
H-10	5.75-6.00	C-10	135.62	-	d	-
H-11(2H)	4.95-5.10	C-11	117.58	-	t	-
H-12(3H)	1.14	C-12	18.83	s	q	-
H-13(2H)	3.91 + 4.21	C-13	64.51/	AB quartet	t	14.54
H-16(2H)	3.80-	C-16	64.77/	-	t	-
H-17(2H)	4.00	C-17	65.52	-	t	-
-	-	C-14	170.38	-	s	-
H-15(3H)	2.05	C-15	20.97	s	q	-
H-18(3H)	0.83	C-18	13.15	d	q	6.69

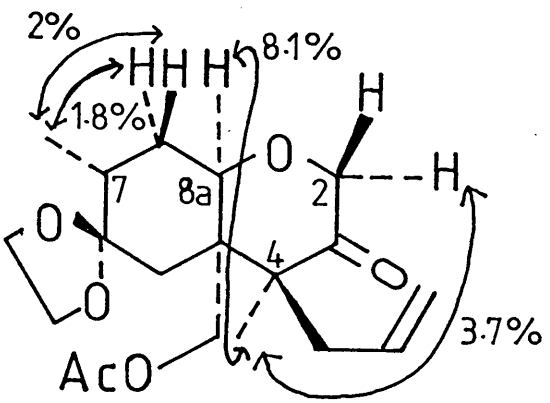
i.r. ($CHCl_3$): 2980, 1740, 1725, 1640, 1240 cm^{-1}

M.S: 352.1888 (M^+); calc. for $C_{19}H_{28}O_6$: 352.1886

n.O.e. Results



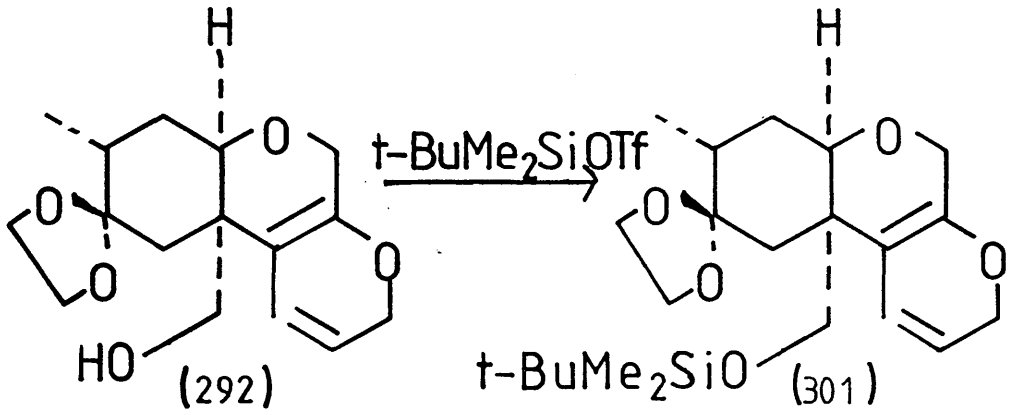
n.O.e.



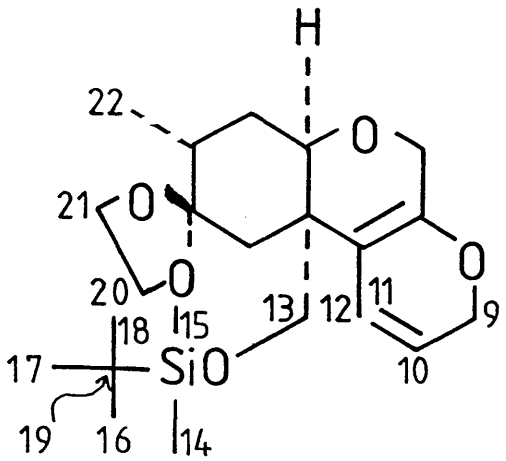
(300)

Irradiate	% enhancement
H-12	8.1% H-8a
H-12	3.7% H-2α
H-18	1.8% H-8α
H-18	2.0% H-8β

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-3-allyloxy-4,7α-dimethyl-4a-(tert-butyldimethylsiloxymethyl)-6-oxo-2H-1-benzopyran ethylene ketal (301).



To a solution of the alcohol (292) (207 mg, 0.67 mmol) in CH_2Cl_2 (10 ml) was added 2,6-lutidine (144 mg, 156 µl, 1.34 mmol) and TBDMSOTf (264 mg, 229 µl, 1 mmol in CH_2Cl_2) with stirring at room temperature. Stirring was continued for 30 minutes whereupon the mixture was poured into Et_2O. This solution was washed once with H_2O, saturated aqueous $CuSO_4$ solution and brine. After drying and concentration, purification of the residue by dry column flash chromatography gave the silyl ether (301) (254 mg, 89%) as an oil.



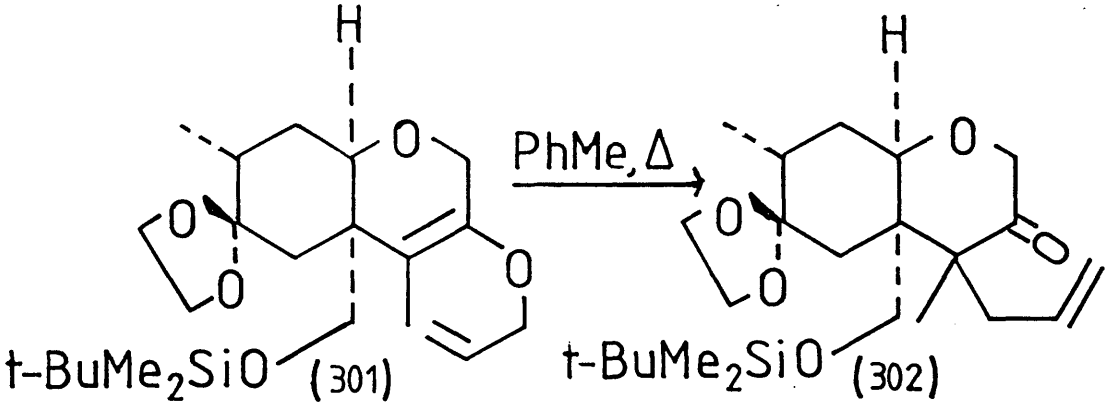
PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2(2H)	4.10-4.30	C-2	71.60	-	t	-
-	-	C-3	146.27	-	s	-
-	-	C-4	120.06	-	s	-
-	-	C-4a	44.27	-	s	-
H-5(2H)	1.50-1.90	C-5	31.92	-	t	-
-	-	C-6	110.36	-	s	-
-	-	C-7	33.70	-	d	-
H-8(2H)	1.50-1.90	C-8	29.36	-	t	-
H-8a	3.68	C-8a	72.68	m	d	-
H-9(2H)	4.00-4.10	C-9	63.91/	-	t	-
H-13(2H)	3.80-	C-13	64.51/		t	
H-20(2H)	4.00	C-20	64.79/	-	t	-
H-21(2H)		C-21	65.37		t	
H-10	5.80-6.60	C-10	134.50	m	d	-
H-11(2H)	5.05-5.40	C-11	117.01	m	t	-
H-12(3H)	1.60	C-12	13.50	m	q	-
H-14(3H)	0.06/	C-14	1.01	s	q	-
H-15(3H)	0.17	C-15		s	q	-
H-16(3H)		C-16				
H-17(3H)	0.86	C-17	25.79	s	q	-
H-18(3H)		C-18				
-	-	C-19	18.08	-	s	-
H-22(3H)	0.84	C-22	9.02	d	q	-

i.r. ($CHCl_3$): 2950, 2920, 1465, 1455, 1250, 1105, 1085 cm^{-1}

M.S: 424.2658 (M^+); calc. for $C_{23}H_{40}O_5Si$: 424.2645

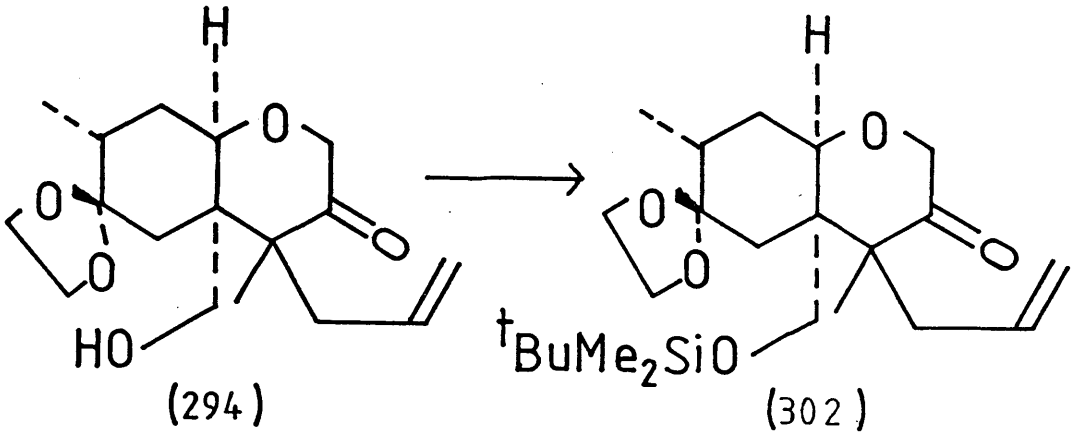
(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-4-allyl-4,7α-dimethyl-4a-(tert-butyldimethylsiloxymethyl)-6-(oxo-ethylene ketal)-2H-1-benzopyran-3(4H)-one (302).

METHOD 1.

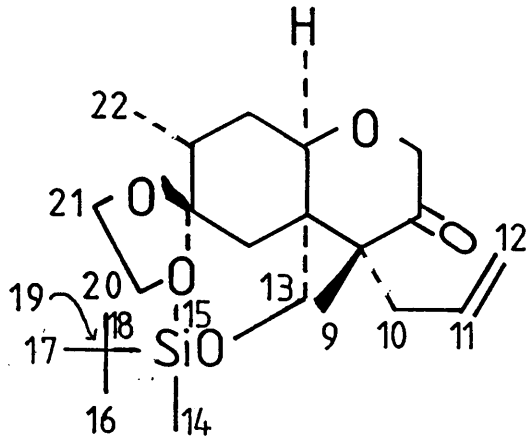


A solution of the allyl enol ether (301) (450 mg, 1.06 mmol) in toluene (45 ml) was heated under reflux for 24 hours. Concentration in vacuo and purification by dry column flash chromatography yielded the allyl ketone (302) (419 mg, 93%) as a 2.2:1 mixture of α-allyl:β-allyl epimers. Tabulated spectroscopic data refer to the major, α, component.

METHOD 2.



To a solution of the alcohol (294) (713 mg, 2.3 mmol) in CH_2Cl_2 (35 ml) was added 2,6-lutidine (492 mg, 535 µl, 4.6 mmol) and TBDMSOTf (910 mg, 791 µl, 3.45 mmol in CH_2Cl_2) with stirring at room temperature. Stirring was continued for 30 minutes whereupon the mixture was poured into Et_2O. This solution was washed once with H_2O, saturated aqueous $CuSO_4$ solution and brine. After drying and concentration, purification of the residue by dry column flash chromatography gave the allyl ketone (302) (956 mg, 98%) as an oil. Tabulated spectroscopic data refer to the major, α, component.

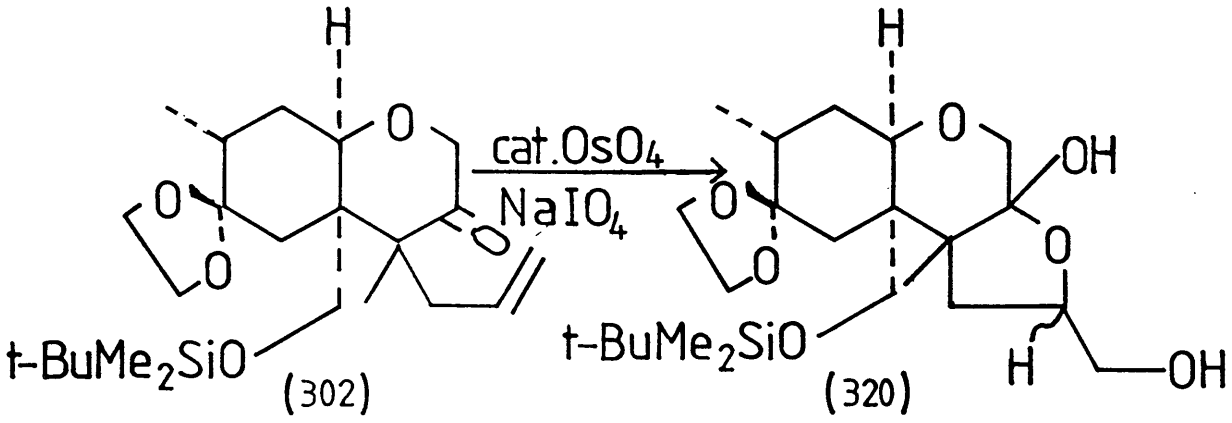


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2(2H)	4.0-4.2	C-2	71.55	-	t	-
-	-	C-3	209.26	-	s	-
-	-	C-4	54.56	-	s	-
-	-	C-4a	48.57	-	s	-
H-5(2H)	1.5-2.0	C-5	35.15	-	t	-
-	-	C-6	110.26	-	s	-
-	-	C-7	32.47	-	d	-
H-8(2H)	1.5-2.0 2.75-2.95	C-8	33.88	-	t	-
-	-	C-8a	71.51	-	d	-
H-9(3H)	1.05	C-9	14.66	s	q	-
H-10(2H)	2.0-2.5	C-10	38.85	-	t	-
H-11	5.30-5.60	C-11	133.30	m	d	-
H-12(2H)	4.85-5.20	C-12	117.80	m	t	-
H-13(2H) H-20(2H) H-21(2H)	3.6-4.2	C-13 C-20 C-21	62.42/ 64.55/ 65.58	-	t t t	-
H-14(3H) H-15(3H)	0.04	C-14 C-15	-4.95/ -4.90	s	q q	-
H-16(3H) H-17(3H) H-18(3H)	0.88	C-16 C-17 C-18	25.76	s	q	-
-	-	C-19	18.02	-	s	-
H-22(3H)	0.80	C-22	13.22	d	q	6.66

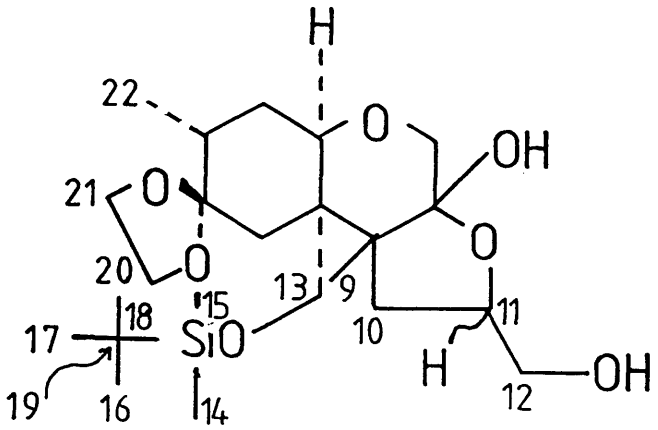
i.r. ($CHCl_3$): 2960, 2940, 1715, 1640, 1100, 840 cm^{-1}

M.S: 424.2626 (M^+); calc. for $C_{23}H_{40}O_5Si$: 424.2645

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-4-(2',3'-dihydroxypropane)-4,7α-dimethyl-4a-(tert-butyldimethylsiloxymethyl)-6-(oxo-ethylene ketal)-2H-1-benzopyran-3(4H)-one furan hemiacetal (320).



To a solution of the allyl ketone (302) (285 mg, 0.67 mmol) in Et_2O (10 ml) was added sodium periodate (158 mg, 0.74 mmol) in water (10 ml) and osmium tetroxide (18 mg, 0.07 mmol) in ^tBuOH (1.8 ml). The mixture was stirred at room temperature for 18 hours whereupon the solution was diluted with Et_2O (25 ml) and solid NaCl added. The aqueous layer was washed with Et_2O (3 x 30 ml) and the combined ethereal extracts were washed with 1M NaOH (30 ml) and brine. After drying and concentration, purification of the residue by dry column flash chromatography gave the diol (320) (270 mg, 88%) as a viscous oil. Acetylation of this product resulted in an integrated downfield shift of two protons as determined by 200 MHz ^1H n.m.r, verifying the formation of tetrahydrofuran (320).

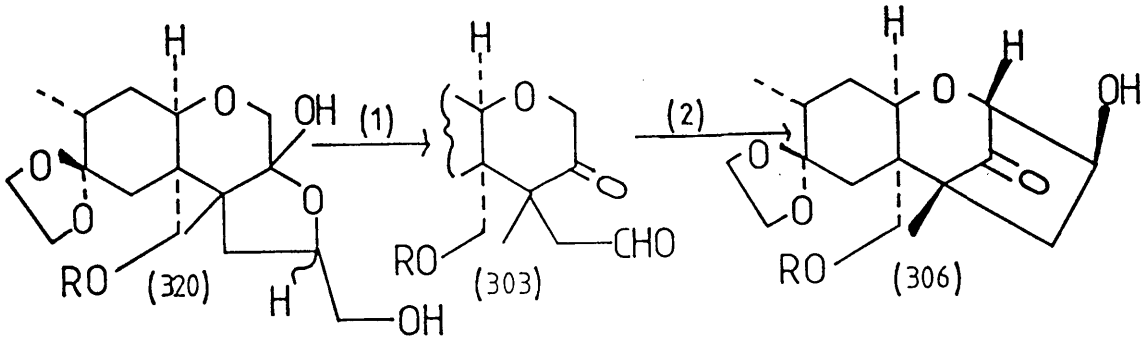


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2(2H)	3.2-4.0	C-2	74.24	-	t	-
-	-	C-3	102.12	-	s	-
-	-	C-4	47.77	-	s	-
-	-	C-4a	43.30	-	s	-
H-5(2H)	1.4-2.7	C-5	33.06/	-	t	-
H-8(2H)		C-8	34.01/		t	
H-10(2H)		C-10	35.32		t	
-	-	C-6	110.98	-	s	-
H-7	-	C-7	32.58	-	d	-
H-8a	-	C-8a	73.18	-	d	-
H-9(3H)	1.14	C-9	15.48	s	q	-
H-11	-	C-11	76.20	-	d	-
H-12(3H)	3.2-4.0	C-12	63.92/	-	t	-
H-13(3H)		C-13	64.50/		t	
H-20(3H)		C-20	65.48/		t	
H-21(3H)		C-21	65.93		t	
H-14(3H)	-0.04+	C-14	-0.06	s	q	-
H-15(3H)	0.00	C-15		s	q	-
H-16(3H)	0.85	C-16	25.83	s	q	-
H-17(3H)		C-17			q	
H-18(3H)		C-18			q	
-	-	C-19	18.07	-	s	-
H-22(3H)	0.78	C-22	13.26	d	q	6.54

i.r. ($CHCl_3$): 3600, 3450, 2960, 2930, 1100, 860, 840 cm^{-1}

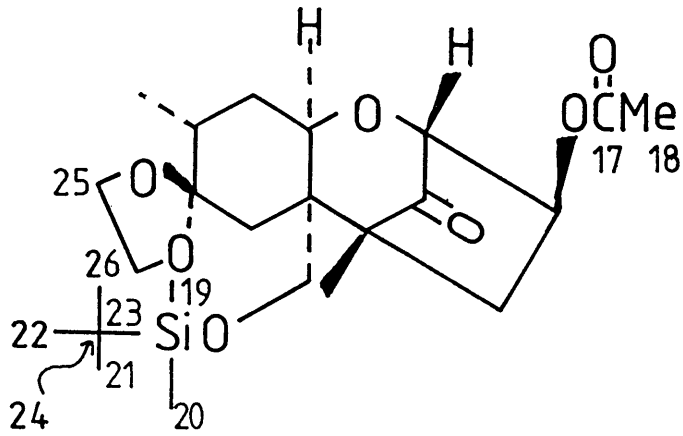
M.S: 458.2708 (M^+); calc. for $C_{23}H_{42}SiO_7$: 458.2700

(±)-3β-Hydroxy-8-(oxo-ethylene ketal)-12-oxo-15-(tert-butyldimethyl-siloxy)-nortrichothecane (306)



R=t-BuMe$_2$Si ; (1) H_5IO_6 , (2) NaOMe

Periodic acid dihydrate (330 mg, 1.44 mmol) was stirred in dry Et_2O (25 ml) for 1 hour. The ethereal solution was decanted and added to a stirred solution of the diol (600 mg, 1.31 mmol) in dry Et_2O (10 ml). On addition a white precipitate of iodic acid was formed. Stirring was continued for 5 min then the ethereal solution was filtered through Celite and evaporated to dryness in vacuo. The solid residue obtained was diluted with Et_2O and refiltered through Celite. Removal of the solvent in vacuo gave a yellow oil which was added to a solution of freshly prepared sodium methoxide in methanol [from sodium (241 mg, 10.48 mmol) and methanol (30 ml)]. The resulting solution was heated under reflux for 35 min, then it was concentrated to half-volume. This mixture was poured on to ice and extracted with ether (5 x 30 ml). After drying and concentration, purification of the residue by dry column flash chromatography gave the ketol (306) (345 mg, 62%) as a viscous oil. This material was fully characterised as the acetate (326). The minor α-alcohol epimer of (306) could not be separated from the ketols obtained on cyclisation of the epimeric keto-aldehyde (329).



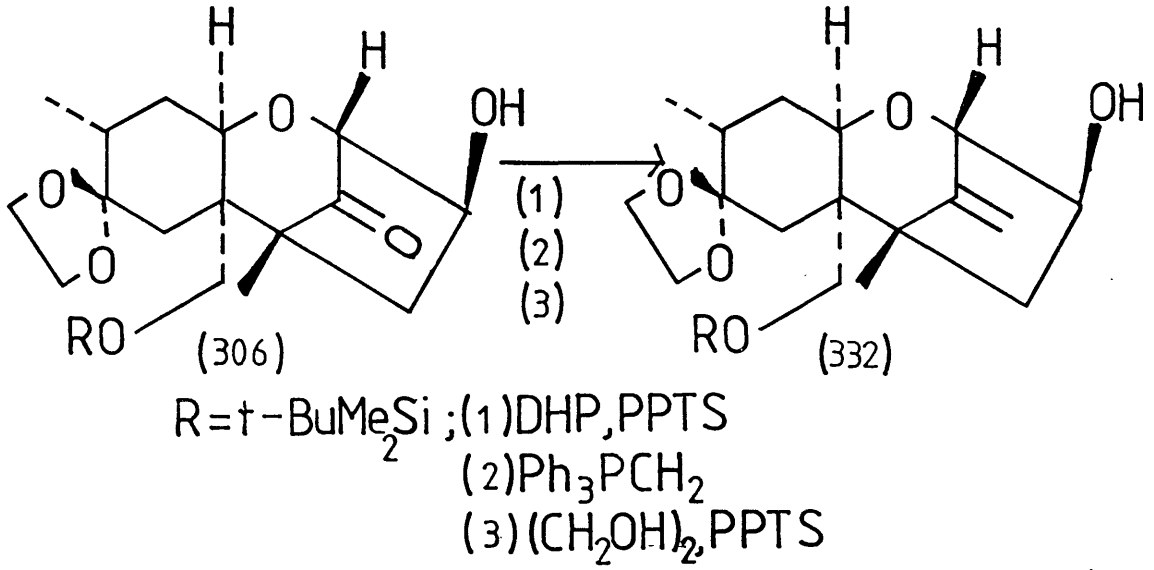
PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	3.67	C-2	68.48	bs	d	-
H-3	5.16	C-3	79.01	dd	d	3.07,8.90
-	-	C-4	37.95	-	t	-
-	-	C-5	51.87/	-	s	-
-	-	C-6	52.09	-	s	-
H-7(2H)	1.3-1.85	C-7	34.34	m	t	-
-	-	C-8	110.09	-	s	-
-	-	C-9	32.45	-	d	-
H-10(2H)	1.3-1.85	C-10	33.08	m	t	-
H-11	4.15	C-11	69.75	m	d	-
-	-	C-12	212.38	-	s	-
H-14(3H)	1.04	C-14	13.05/	s	q	-
H-16(3H)	0.79	C-16	13.40	d		6.60
H-15(2H)	3.97+ 4.09	C-15	64.18/	AB quartet	t	11.99
H-25(3H)	3.79-	C-25	64.68/	-	t	-
H-26(3H)	3.95	C-26	65.51	-	t	-
-	-	C-17	169.99	-	s	-
H-18(3H)	1.99	C-18	20.93	s	q	-
H-19(3H) H-2o(3H)	0.05	C-19 C-20	-5.63	s	q	-
H-21(3H) H-22(3H) H-23(3H)	0.90	C-21 C-22 C-23	25.89	s	q	-
-	-	C-24	29.69	-	s	-

ACETATE i.r. ($CHCl_3$): 3025, 2960, 2940, 1755, 1735, 1230, 1100 cm^{-1}

KETOL i.r. ($CHCl_3$): 3600, 3010, 2960, 2935, 1755, 1090, 850 cm^{-1}

M.S: 426.2428 (M^+); calc. for $C_{22}H_{38}O_6Si$: 426.2438 (KETOL)

(±)-3β-Hydroxy-8-oxo-15-(tert-butyldimethylsilyloxy)-trichothec-12-ene ethylene ketal (332).



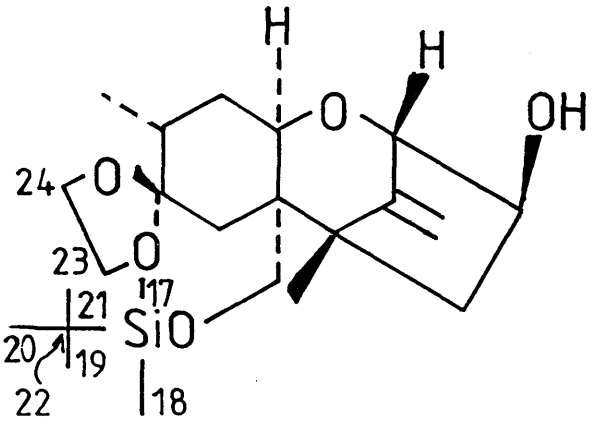
To a stirred solution of the ketol (306) (555 mg, 1.3 mmol) in dihydropyran (3 ml) was added a few crystals of PPTS. The mixture was stirred at room temperature overnight and then concentrated in vacuo. The residual oil was taken up in Et_2O and washed once with water. After drying and concentration, purification by dry column flash chromatography gave the THP ether (333) as a mixture of diastereoisomers.

To a suspension of methyltriphenylphosphonium bromide (2.8 g, 7.8 mmol) in dry THF (30 ml) in a r.b. flask fitted with side-arm and condenser was added, with stirring, and under N_2, a solution of n-BuLi (2.4M in hexane, 3.5 ml, 8.5 mmol). The reaction mixture was stirred until all the salt has dissolved, whereupon a solution of the ketone (333) in THF was added. The mixture was heated under reflux for 18 hours, then cooled, diluted with H_2O and extracted with Et_2O (3 x 25 ml). The combined ethereal extracts were washed with

1M HCl and brine, then dried and concentrated *in vacuo*. Purification by dry column flash chromatography gave the *olefin-ether* (334).

To a stirred solution of the olefin-ether (334) in CH_2Cl_2 (25 ml) was added ethylene glycol (1 ml) and a few crystals of PPTS. The mixture was heated under reflux for 18 hours, then concentrated *in vacuo*. Ether (40 ml) was added and the mixture washed once with water (15 ml). After drying and concentration, purification by dry column flash chromatography gave the *olefin-alcohol* (332) (337 mg, 61% yield overall) as an oil.

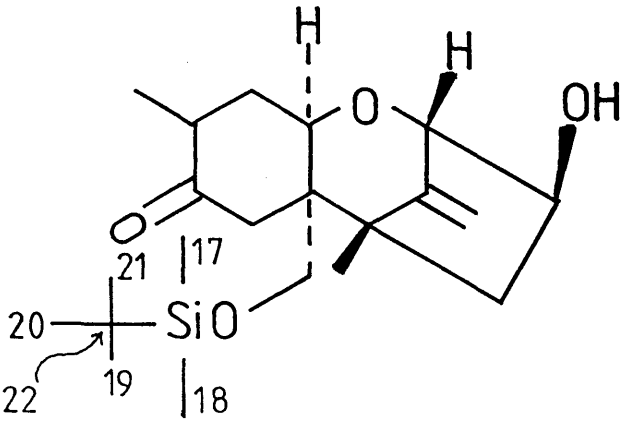
Using methanol as the hydroxylic exchange source resulted in non-selective deprotection giving rise to hydroxy-ketone (335).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	3.95	C-2	69.45	bs	d	-
H-3	4.26	C-3	84.67	dd	d	2.62, 7.33
H-4(2H)	1.52-1.67	C-4	45.25	m	t	-
-	-	C-5	48.80	-	s	-
-	-	C-6	46.44	-	s	-
H-7α	1.74	C-7	33.85/	d	t	14.16
H-7β	1.45			dd		1.15(w),14.19
H-10(2H)	1.52-1.67	C-10	34.12	m	t	-
-	-	C-8	111.04	-	s	-
H-9	1.93-2.13	C-9	32.68	m	d	-
H-11	3.37	C-11	71.80	dd	d	7.48, 14.46
-	-	C-12	153.23	-	s	-
H-13(2H)	4.81 + 5.12	C-13	106.87	2 x s	t	-
H-14(3H)	1.08	C-14	17.30	s	q	-
H-15(2H)	3.48 + 3.88	C-15	63.76/	AB quartet	t	11.24
H-23(2H)	3.7-	C-23	64.73/	m	t	-
H-24(2H)	4.0	C-24	65.36		t	-
H-17(3H)	0.04	C-17	Off Scale	s	-	-
H-18(3H)	0.04	C-18	Off Scale	s	-	-
H-19(3H) H-20(3H) H-21(3H)	0.89	C-19 C-20 C-21	25.94	s	q	-
-	-	C-22	18.13	-	s	-
H-16(3H)	0.79	C-16	13.23	d	q	6.68

i.r. ($CHCl_3$) : 3600, 2960, 2930, 1460, 1260, 1090, 1040, 855 cm^{-1}

M.S: 424.2637 (M^+); calc. for $C_{23}H_{40}O_5Si$: 424.2645

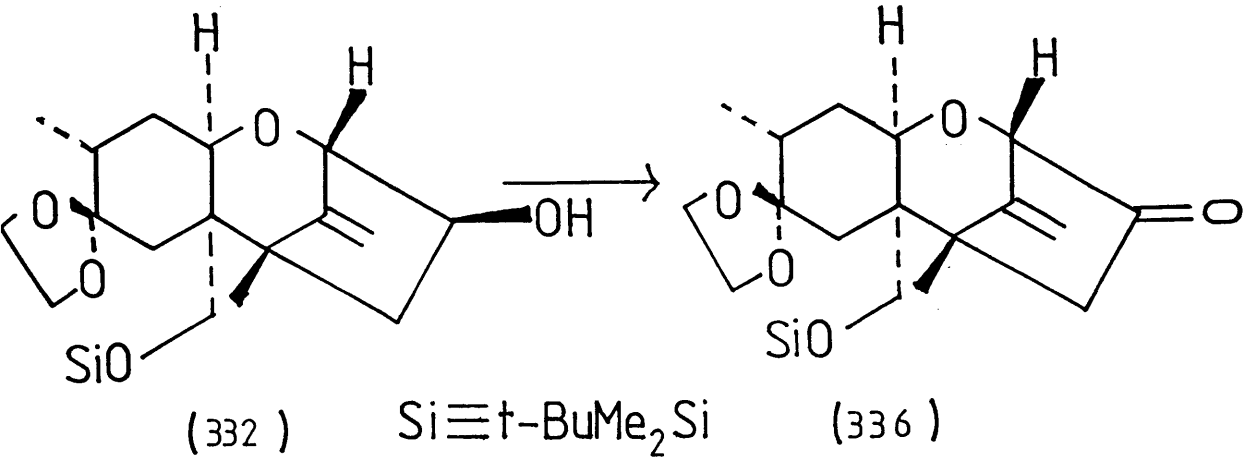


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	4.08	C-2	71.78	bs	d	-
H-3	4.38	C-3	84.78	dd	d	2.6, 7.36
H-4(2H)	1.75-2.20	C-4	42.50	-	t	-
-	-	C-5	50.75	-	s	-
-	-	C-6	48.04	-	s	-
H-7(2H)	2.50-2.80	C-7	45.09	-	t	-
-	-	C-8	212.49	-	s	-
H-9	2.50-2.80	C-9	38.09	-	d	-
H-10(2H)	1.75-2.20	C-10	36.94	-	t	-
H-11	3.17	C-11	70.42	dd	d	7.38, 14.49
-	-	C-12	152.87	-	s	-
H-13(2H)	4.87+ 5.21	C-13	107.44	2 x s	t	-
H-14(3H)	1.05	C-14	16.23	s	q	-
H-15(2H)	3.37 + 3.59	C-15	65.54	AB quartet	t	11.12
H-17(3H)	0.02/	C-17	-4.55	s	q	-
H-18(3H)	-0.01	C-18				
H-19(3H)	0.86	C-19	25.85	s	q	-
H-20(3H)		C-20				
H-21(3H)		C-21				
-	-	C-22	29.68	-	s	-
H-16(3H)	0.95	C-16	13.75	d	q	6.6

i.r. ($CHCl_3$) : 3600, 3020, 2960, 2930, 2860, 1710, 1260, 1090, 1040, 940 cm^{-1}

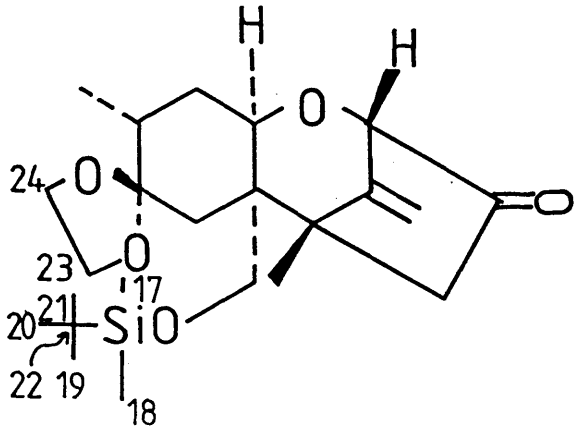
M.S: 323.1644 ($M^+ - {}^tBu$, 100%); calc. for $C_{17}H_{27}O_4Si$: 323.1678

(±)-3-Oxo-8-(oxo-ethylene ketal)-15-(tert-butyldimethylsilyloxy)-trichothec-12-ene (336)



(332) Si≡t-BuMe$_2$Si (336)

To a suspension of CrO_3 (240 mg, 2.4 mmol) in CH_2Cl_2 (15 ml) at room temperature and under N_2 was added 3,5-dimethylpyrazole (230 mg, 2.4 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 30 minutes during which time the solution became homogeneous and deep red in colour. The olefin-alcohol (332) (337 mg, 0.8 mmol) in CH_2Cl_2 (5 ml) was added in one portion and stirring was continued for 1 hour. The mixture was concentrated in vacuo and the residue taken up in Et_2O. The ethereal solution was filtered through Celite and concentrated under reduced pressure. The residual oil was diluted with pentane and refiltered through Celite. After concentration, purification by dry column flash chromatography gave the ketone (336) (274 mg, 81%) as an oil.

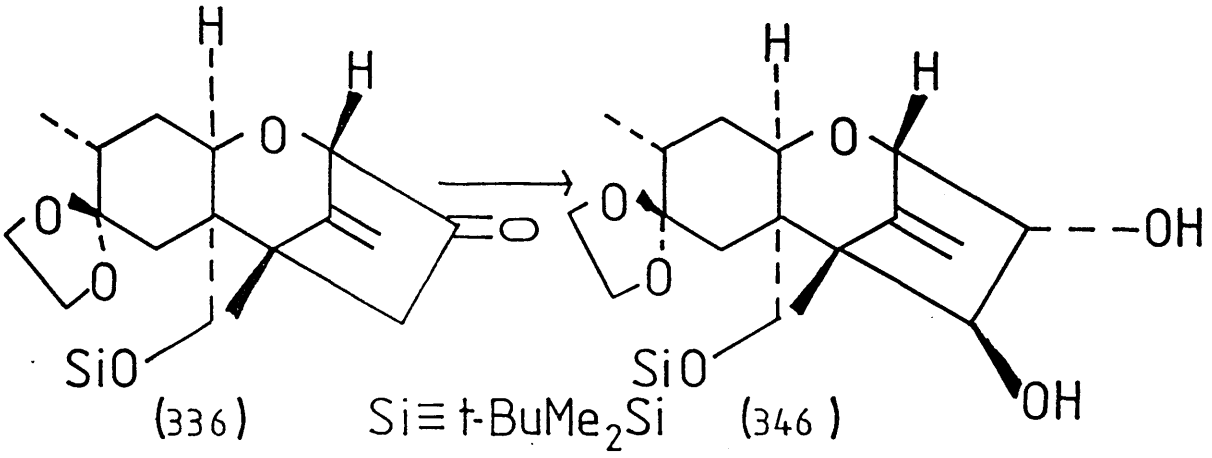


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	3.88	C-2	80.52	bs	d	-
-	-	C-3	214.31	-	s	-
H-4(2H)	1.70-2.00	C-4	50.69	-	t	-
-	-	C-5	47.49/	-	s	-
-	-	C-6	48.62	-	s	-
H-7(2H)	1.38-	C-7	33.91/	m	t	-
H-10(2H)	1.75	C-10	34.78		t	-
-	-	C-8	110.75	-	s	-
H-9	1.95-2.25	C-9	32.56	m	d	-
H-11	-	C-11	70.33	-	d	-
-	-	C-12	151.97	-	s	-
H-13(2H)	4.99+5.20	C-13	109.31	2 x s	t	-
H-14(3H)	1.19	C-14	16.79	s	q	-
H-15(2H)	3.57 + 4.09	C-15	64.32/	AB quartet	t	11.64
H-23(2H)	3.80-	C-23	64.81/	-	t	-
H-24(2H)	4.0	C-24	65.45	-	t	-
H-17(3H)	0.43	C-17	Off	s	-	-
H-18(3H)		C-18	Scale		-	-
H-19(3H) H-20(3H) H-21(3H)	0.87	C-19 C-20 C-21	25.91	s	q	-
-	-	C-22	18.12	-	s	-
H-16(3H)	0.80	C-16	13.14	d	q	6.67

i.r. (CCl_4): 2970, 2940, 2860, 1760, 1615, 1260, 1090 cm^{-1}

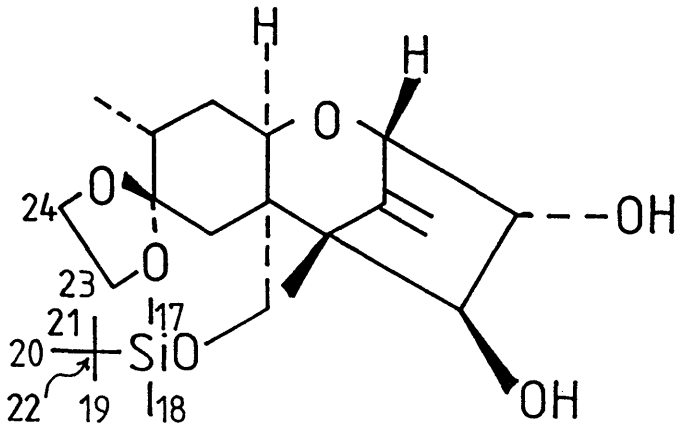
M.S: 422.2488 (M^+); calc. for $C_{23}H_{38}O_5Si$: 422.2488

(±)-3α,4β-Dihydroxy-8-oxo-15-(tert-butyldimethylsilyloxy)-trichothec-12-ene ethylene ketal (346).



(336) Si≡ t-BuMe$_2$Si (346)

To a stirred solution of KHMDS (0.75M in toluene, 440 µl, 0.33 mmol) in THF (5 ml) at 0°C and under N_2 was added the ketone (336) (93 mg, 0.22 mmol) in THF (5 ml). Stirring was continued for 1 hour at this temperature during which time the solution turned yellow. The mixture was cooled to -78°C and the oxaziridine[158] (344) (106 mg, 0.33 mmol) in THF (5 ml) was added in one portion. This solution was kept at -78°C for 2 hours before being allowed to warm to room temperature overnight. The mixture was diluted with Et_2O (20 ml) and washed with H_2O (2 x 10 ml). After drying and concentration, the crude product was dissolved in a mixture of MeOH (10 ml) and H_2O (1 ml). This solution was cooled to 0°C and excess $NaBH_4$ was added. After stirring for 30 minutes, the solution was concentrated in vacuo and H_2O added. Once the effervescence had subsided, solid NaCl was added and the mixture was thoroughly extracted with EtOAc. After drying and concentration, purification by dry column flash chromatography gave the diol (346) (37 mg, 37%, unoptimised) as a solid. No attempt was made at recrystallisation due to the small quantity of material being fully required for the subsequent steps.

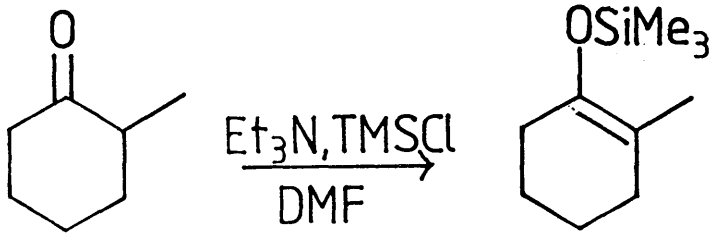


PROTON NUMBER	δPPM ^1H	CARBON NUMBER	δPPM ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
H-2	-	C-2	79.56/	-	d	-
H-3	3.76	C-3	80.70/	dd	d	2.69,4.74
H-4	4.96	C-4	80.86	d	d	2.71
-	-	C-5	53.02	-	s	-
-	-	C-6	47.20	-	s	-
H-7(2H)	1.15-	C-7	33.78/	-	t	-
H-10(2H)	1.90	C-10	34.46	-	t	-
-	-	C-8	110.86	-	s	-
H-9	2.0-2.2	C-9	32.89	m	d	-
H-11	4.20	C-11	69.27	dd	d	1.66,5.75
-	-	C-12	150.99	-	s	-
H-13(2H)	4.73+ 5.13	C-13	108.46	2 x s	t	-
H-14(3H)	0.98	C-14	10.81/	s	q	-
H-16(3H)	0.81	C-16	13.20	d	q	6.69
H-15(2H)	3.5-	C-15	64.31/	-	t	-
H-23(2H)	4.15	C-23	64.77/	-	t	-
H-24(2H)		C-24	65.42	-	t	-
H-17(3H)	0.06	C-17	OFF	s	-	-
H-18(3H)		C-18	SCALE		-	
H-19(3H)	0.90	C-19	25.92	s	q	-
H-20(3H)		C-20				
H-21(3H)		C-21				
-	-	C-22	18.12	-	s	-

i.r (CCl_4) : 3630, 3450, 2960, 2940, 1465, 1100 cm^{-1}

M.S : 440.2605 (M^+); calc. for $C_{23}H_{40}O_6Si$: 440.2594

1-Trimethylsiloxy-2-methylcyclohex-1-ene (377).

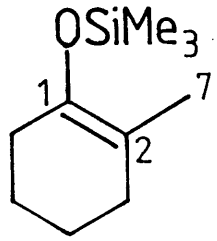


(368) (377)

A mixture of 2-methylcyclohexanone (368) (28 g, 30.3 ml, 250 mmol), trimethylsilyl chloride (32.6 g, 38.1 ml, 300 mmol) and triethylamine (60.7 g, 83.6 ml, 600 mmol) in dry DMF (90 ml) was heated under reflux in a N_2 atmosphere for 48 hours.

After cooling, the reaction mixture was diluted with pentane (200 ml) and washed sequentially with saturated aqueous $NaHCO_3$ solution (3 x 300 ml), cold aqueous HCl (1M, 1 x 50 ml) and saturated aqueous $NaHCO_3$ solution (1 x 50 ml).

After drying and concentration, distillation of the crude residue gave the silyl enol ether (377) (38.4 g, 83%) as a clear oil, b.p. 68-70°C/10 mm Hg, lit.[154] 82-84°C/16 mmHg.

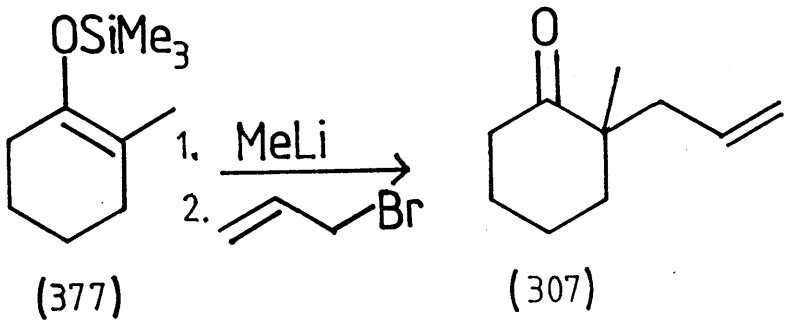


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	142.87	-	s	-
-	-	C-2	111.74	-	s	-
H-3(2H)	1.87-	C-3	30.17/	m	t	-
H-6(2H)	2.06	C-6	30.27		t	
H-4(2H)	1.43-	C-4	23.03/	m	t	-
H-5(2H)	1.70	C-5	23.79		t	
H-7(3H)	1.53	C-7	16.30	-	q	-
Me_3Si	0.14	Me_3Si	0.65	s	q	-

i.r. ($CHCl_3$) : 2940, 2860, 1687, 1255, 1180, 1170 cm^{-1}

M.S: 184.1269 (M^+); calc. for $C_{10}H_{20}OSi$: 184.1283

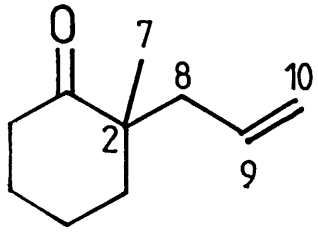
(±)-2-Allyl-2-methylcyclohexanone (307)



(377) (307)

To the silyl enol ether (377) (25 g, 136 mmol) in a r.b. flask equipped with side-arm and condenser was added MeLi (1.5M in Et_2O, 100 ml, 150 mmol)[87] at room temperature and under N_2. The reaction mixture was stirred for 30 minutes, then the solvent was carefully removed *in vacuo*. A sealed N_2 atmosphere was re-established and dry THF (100 ml) added. Allyl bromide (18.2 g, 13 ml, 150 mmol) was then added in one portion *via syringe* and the reaction mixture was stirred at room temperature for 1 hour. Pentane (250 ml) was added to the reaction mixture which was transferred to a separating funnel before being washed with saturated aqueous $NaHCO_3$ solution.

After drying and concentration, distillation of the crude residue gave the *allyl ketone* (307) (17.9 g, 87%) as a colourless oil, b.p. 80-85°C/18 mmHg.

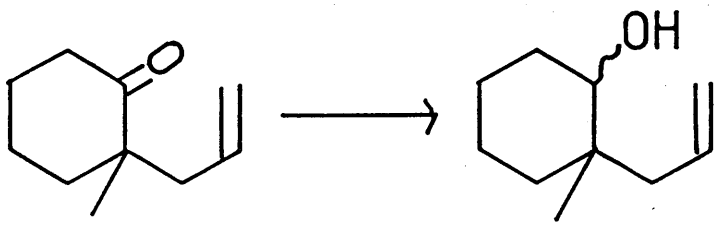


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	214.88	-	s	-
-	-	C-2	48.20	-	s	-
H-3(2H)	1.4-1.9	C-3	38.43	-	t	-
H-4(2H)		C-4	20.89	-	t	-
H-5(2H)		C-5	27.19	-	t	-
H-6(2H)	2.0-2.6	C-6	41.80	-	t	-
H-8(2H)		C-8	38.57	-	t	-
H-7(3H)	1.00	C-7	22.46	s	q	-
H-9	5.4-5.9	C-9	133.66	m	d	-
H-10(2H)	4.83-5.05	C-10	117.64	m	t	-

i.r. ($CHCl_3$) : 2940, 2860, 1700, 1440 cm^{-1}

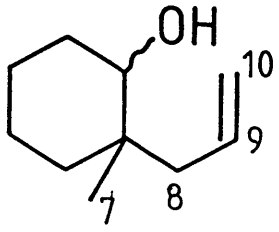
M.S : 152.1190 (M^+); calc. for $C_{10}H_{16}O$: 152.1201

(±)-2-Allyl-2-methylcyclohexanol (359)



(307) (359)

To a suspension of $LiAlH_4$ (1 g, 26.4 mmol) in dry Et_2O (50 ml) at 0°C was added the allyl ketone (307) (4 g, 26.4 mmol) in dry Et_2O (5 ml). Stirring was continued at room temperature overnight. The reaction mixture was decomposed by the dropwise addition of saturated aqueous Na_2SO_4 solution followed by the addition of excess anhydrous Na_2SO_4. The white granular suspension was removed by filtration through Celite. After drying and concentration, distillation of the crude residue gave the alcohol (359) (3.93 g, 97%) as a clear oil, b.p. 130-135°C/18 mmHg.

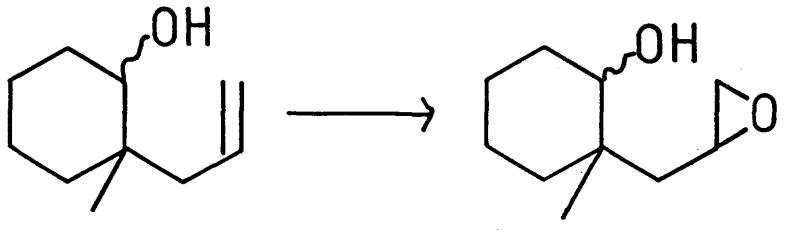


PROTON NUMBER	δPPM ^1H	MULTIPLICITY ^1H
H-1	3.32-3.50	m
H-3(2H) H-4(2H) H-5(2H) H-6(2H)	1.0-1.80	-
H-7(3H)	0.85+0.90	2 x s
H-8(2H)	2.0-2.20	-
H-9	5.50-6.10	m
H-10(2H)	4.90-5.20	m

i.r. ($CHCl_3$): 3600, 3000, 2920, 2860, 1660, 1440, 1035, 900 cm^{-1}

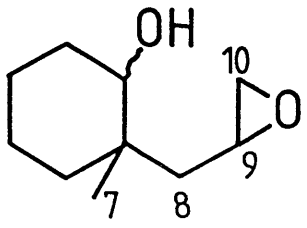
M.S : 153.1270 (M^+-H); calc. for $C_{10}H_{17}O$: 153.1279

(±)-2-Methyl-2-(2',3'-epoxypropyl)cyclohexan-1-ol (360)



(359) (360)

To the allyl alcohol (359) (3.58 g, 23.3 mmol) dissolved in dry CH_2Cl_2 (50 ml) was added m-CPBA (6.6 g, 35 mmol) and Na_2HPO_4 (5 g, 35 mmol). The reaction mixture was stirred at 0°C for 1 hour, then left to warm to room temperature overnight. The mixture was filtered, poured into H_2O (25 ml) and extracted with Et_2O (3 x 50 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 ml). After drying and concentration, distillation of the crude residue gave the epoxy-alcohol (360) (2.51 g, 64%) as a colourless oil, b.p. 132-135°C/18 mmHg.

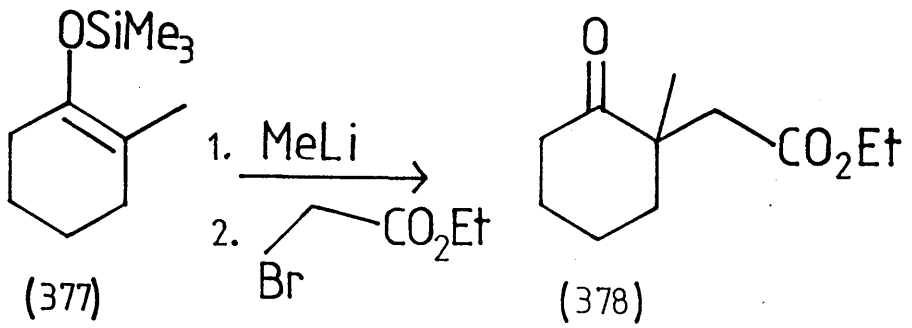


PROTON NUMBER	δPPM ^1H	MULTIPLICITY ^1H
H-1	3.0 - 3.3	m
H-3(2H) H-4(2H) H-5(2H) H-6(2H)	1.2 - 1.8	-
H-7(3H)	0.82,0.87 0.97, 1.0	4 x s
H-8(2H)	1.2 - 1.8	-
H-9	3.9 - 4.3	m
H-10(2H)	3.45 - 3.75	m

i.r. ($CHCl_3$) : 3600, 3400, 2920, 1450, 1020 cm^{-1}

M.S : 170.1303 (M^+); calc. for $C_{10}H_{18}O_2$: 170.1306

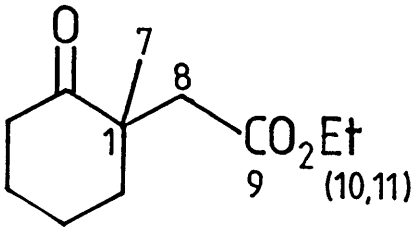
(±)-Ethyl 1-methyl-2-oxo-cyclohexaneacetate (378)



(377) (378)

To the silyl enol ether (377) (5 g, 27.2 mmol) in a r.b. flask fitted with side-arm and condenser was added MeLi (1.5M in Et_2O, 19.9 ml, 29.9 mmol) at room temperature and under N_2. The reaction mixture was stirred for 30 minutes, then the solvent was carefully removed in vacuo. A sealed N_2 atmosphere was re-established and dry THF (20 ml) added. Ethyl bromoacetate (4.99 g, 3.31 ml, 29.9 mmol) was then added in one portion via syringe and the reaction mixture stirred at room temperature for 1 hour. Pentane (100 ml) was added to the reaction mixture which was transferred to a separating funnel before being washed with saturated aqueous $NaHCO_3$ solution.

After drying and concentration, distillation of the crude residue gave the keto-ester (378) (5.22 g, 97%) as a clear oil, b.p. 150-155°C/18 mmHg.



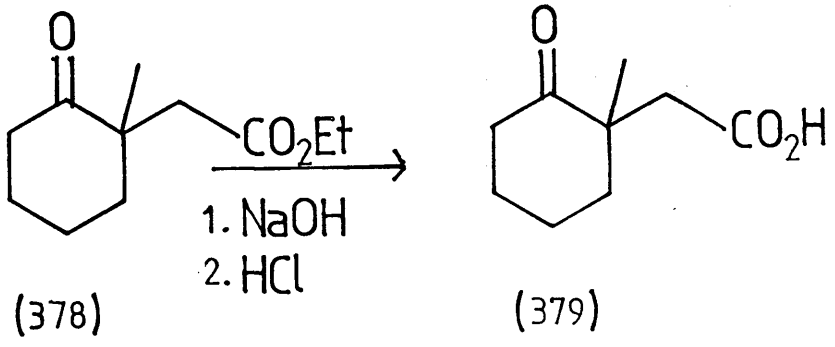
PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	46.56	-	s	-
-	-	C-2	212.93	-	s	-
H-3(2H)	1.1 - 1.9	C-3	42.04	-	t	-
H-4(2H)		C-4	26.31	-	t	-
H-5(2H)		C-5	20.69	-	t	-
H-6(2H)		C-6	37.81	-	t	-
H-7(3H)	0.97	C-7	22.92	s	q	-
H-8(2H)	2.25 + 2.37	C-8	37.81	AB quartet	t	13.4
-	-	C-9	170.91	-	s	-
H-10(2H)	3.86	C-10	59.59	q	t	7.1
H-11(3H)	1.00	C-11	13.62	t	q	7.1

i.r. (CCl_4) : 2980, 2940, 1740, 1715, 1190 cm^{-1}

M.S : 198.1260 (M^+); calc. for $C_{11}H_{18}O_3$: 198.1256

(±)-1-Methyl-2-oxo-cyclohexaneacetic acid (379)

METHOD 1.

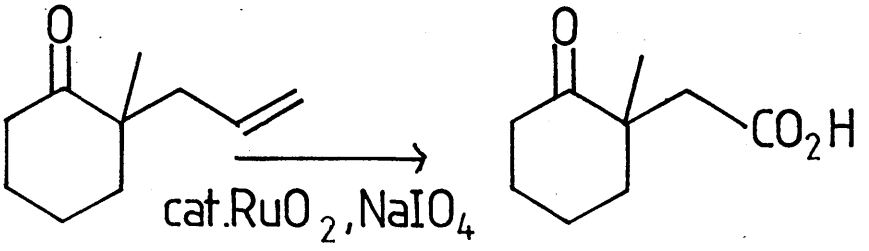


(378) (379)

To a stirred solution of the keto-ester (378) (655 mg, 3.3 mmol) in MeOH (7 ml) was added a solution of sodium hydroxide (277 mg, 6.9 mmol in 15 ml H_2O) and stirring was continued for 18 hours at room temperature.

The reaction mixture was concentrated in vacuo then extracted with $CHCl_3$ (30 ml) to remove the neutrals. The aqueous layer was acidified with 1M HCl and extracted thoroughly with $CHCl_3$ (3 x 25 ml). These combined organic layers were dried and the solvent was removed in vacuo. Recrystallisation of the crude residue gave the keto-acid (379) (477 mg, 85%), m.p. 70-72°C (from CCl_4/petroleum ether).

METHOD 2.

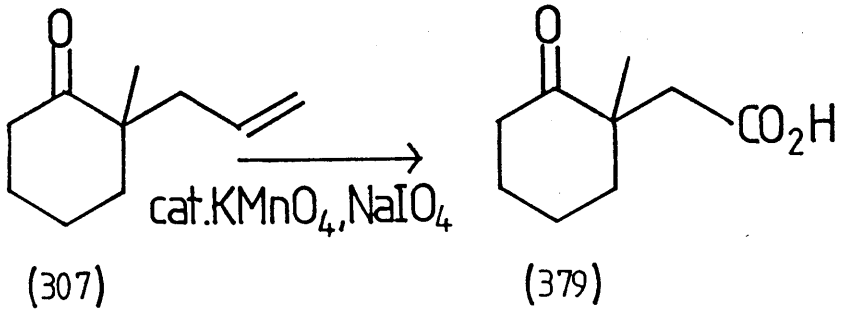


(307) (379)

A mixture of the allyl ketone (307) (500 mg, 3.25 mmol), sodium metaperiodate (2.8 g, 13.3 mmol) and ruthenium(IV) oxide (87 mg, 0.65 mmol) was stirred in a mixture of CCl_4 (2 ml), H_2O (3 ml) and CH_3CN (2 ml) for 18 hours.

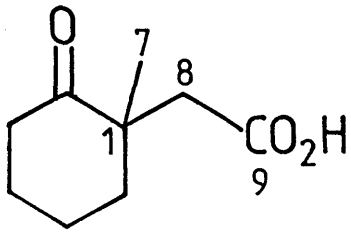
The reaction mixture was acidified with 1M HCl, diluted with EtOAc (30 ml) and filtered through Celite. Solid NaCl was added to the aqueous layer which was extracted thoroughly with EtOAc (3 x 25 ml). The combined organic layers were extracted with 1M NaOH. This basic extract was acidified with 1M HCl, solid NaCl was added, and the aqueous layer extracted with EtOAc (3 x 25 ml). The combined organic layers were dried and the solvent removed in vacuo. Recrystallisation of the crude residue gave the keto-acid (379) (402 mg, 73%).

METHOD 3.



(307) (379)

The allyl ketone (307) (200 mg, 1.3 mmol) was stirred with $NaIO_4$ (1.1 g, 5.2 mmol) and a few crystals of $KMnO_4$ in a mixture of ^tBuOH (10 ml), H_2O (10 ml) and 5% aqueous K_2CO_3 solution (5 ml) for 4 hours at room temperature. The reaction mixture was extracted with 1M NaOH and the basic extract washed with EtOAc. This basic extract was acidified with 1M HCl and solid NaCl added. Thorough extraction of the aqueous layer with EtOAc (3 x 40 ml) was followed by drying and concentration of the combined organic layers. The crude residue so obtained was recrystallised to give the keto-acid (379) (131 mg, 59%).



PROTON NUMBER	δPPM ^1H
-	-
-	-
H-3(2H) H-4(2H) H-5(2H) H-6(2H)	1.2 - 2.0
H-7(3H)	0.98
H-8(2H)	1.2 - 2.0

^{13}C n.m.r spectrum indecipherable due to acid-pseudo acid interconversion.

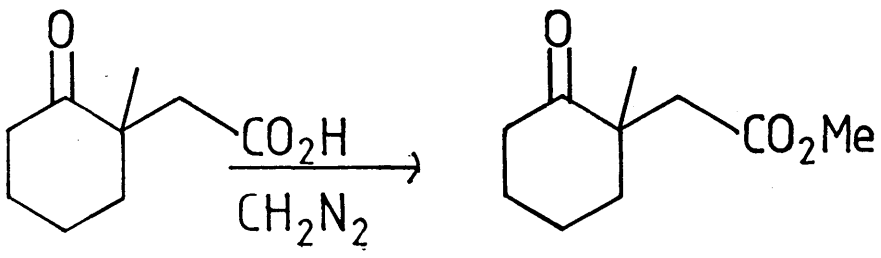
i.r. ($CHCl_3$): 3575, 3000, 2920, 1780, 1760, 1690, 1220, 1070 cm^{-1}

M.S : 170.0945 (M^+); calc. for $C_9H_{14}O_3$: 170.0943.

$C_9H_{14}O_3$ requires C, 63.53; H, 8.24%

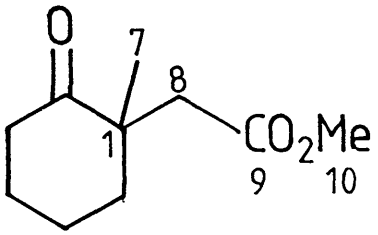
Found: C, 63.42; H, 8.27%

(±)-Methyl 1-methyl-2-oxo-cyclohexaneacetate (381)



(379) (381)

To a solution of the keto-acid (379) (98 mg, 0.58 mmol) in Et_2O (10 ml) was added an excess of an ethereal solution of CH_2N_2 (ex DIAZALD). The reaction mixture was allowed to stir for 18 hours during which the excess CH_2N_2 polymerised. The ethereal solution was filtered through Celite and the solvent removed in vacuo. Purification of the residue by dry column flash chromatography gave the keto-ester (381) (99 mg, 93%) as a colourless oil.

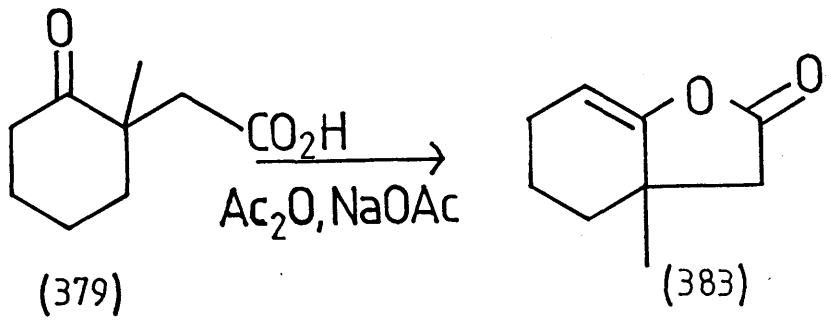


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	47.13	-	s	-
-	-	C-2	213.76	-	s	-
H-3(2H)	2.15-2.65	C-3	42.41	-	t	-
H-4(2H)	1.38-2.15	C-4	26.80	-	t	-
H-5(2H)		C-5	21.22	-	t	-
H-6(2H)		C-6	38.34	-	t	-
H-7(3H)	1.06	C-7	23.49	s	q	-
H-8(2H)	2.15-2.65	C-8	38.34	-	t	-
-	-	C-9	172.10	-	s	-
H-10(3H)	3.52	C-10	51.37	s	q	-

i.r. ($CHCl_3$) : 3030, 2950, 2870, 1730, 1705, 1220 cm^{-1}

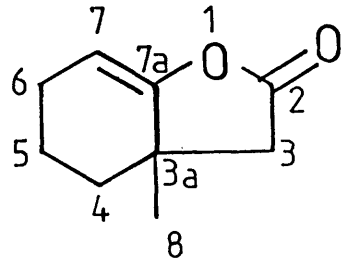
M.S: 184.1098 (M^+); calc. for $C_{10}H_{16}O_3$: 184.1099

(±)-2,3,3a,4,5,6-Hexahydro-3a-methyl-2H-1-benzofuran-2-one (383)



(379) (383)

To a solution of the keto-acid (379) (3.39 g, 20 mmol) in Ac_2O (35 ml) was added freshly fused sodium acetate (164 mg, 2 mmol) and the reaction mixture was heated under reflux for 18 hours. The acetic anhydride was removed by repeated azeotropic distillation with toluene and the residual oil taken up in Et_2O. The ethereal solution was transferred to a separating funnel and washed sequentially with saturated aqueous $NaHCO_3$ solution and brine. After drying and concentration, purification of the crude residue by dry column flash chromatography gave the enol-lactone (383) (2.05g, 67%) as a colourless oil.

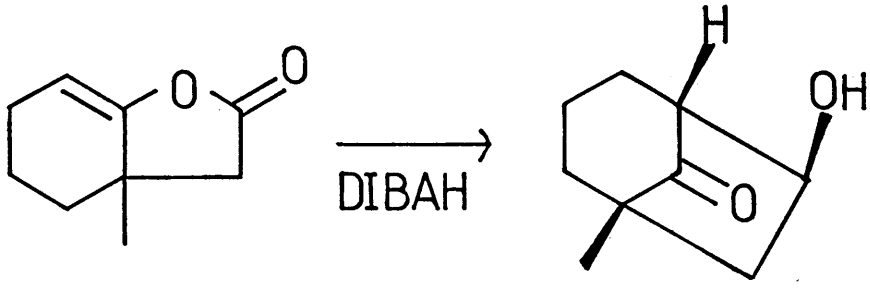


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	173.90	-	s	-
H-3(2H)	2.40	C-3	44.37	s	t	-
-	-	C-3a	38.46	-	s	-
H-4(2H)	1.4-	C-4	22.62	-	t	-
H-5(2H)	1.95	C-5	18.28	-	t	-
H-6(2H)	2.0-2.3	C-6	34.22	-	t	-
H-7	5.17	C-7	100.84	t	d	4.5
-	-	C-7a	155.12	-	s	-
H-8(3H)	1,22	C-8	24.50	s	q	-

i.r. ($CHCl_3$) : 3010, 2930, 2850, 1790, 1740, 1700, 1230, 1080, 900 cm^{-1}

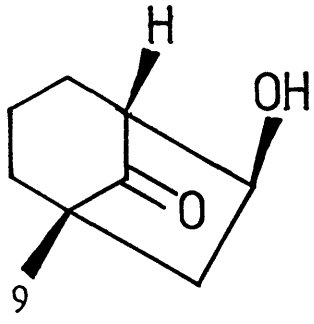
M.S: 152.0838 (M^+); calc. for $C_9H_{12}O_2$: 152.0837

(±)-6β-Hydroxy-1-methylbicyclo[3.2.1]octan-8-one (384).



(383) (384)

To the enol lactone (383) (500 mg, 3.29 mmol) in dry Et_2O (30 ml) at -25°C and under N_2 was added DIBAH (1M in CH_2Cl_2, 3.62 ml, 3.62 mmol) and the reaction mixture allowed to warm to room temperature over 18 hours. Saturated Na_2SO_4 solution was added to the stirred reaction mixture until it coagulated. At this point Et_2O and anhydrous Na_2SO_4 were added. The reaction mixture was filtered through a pad of Celite and the solvent removed in vacuo. Purification of the crude residue by dry column flash chromatography gave the ketol (384) (177 mg, 35%) as a white crystalline solid, m.p. 69-71°C (Et_2O/petroleum ether).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	47.92	-	s	-
H-2(2H)	1.5-2.2	C-2	34.06	-	t	-
H-3(2H)		C-3	19.05	-	t	-
H-4(2H)		C-4	43.74/	-	t	-
H-7α		C-7	43.87		t	
H-7β	2.50			dd		2.3, 7.5
H-5	2.3	C-5	55.73	m	d	-
H-6	4.25	C-6	69.05	dd	d	2.25, 9
-	-	C-8	222.38	-	s	-
H-9(3H)	1.05	C-9	19.22	s	q	-

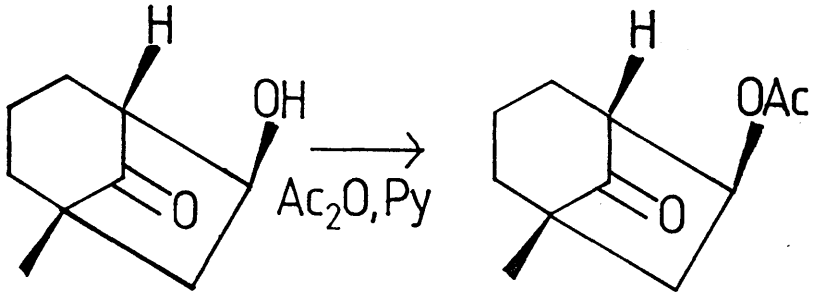
i.r. ($CHCl_3$) : 3600, 3010, 2920, 1735, 1220, 790 cm^{-1}

M.S: 154.0982 (M^+); calc. for $C_9H_{14}O_2$: 154.0994.

$C_9H_{14}O_2$ requires C, 70.11; H, 9.14%

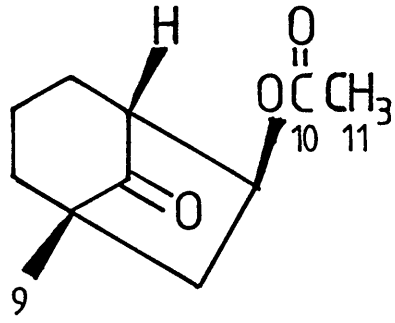
Found: C, 70.12; H, 9.07%

(±)-1-Methyl-8-oxobicyclo[3.2.1]octan-6β-yl Acetate (385)



(384) (385)

To a solution of the ketol (227 mg, 1.47 mmol) in Et_2O (3 ml) was added a preformed mixture of Ac_2O (2 ml) and pyridine (1 ml). The reaction mixture was stirred at room temperature overnight then concentrated in vacuo using toluene to azeotropically remove the excess pyridine and acetic anhydride. Purification by dry column flash chromatography gave the keto-acetate (385) (251 mg, 87%) as a colourless oil.

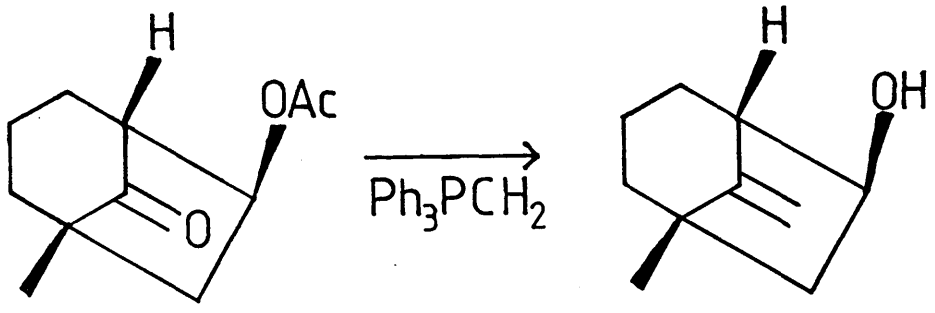


PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	47.63	-	s	-
H-2(2H)	1.5-	C-2	19.07	m	t	-
H-3(2H)	1.9	C-3			t	-
H-4(2H)		C-4	40.00	m	t	-
H-5	2.5	C-5	52.34	m	d	-
H-6	5.10	C-6	71.71	dd	d	3,8
H-7(2H)	1.5-1.9+ 2,4-2.7	C-7	43.85	m	t	-
-	-	C-8	219.99	-	s	-
H-9(3H)	1.06	C-9	21.11	s	q	-
-	-	C-10	170.45	-	s	-
H-11(3H)	2.00	C-11	40.82	s	q	-

i.r. ($CHCl_3$) : 3020, 2940, 2860, 1740, 1720, 1380, 1250 cm^{-1}

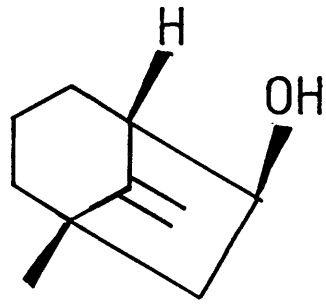
M.S: 196.1094 (M^+); calc. for $C_{11}H_{16}O_3$: 196.1099

(±)-1-Methyl-8-methylenebicyclo[3.2.1]octan-6β-ol (386)



(385) (386)

To a suspension of methyl triphenylphosphonium bromide (2.27 g, 6.38 mmol) in THF (35 ml) in a r.b. flask fitted with side-arm and condenser was added with stirring and under N_2, a solution of n-BuLi (2.4M in hexane, 2.92 ml, 7 mmol). The reaction mixture was stirred until all the salt had dissolved whereupon a solution of the keto-acetate (385) (500 mg, 2.55 mmol) in THF was added. The mixture was heated under reflux for 2 hours, then cooled, diluted with H_2O and extracted with Et_2O (3 x 25 ml). The combined ethereal extracts were washed with dilute HCl and brine then dried and concentrated in vacuo. Purification by dry column flash chromatography gave the olefin-alcohol (386) (174 mg, 45%) as a white crystalline solid, m.p. 70-72°C (petroleum ether).



PROTON NUMBER	δppm ^1H	CARBON NUMBER	δppm ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-1	43.8	-	s	-
H-2(2H)	1.3-	C-2	41.9		t	
H-3(2H)	1.8	C-3	20.1	-	t	-
H-4(2H)		C-4	32.7	-	t	-
H-5	2.4	C-5	53.5	m	d	-
H-6	4.05	C-6	73.7	d	d	4,8
H-7(2H)	1.3-1.8 2.4-2.7	C-7	48.5	m	t	-
-	-	C-8	161.4	-	s	-
H-9(2H)	4.68 + 4.75	C-9	99.6	2 x s	t	-
H-10(3H)	1.08	C-10	23.0	s	q	-

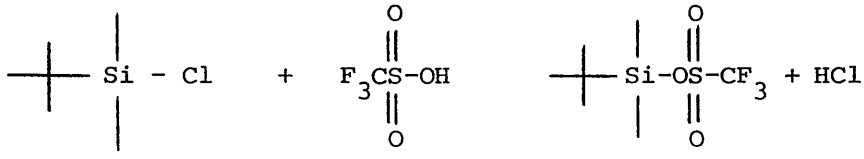
i.r. (CCl_4): 3610, 3580, 3070, 2980, 2930, 2870, 2860, 1665, 1465, 1450, 1445, 1390, 1370, 1120, 1020, 960, 930, 915, 885 cm^{-1}

M.S : 152.1197 (M^+); calc. for $C_{10}H_{16}O$: 152.1201

$C_{10}H_{16}O$ requires C, 78.90; H, 10.59%

Found: C, 78.75; H, 10.65%

Preparation of Tert-butyldimethylsilyltrifluoromethane sulphonate[117]



Trifluoromethanesulphonic acid (2.65 ml, 30 mmol) was added dropwise to tert-butyldimethylsilyl chloride (4.5 g, 30 mmol) in a r.b. flask fitted with a condenser and under N_2. The resulting mixture was heated at 60°C for 18 hours. The liquid so obtained was distilled directly from the reaction flask by means of bulb-to-bulb Kugelrohr distillation apparatus to give tert-butyldimethylsilyl trifluoromethanesulphonate (7.18 g, 27 mmol, 90%), b.p. 135°C/20 mmHg.

Purification of cuprous iodide[157]

To 260 g KI dissolved in 200 ml H_2O was added 26 g of impure CuI. The solution became yellow-orange in colour. To this was added 2 g of partially ground animal charcoal, the solution vigorously shaken and the whole mixture was filtered through a pad of Celite.

The orange aqueous solution was added to a large excess of H_2O, precipitating the cuprous iodide as very fine off-white particles. The solid particles were removed by filtration, washed firstly with water, then with methanol and finally with pentane. The cuprous iodide so obtained was oven dried and stored in a desiccator (21.48 g).

Preparation of MoO_5.py.HMPA[111]

A 500 ml 3-necked flask was charged with MoO_3 (30 g, 208 mmol) and 30% H_2O_2 solution (150 ml). The mixture was stirred vigorously with a paddle stirrer and the internal temperature was monitored throughout. An oil bath preheated to 40°C was used to heat the mixture until a mild exothermic reaction was observed. As soon as the internal temperature reached 35°C the heating bath was removed and the reaction temperature was maintained between 35° and 40°C by cooling with a water bath as necessary. After the initial exothermic period, the mixture was heated at 40°C for a total of 3.5h with stirring throughout. Failure to maintain internal temperature control results in formation of amorphous side products.

After cooling to 20°C, the reaction mixture was filtered to remove solids and the yellow solution was cooled to 10°C. Hexamethyl phosphoramide (36.2 ml, 37.3 g, 208 mmol) was added with stirring and the crystalline precipitate was collected on a Buchner funnel. Recrystallisation from methanol (70 ml, maximum temperature 40°C) gave MoO_5.HMPA as yellow needles. The yellow crystals were pumped dry on an oil pump over P_2O_5 for several days (until no change in weight).

A solution of MoO_5.HMPA (48 g, 135 mmol) in 120 ml dry THF was stirred magnetically and cooled with a waterbath while pyridine (10.7 g, 11 ml, 135 mmol) was added dropwise. The yellow crystalline precipitate was collected, washed with a small amount of THF (10 ml), and anhydrous Et_2O (100 ml) and dried under vacuum to

give MoO_5.Py.HMPA as finely divided, free flowing crystalline material. The MoOPH (50.32 g, 116 mmol, 56%) so obtained was placed in a dark glass bottle and stored in a larger container over silica gel in the refrigerator.

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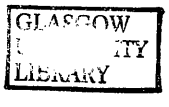
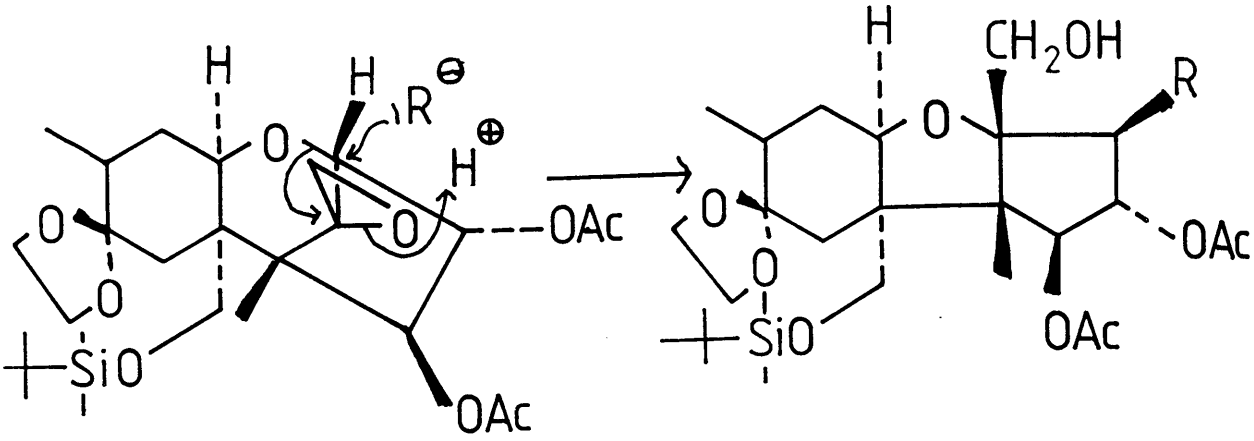
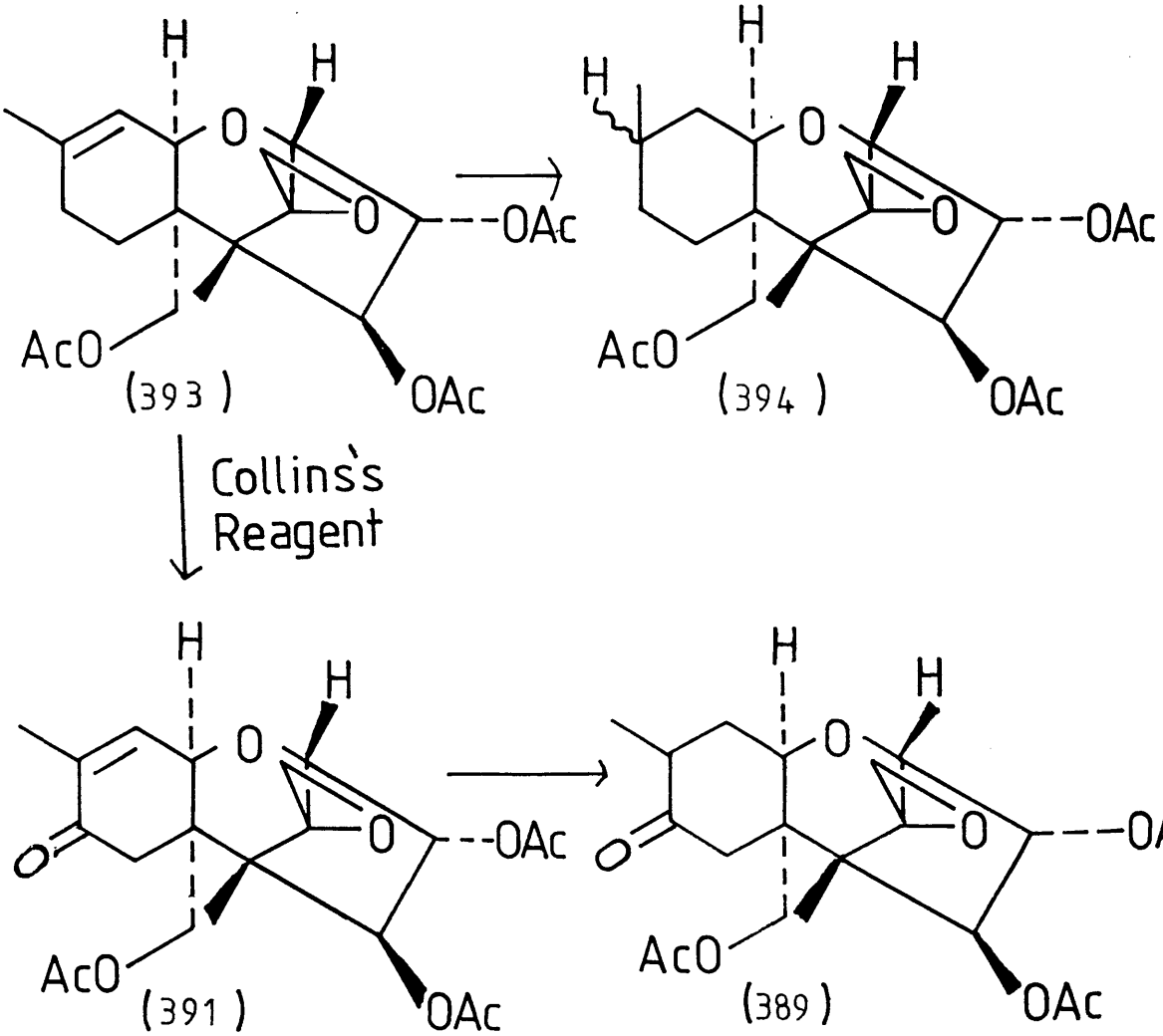
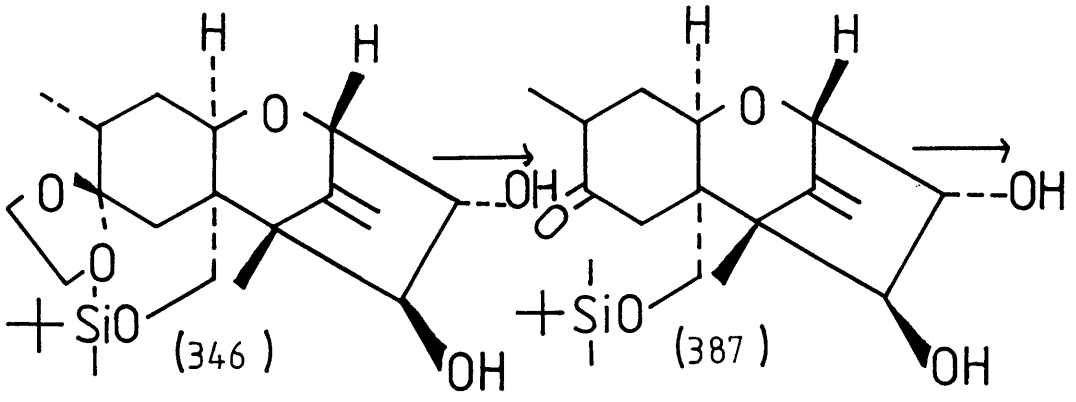


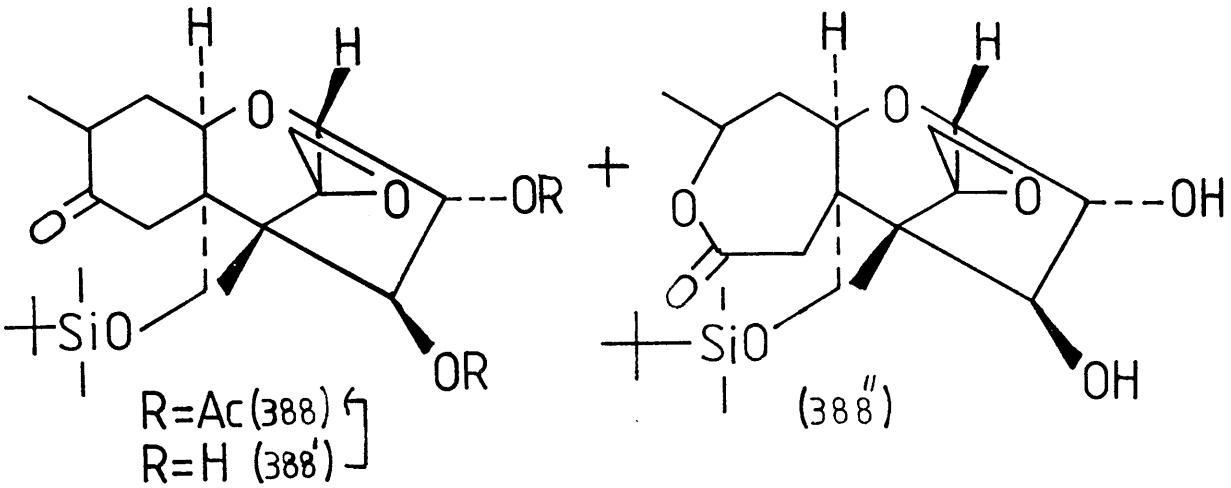


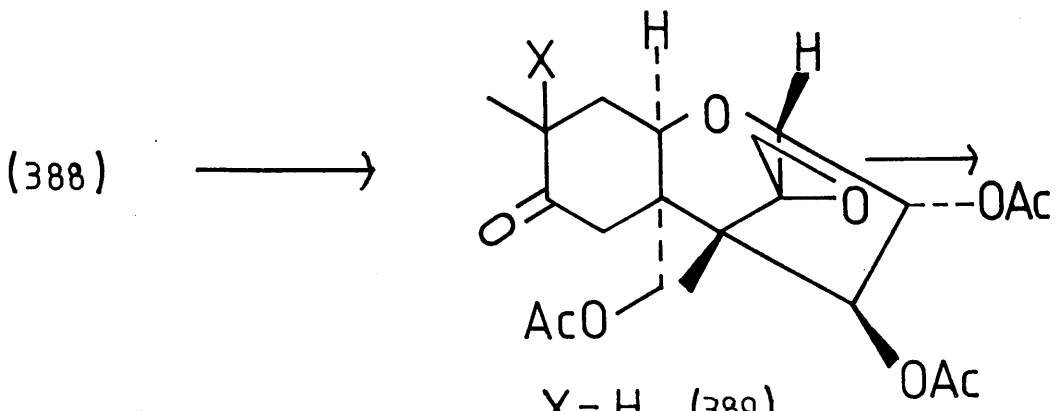
Scheme (21)
Trichothecene - Apotrichothecene rearrangement

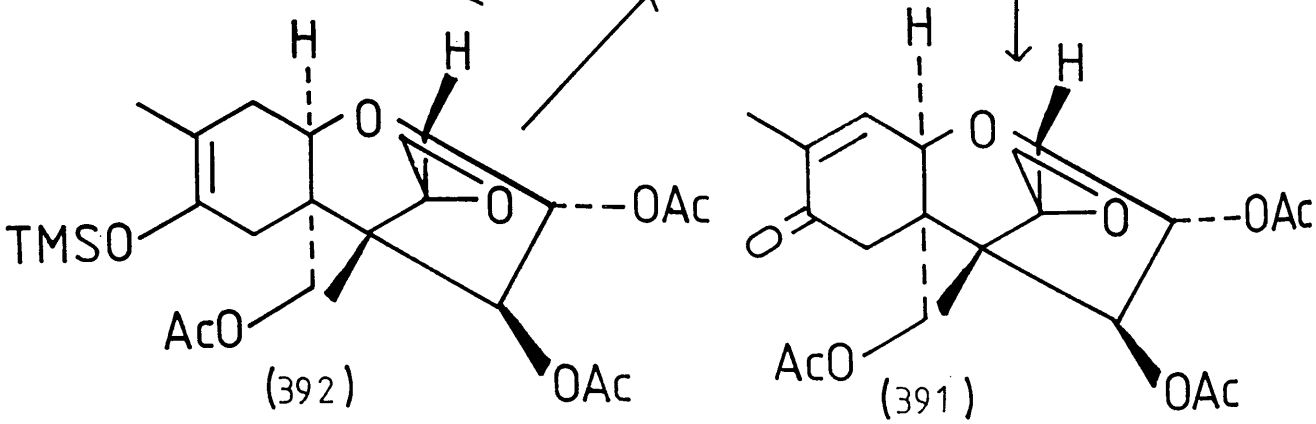


Scheme (22)


H
H
O
O
O
SiO
OH
OH
(346)
H
H
O
O
SiO
OH
OH
(387)


H
H
O
O
OR
SiO
OR
R=Ac (388)
R=H (388')
+
H
H
O
O
O
OH
SiO
OH
(388'')


(388)
X
H
H
O
O
OAc
AcO
OAc
X=H (389)
X=PhSe (390)

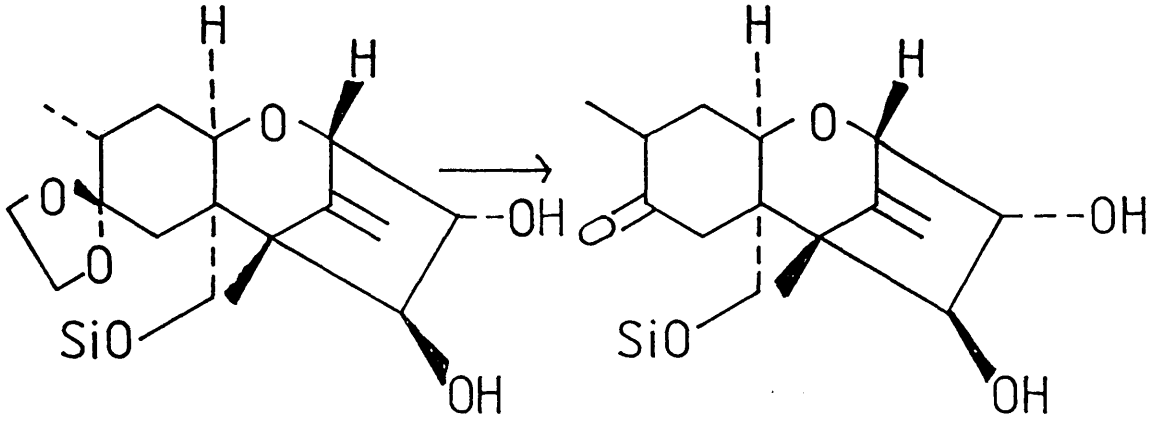

H
H
O
O
OAc
TMSO
AcO
OAc
(392)
H
H
O
O
OAc
AcO
OAc
(391)

APPENDIX

At this stage two possible sequences were considered to advance the total synthesis; either to epoxidise (346) immediately and then remove the ketal protecting group or to perform these operations in the reverse order. The first option required the cleavage of a ketal in the presence of an epoxide, a process which under acidic conditions might trigger off the facile apotrichothecene rearrangement (Scheme 21). Consequently it was decided to adopt the second option. Conversion of (346) into (387) was achieved by stirring a methanolic solution of (346) with catalytic PPTS. Alkene (387) reacted with m-CPBA very slowly to give a mixture of (388') and over-oxidised Baeyer-Villiger product (388''). Fluoride ion induced desilylation followed by in situ acetylation furnished triacetate (389). Having correctly constructed the BC ring system, it was planned to dehydrogenate ring A by forming α-phenylseleno ketone (390) followed by oxidative fragmentation to enone (391). Direct α-selenylation can be achieved without prior activation of the ketone functionality by simply stirring the substrate and PhSeCl in EtOAc, the reaction occurring via the small equilibrium amount of thermodynamic enol. To establish whether the epoxy triacetate functionality would be stable to PhSeCl, model compound (394), formed by hydrogenation of naturally occurring triacetoxyscirpenol (393) was subjected to these conditions. Fortunately no apotrichothecene rearrangement occurred. Based on this evidence it was anticipated that formation of (390) would proceed uneventfully. However, only starting material was recovered when (389) was stirred for 72 hours with PhSeCl. Activation of the ketone by forming the thermodynamic silyl enol ether (392) was then considered but lack of material prevented further progress in this direction.

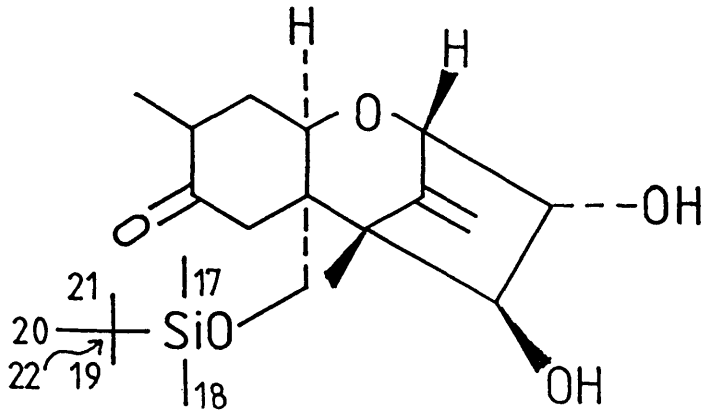
Although it appears that this project has failed at the penultimate hurdle, sufficient quantities of triacetate (389) to complete this total synthesis should be available from conjugate reduction of semisynthetic enone (391) (Scheme 22). These reactions are under active investigation by other members of this research group.

(±)-3α,4β-Dihydroxy-8-oxo-15-(tert-butyldimethylsilyloxy)-trichothec-12-ene (387).



(346) Si≡t-BuMe$_2$Si (387)

To a stirred solution of the diol (346) (37 mg, 0.084 mmol) in a mixture of MeOH (10 ml) and H_2O (1 ml) was added a few crystals of PPTS. Stirring was continued for 48 hours whereupon the reaction mixture was concentrated in vacuo. The mixture was diluted with EtOAc and washed twice with H_2O. After drying and concentration, purification by dry column flash chromatography gave the ketone (387) (30 mg, 90%, unoptimised) as a solid. No attempt at recrystallisation was made due to all of this material being required for the subsequent steps.

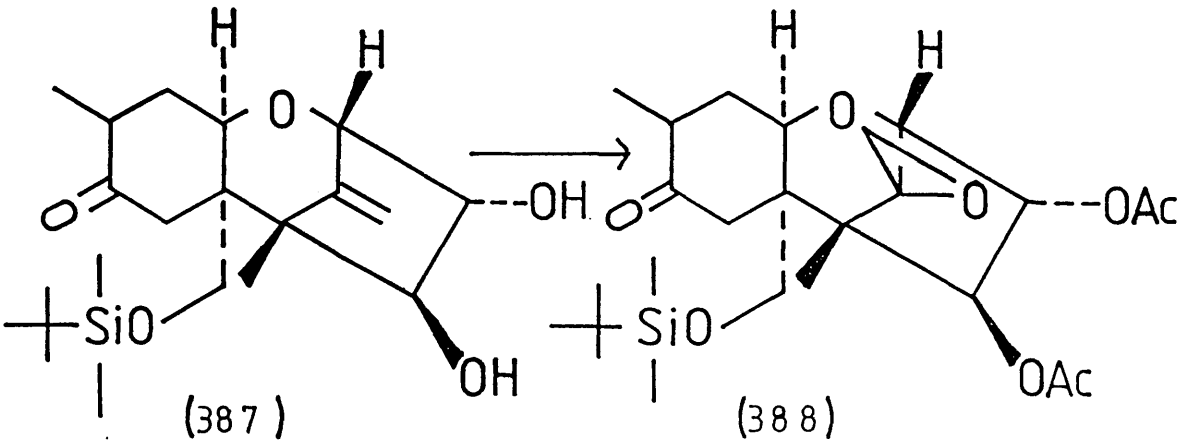


PROTON NUMBER	δPPM ^1H	CARBON NUMBER	δPPM ^{13}C	MULTIPLICITY ^1H	MULTIPLICITY ^{13}C	J(Hz) ^1H
-	-	C-2	79.82/	-	d	-
H-3	3.89	C-3	80.40/	dd	d	2.64,4.87
H-4	4.68	C-4	81.23	d	d	2.59
-	-	C-5	51.62/	-	s	-
-	-	C-6	52.38	-	s	-
H-7(2H)	1.6-2.9	C-7	42.50	-	t	-
-	-	C-8	212.19	-	s	-
H-9	1.6-2.9	C-9	38.43	-	d	-
H-10(2H)	1.13-1.45	C-10	36.77	-	t	-
H-11	3.37	C-11	70.18	t	d	7.19
-	-	C-12	150.95	-	s	-
H-13(2H)	4.79+5.20	C-13	108.91	2 x s	t	-
H-14(3H)	0.94	C-14	10.26/	s	q	-
H-16(3H)	0.87	C-16	13.72	d	q	6.71
H-15(2H)	3.46+3.67	C-15	65.38	AB quartet	t	11.09
H-17(3H) H-18(3H)	-0.00 + 0.02	C-17 C-18	-4.90	2 x s	q	-
H-19(3H) H-20(3H) H-21(3H)	0.86	C-19 C-20 C-21	25.81	s	q	-
-	-	C-22	25.90	-	s	-

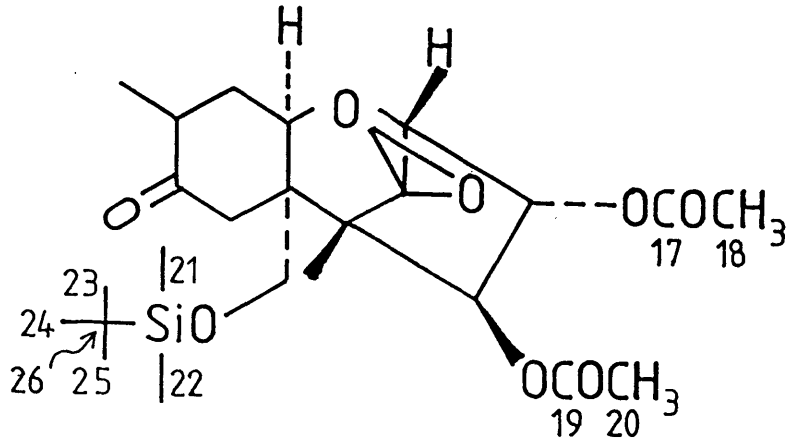
i.r. ($CHCl_3$) : 3620, 2960, 2940, 1720, 1260, 1100, 1080 cm^{-1}.

M.S : 339.1616 ($M^+ - {}^tBu$); calc. for $C_{17}H_{27}O_5Si$: 339.1628

(+)-3α,4β-Diacetoxy-8-oxo-12,13-epoxy-15-(tert-butyldimethylsilyloxy)-trichothecane(388)



To a stirred solution of the alkene (387) (27 mg, 0.061 mmol) in dry CH_2Cl_2 (10ml) was added Na_2HPO_4 (45 mg, 0.32 mmol) and m-CPBA (14 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 48 hours, filtered and then poured into saturated aqueous $NaHCO_3$ solution (10ml). Solid NaCl was added to the aqueous layer which was then thoroughly extracted with EtOAc. After drying and concentration, purification by dry column flash chromatography gave the epoxy-diol as a solid, which was acetylated in the usual manner. Purification of the acetylated product by dry column flash chromatography gave the epoxide (388) (16 mg, 49%, unoptimised) as a solid. No attempt was made at recrystallising this compound since it was fully required for the subsequent reaction steps.

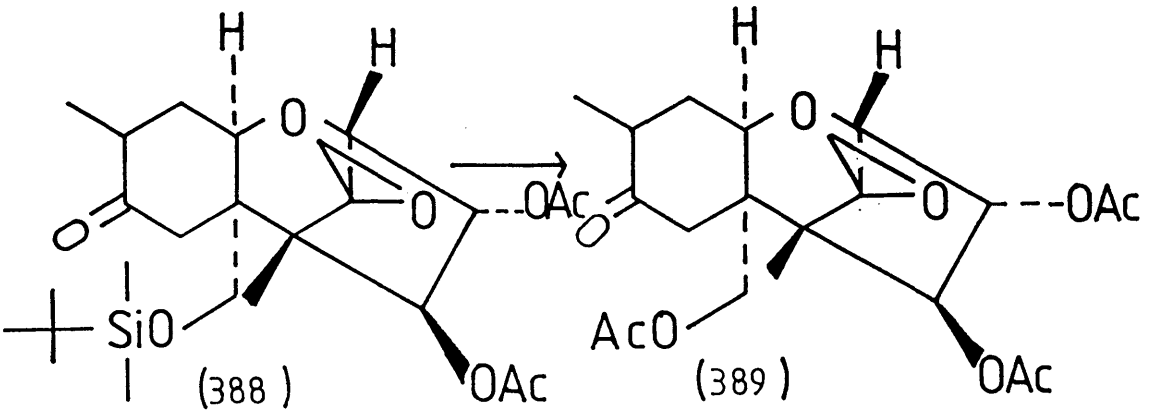


PROTON NUMBER	δPPM ^1H	CARBON NUMBER	δPPM ^{13}C	MULTIPLICITY J(Hz) ^1H	^{13}C	^1H
H-2	3.97	C-2	77.99/	d	d	4.87
H-3	5.19	C-3	78.68/	dd	d	3.10,4.88
H-4	5.87	C-4	78.80	d	d	3.10
-	-	C-5	51.88	-	s	-
-	-	C-6	48.28	-	s	-
H-7(2H)	2.57-2.85	C-7	41.99	m	t	-
-	-	C-8	210.48	-	s	-
H-9	2.57-2.85	C-9	38.58	m	d	-
H-10(2H)	1.8-2.3	C-10	36.39	m	t	-
H-11	4.25	C-11	70.48	m	d	-
-	-	C-12	64.58	-	s	-
H-13(2H)	2.78+3.10	C-13	47.14	AB QUARTET	t	3.93
H-14(3H)	0.66	C-14	5.77	s	q	-
H-15(2H)	3.50+3.79	C-15	65.05	AB QUARTET	t	11.18
H-16(3H)	1.00	C-16	13.73	d	q	6.56
-	-	C-17	169.89	-	s	-
-	-	C-19	170.27	-	s	-
H-18(3H)	2.08/	C-18	20.78/	s	q	-
H-20(3H)	2.14	C-20	20.82	s	q	-
H-21(3H)	0.03/	C-21	-5.96/	s	q	-
H-22(3H)	0.05	C-22	-5.86	s	q	-
H-23(3H)		C-23				
H-24(3H)	0.90	C-24	25.84	s	q	-
H-25(3H)		C-25				
-	-	C-26	18.22	-	s	-

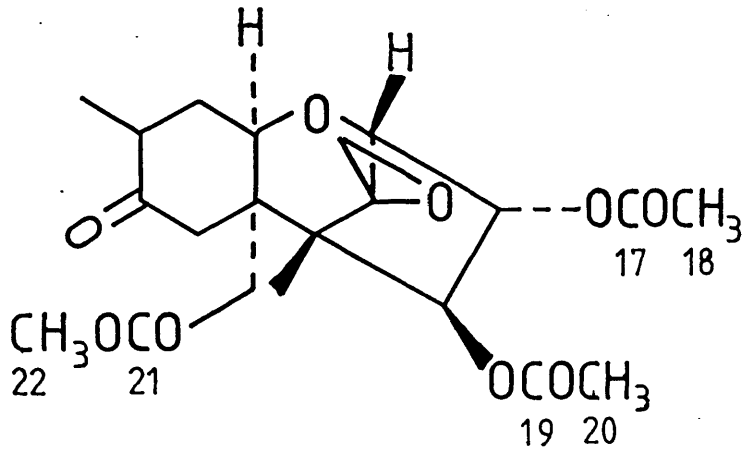
i.r (CCl_4) : 2960, 2930,1745, 1720, 1245, 1225, 1100 cm^{-1}

M.S : 439.1738 ($M^+ - {}^tBu$); calc. for $C_{21}H_{31}O_8Si$: 439.1788

(±) 3α,4β,15-Triacetoxy-8-oxo-12,13-epoxy-trichothecane (389)



To a stirred solution of the silyl ether (388) (14mg, 0.028 mmol) in THF (5ml) was added tetrabutylammonium fluoride trihydrate (14mg, 0.044 mmol). The reaction mixture was stirred at room temperature for 48 hours, when t.l.c indicated completion. A preformed mixture of Ac_2O (2ml) and pyridine (1ml) was added, stirring was continued for an additional 18 hours and then the solution was concentrated in vacuo. Purification by dry column flash chromatography gave the triacetate (389) (10mg, 84%, unoptimised) as a solid. No attempt was made at recrystallising this compound since it was fully required for the subsequent reaction steps.



PROTON NUMBER	^1H δPPM	CARBON NUMBER	^{13}C δPPM	MULTIPLICITY J(Hz) ^1H	^{13}C	^1H
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H-3	5.20	C-3	78.04/	dd	d	3.28,4.82
H-4	5.72	C-4	78.65	d	d	3.22
-	-	C-5	50.99	-	s	-
-	-	C-6	48.38	-	s	-
H-7(2H)	1.7-2.35	C-7	41.58	-	t	-
-	-	C-8	209.82	-	s	-
H-9	2.6-2.85	C-9	38.66	-	d	-
H-10(2H)	1.5-1.7	C-10	36.64	-	t	-
H-11	4.19	C-11	70.67	m	d	-
-	-	C-12	64.24	-	s	-
H-13(2H)	2.79+3.13	C-13	47.19	AB quartet	t	3.90
H-14(3H)	0.68	C-14	5.79	s	q	-
H-15(2H)	4.10+4.22	C-15	65.10	AB quartet	t	12.48
H-16(3H)	1.02	C-16	13.78	d	q	6.50
-	-	C-17	169.84/	-	s	-
-	-	C-19	170.14/	-	s	-
-	-	C-21	170.38	-	s	-
H-18(3H)	2.06/	C-18	20.73/	s	q	-
H-20(3H)	2.10/	C-20	20.77/	s	q	-
H-21(3H)	2.15	C-22	20.83	s	q	-

i.r. ($CDCl_3$) : 2960, 2940, 1745, 1715, 1250 cm^{-1}

M.S : 424.1737 (M^+); calc. for $C_{21}H_{28}O_9$: 424.1733