Trichothecene Mycotoxin Interconversions: Partial Syntheses of Calonectrin and Deoxynivalenol, and of a Trichothecene *epi*-Epoxide, 3α,4β,15-Triacetoxy-12,13-*epi*-epoxytrichothec-9-ene

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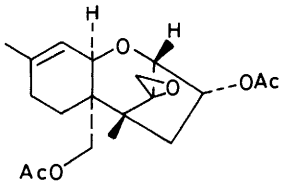
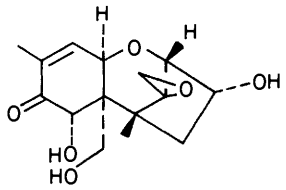
The partial syntheses of two trichothecenes, calonectrin (**1**) (4β,15-diacetoxy-12,13-epoxytrichothec-9-ene) and deoxynivalenol (**2**) (3α,7α,15-trihydroxy-12,13-epoxytrichothec-9-ene), from a readily available trichothecene, anguidine (**3**) (4β,15-diacetoxy-3α-hydroxy-12,13-epoxytrichothec-9-ene) are described. In addition, and in order to provide further insight into the mode of action of the trichothecene mycotoxins, 3α,4β,15-triacetoxy-12,13-*epi*-epoxytrichothec-9-ene (**31**), of the first semi-synthetic trichothecene *epi*-epoxides, has been prepared and its *X*-ray crystal structure determined. In significant contrast to its natural isomer (**10**), *epi*-epoxide (**31**) proved to be biologically inactive.

The trichothecenes [1] are a group of sesquiterpenoid mycotoxins produced by, *inter alia*, *Fusarium* species. All show a high degree of largely adverse biological behaviour, and are important for both economic and environmental reasons. Although wide spread in distribution, provision of some members from culture can be low yielding. Partial synthesis, from readily available trichothecenes, is an attractive alternative, carrying with it the additional possibility of analogue preparation.

Continuing our studies on the synthesis [2] and synthetic transformations [3] of the trichothecene mycotoxins, we wish to describe [4] in detail the partial syntheses of two natural trichothecenes, calonectrin (**1**) (4β,15-diacetoxy-12,13-epoxytrichothec-9-ene) and deoxynivalenol (**2**) (3α,7α,15-trihydroxy-12,13-epoxytrichothec-9-ene), from a common precursor, anguidine (**3**) (4β,15-diacetoxy-3α-hydroxy-12,13-epoxytrichothec-9-ene). The total synthesis of calonectrin, in racemic



(**1**)



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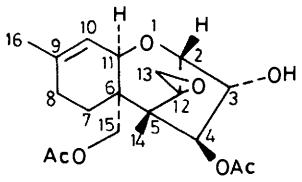
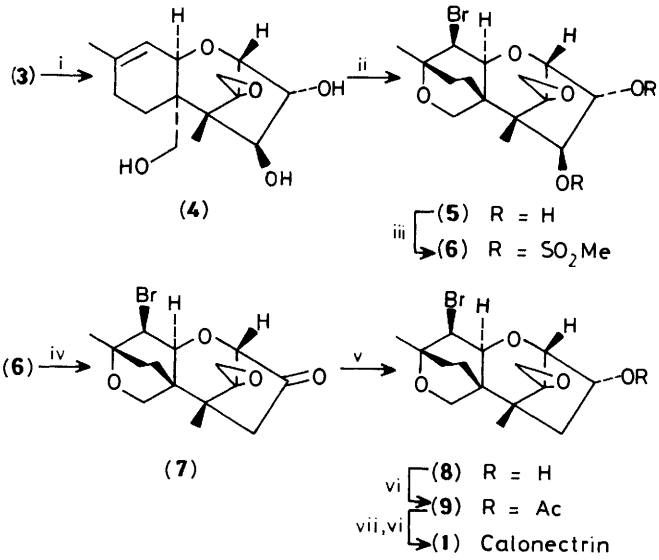


(**3**)

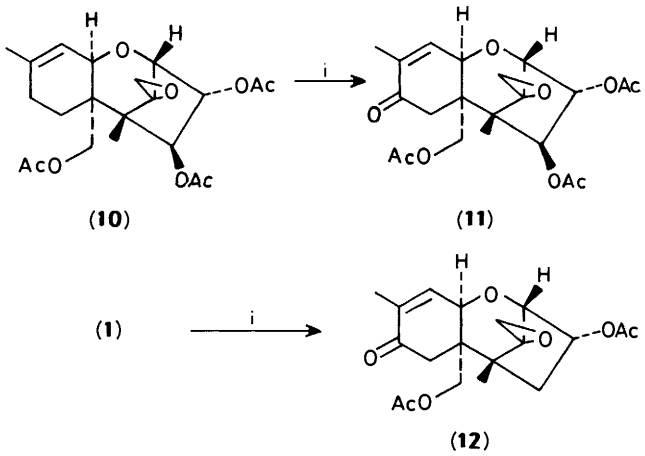
form, has been reported,[5] as has its partial synthesis [6] from anguidine, by Barton deoxygenation of the C-4 hydroxy group. Deoxynivalenol, also known as vomitoxin, is produced [7] when cereal grains suffer infestation by *Fusarium* species: consumption of feedstuffs so contaminated induces feed refusal and sub-lethal toxicoses. Deoxynivalenol has not succumbed hitherto to either partial or total synthesis.

The synthetic sequence employed is outlined in Scheme 1. Anguidine (**3**), obtained from culture,[3] was hydrolysed to the triol (**4**), which was converted [8] into the oxabicyclo-



Scheme 1. *Reagents and conditions:* i, NaOH, H_2O, THF, MeOH; ii, NBS, MeCN; iii, $MeSO_2Cl$, pyridine (py); iv, NaOMe, MeOH, reflux, 2 h; v, $NaBH_4$, MeOH, H_2O, O °C; vi, Ac_2O, py, Et_2O; vii, Zn(Ag), THF, EtOH, Et_2O, reflux, 1.5 h

[2.2.2]bromoether [5,9] (**5**), thus selectively protecting the 15-hydroxy group. Reaction of the diol (**5**) with methanesulphonyl chloride in the presence of pyridine provided the bismethanesulphonate (**6**), which, on treatment with sodium methoxide in refluxing methanol, underwent regiospecific elimination to an (unisolated) enol mesylate and thence to the ketone (**7**), in 80% yield. This excellent method for selective C-4 deoxygenation of trichothecene 3α,4β-diols has seen little if any use since its discovery [10] in earlier structural elucidation studies. Stereospecific hydride reduction [5] to the 3α-alcohol (**8**), followed by conversion into the acetate (**9**), regeneration of the 9,10-double bond [5,9] and acetylation of the so-produced C-15 alcohol gave calonectrin (**1**), in an overall yield of 55% from the triol (**4**). Calonectrin obtained in this way possessed spectral data identical with those reported.[11] Having thus established the correct level of oxygenation in ring C, it remained to oxidise the cyclohexene ring of ring A to achieve the functionality possessed by deoxynivalenol (**2**). This required sequential selective allylic oxidation [12] to the 8-ketone and introduction of the 7α-hydroxy group.

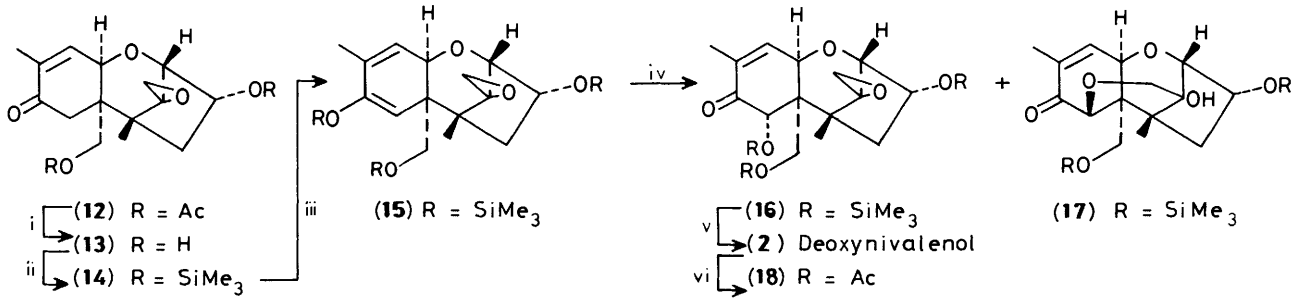


Scheme 2. *Reagents and conditions:* i, py_2·CrO_3, CH_2Cl_2, 48 h

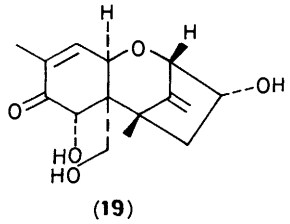
The best allylic oxidant in our hands proved to be freshly prepared dipyridine chromium trioxide.[13] Both anguidine acetate (**10**) and calonectrin (**1**) gave the respective enones (**11**) and (**12**) directly and in good yield (Scheme 2). Introduction of the 7-hydroxy group was achieved by peracid epoxidation of the silyl enol ether derived from (**12**). However, since the acetate functionalities of (**12**) are incompatible with the use of lithium di-isopropylamide (LDA), they were replaced by trimethylsilyl ether moieties. Methanolysis of the diacetate (**12**) gave the diol (**13**), and thence the bistrimethylsilyl ether (**14**), in a combined yield of 79% (Scheme 3). Kinetic deprotonation using LDA, with *in situ* silylation,[14] gave the silyloxy diene (**15**), which on treatment with 1 equiv. of *m*-chloroperbenzoic acid[15] in hexane gave a 1:1 mixture of the tris-trimethylsilyl ether (**16**) of deoxynivalenol (**2**) and the rearranged alcohol (**17**). This outcome can be understood by consideration of the rearrangement of the two diastereoisomeric silyloxyoxiranes involved as intermediates.[16] Both silyloxyoxiranes undergo an acid-catalysed opening to produce 7-hydroxy-8-silyloxycarbenium ion intermediates. In the case of the 7α-hydroxy epimer, 1,4-O→O silyl migration then leads to the observed 7α-silyloxy ketone. The 7β-hydroxy epimer, on the other hand, is prevented by its configuration from participating in a similar migration: instead, the hydroxy group attacks the proximal 12,13-epoxide moiety at C-13.

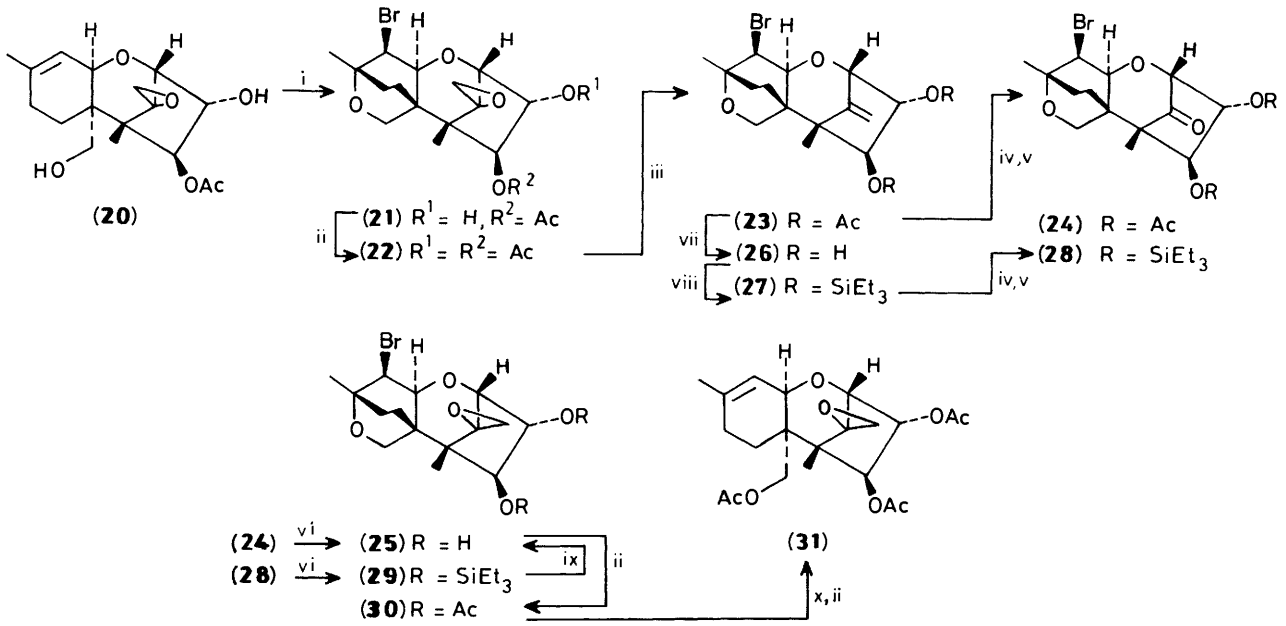
The tris-trimethylsilyl ether (**16**) proved to be identical in all respects with an authentic sample prepared from deoxynivalenol (**2**), and it underwent quantitative cleavage on treatment with aqueous HF–acetonitrile[17] to give deoxynivalenol itself, which was characterised fully as the corresponding triacetate (**18**). Application of similar methodology should provide access to useful amounts of less abundant trichothecenes; such studies are currently in progress.

A characteristic feature of almost all trichothecenes is the possession of a spiro 12,13-epoxide function. Its presence seems to be essential for the manifestation of deleterious biological effects: activity is lost when this function is removed,[18] but only by demonstrably deep-seated alterations to the molecule. Additionally, studies with rumen micro-organisms *in vitro*[19] and with rats *in vivo*[7] have revealed that the predominant biological transformation, and presumed detoxification, of deoxynivalenol (**2**) is one of deoxygenation to form the 9,12-diene (**19**). This has added to speculation[20] that the biological mode of action may involve the epoxide group acting as an electrophilic alkylating agent. However, it is now well-established that the 12,13-epoxide unit is very unreactive under normal S_N2 conditions.[21] Under acidic conditions, on the other hand, many trichothecenes undergo a facile rearrangement to biologically inactive *apo*-trichothecenes.[22] This rearrangement involves *O*-protonation of the epoxide, which is then attacked intramolecularly at C-12 by the pyran oxygen (less frequently, the ring A double bond can attack C-13). Nucleophilic capture of the cation so generated at C-2 then leads to the *apo*-trichothecenes. Such nucleophilic capture may also be a key step in providing biological activity. Thus, there may be more substance in proposing the requirement of the full OCCCO unit for activity; simple model systems have been reported to show modest activity.[23] Such a rationale also demands a stereochemical requirement for the correct geometry for such intramolecular attack. Indeed, *X*-ray studies[24] have shown that, in simple trichothecenes, the O(1)–C(2) and C(12)–O bonds are almost co-planar and antiparallel. Further, studies[25] of epimeric epoxides derived from ring A-aromatic trichothecene-like compounds have demonstrated the necessity for the epoxide oxygen to be *anti* to ring A for a similar rearrangement to occur. We now describe in detail the synthesis,[26] from a natural trichothecene, of 3α,4β,15-triacetoxy-12,13-*epi*-epoxytrichothec-9-ene (**31**). This is one of the first trichothecene analogues to be prepared with the



Scheme 3. *Reagents and conditions:* i, K_2CO_3, MeOH, H_2O, 1 h; ii, Me_3SiCl, py, Et_2O; iii, $LiNPr^i_2$, Me_3SiCl, THF, −78 °C; iv, *m*-chloroperbenzoic acid, hexane, −15 °C to +30 °C; v, HF, MeCN, H_2O; vi, Ac_2O, Et_3N, DMAP, CH_2Cl_2





Scheme 4. *Reagents and conditions:* i, NBS, MeCN; ii, Ac_2O, py, Et_2O; iii, WCl_6, Bu^nLi, THF; iv, O_3, CH_2Cl_2; v, Et_3N; vi, dimethylsulphonium methylide, THF, 1 h; vii, K_2CO_3, MeOH, H_2O, 2 h; viii, Et_3SiCl, py, DMAP; ix, Bu_4NF, THF; x, Zn(Ag), THF, EtOH, Et_2O, reflux, 2 h

'unnatural' epoxide configuration, in which the epoxide oxygen is *syn* to ring A. When compared to its natural isomer (**10**), it proved to be devoid of sigificant toxicity.

The synthetic sequence followed is outlined in Scheme 4. 4β-Acetoxy-3α,15-dihydroxy-12,13-epoxytrichothec-9-ene (**20**), obtained from culture,[3] was converted into the bromo ether (**21**), thus affording protection to the 9,10-double bond. Treatment of the derived diacetate (**22**) with the Sharpless[27] lower-valent tungsten deoxygenating system, following a protocol successfully applied[3] to deoxynivalenol and anguidine acetates, gave the 12-ene (**23**) in 98% yield. Ozonolysis followed by reductive work-up with triethylamine produced the nor-ketone (**24**). Treatment of this ketone with an excess of dimethylsulphonium methylide[28] gave the diol *epi*-epoxide (**25**), in 35% yield, the ylide having also cleaved the acetate groups. If acetate cleavage occurs prior to ketonic attack, then retro-aldolisation and cleavage of ring C will take place, with consequent destruction of substrate. A more satisfactory procedure, which excluded this possibility, involved hydrolysis of the 12-ene diacetate (**23**) to the diol (**26**), which was then protected as the bistriethylsilyl ether (**27**). Ozonolysis to the nor-ketone (**28**) followed by reaction with a slight excess of the sulphonium ylide, gave the *epi*-epoxide (**29**) in an improved yield of 65%. Fluoride ion-induced cleavage then gave the diol (**25**) identical in all respects with that prepared above. Conversion of the diol into the diacetate (**30**), followed by reductive regeneration of the 9,10-double bond and acetylation, provided the triacetate (**31**). The 'unnatural' epoxide configuration attained by this route, in which the epoxide is *syn* to ring A, was expected by analogy with earlier observations made in the total synthesis of trichodermin,[2a] and in more recent work by Goldsmith *et al.*[25] It was also confirmed by single crystal *X*-ray analysis (Figure).

While preliminary communication of these results was in preparation, Roush informed us of his independent studies which have led to syntheses[29] of the trichothecene analogues 12,13-*epi*- and 12,13-deoxy-12,13-methanoanguidine, and also of [13-^{14}C]anguidine.

Biological evaluation was carried out using human epithelial cells[30] by determining the minimum inhibitory concentration for cell growth. This showed (Table 1) that the *epi*-epoxide (**31**) was essentially non-toxic when compared with its natural isomer (**10**). This finding emphasises the key role played by a correctly orientated epoxide group in conferring the cytotoxicity shown by the trichothecenes, and gives further substance to the concept that the biological activity is related to the mode of chemical reactivity in the acid-catalysed trichothecene→apotrichothecene rearrangement process.

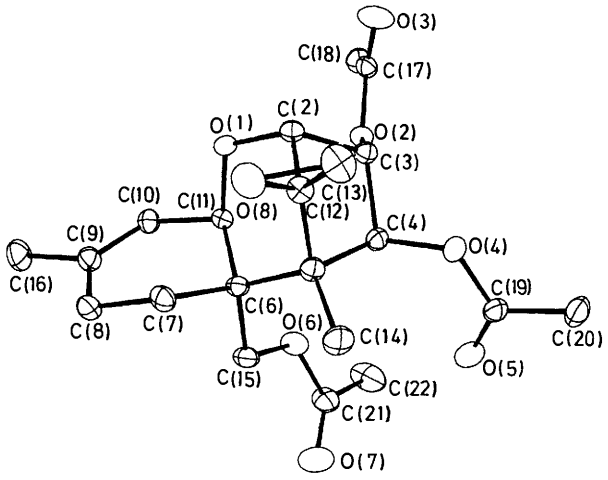


Figure.

Table 1. Cytotoxicity studies on the trichothecenes

Trichothecene	Lethal concentrations μg ml^{-1}
(**10**)	3.4
(**3**)	0.43
(**31**)	920

Experimental

M.p.s were determined on a Kofler hot-stage apparatus, and are uncorrected. I.r. were recorded on a Perkin-Elmer 580 spectrometer, and optical rotations were determined on an Optical Activity AA-100 auto-digital polarimeter. ^{1}H N.m.r. spectra were recorded on a 200 MHz Bruker WP200 SY spectrometer, with two exceptions which were recorded on a Perkin-Elmer R32 spectrometer operating at 90 MHz. ^{13}C N.m.r. spectra were recorded on a Bruker WP200 SY spectrometer operating at 50 MHz. In all cases, deuteriochloroform was used as solvent with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ) relative to Me_4Si, using Me_4Si or the δ 7.25 residual chloroform peak and the δ 77 deuteriochloroform peak as internal references for the ^{1}H and ^{13}C n.m.r. spectra respectively. ^{1}H N.m.r. data are reported using the convention: chemical shift, integrated intensity, multiplicity, observed coupling constant (J) in Hz, and assignment. The multiplicities of the 50 MHz ^{13}C n.m.r. resonances were determined using DEPT spectra with pulse angles of θ = 90° and 135°.

High resolution molecular weights were determined from mass spectra, measured with a VG updated A.E.I. MS902 spectrometer. Elemental analyses were performed using a Carlo-Erba 1106 elemental analyser. Capillary column g.l.c. was performed with a Hewlett-Packard 5880 gas chromatograph equipped with SE-54 and CP Sil 5 CB fused-silica capillary columns (25 m × 0.32 mm i.d.) and Grob-type injectors operating in split mode (50:1). G.c.-m.s. was carried out with an LKB 9000 instrument fitted with a DB-1 fused-silica capillary column (60 m × 0.32 mm i.d.) and a falling-needle injector. Mass spectra (22 eV) were recorded under electron-impact (e.i.) conditions.

Anguidine (**3**) (4β,15-diacetoxy-3α-hydroxy-12,13-epoxytrichothec-9-ene) and 4β-acetoxy-3α,15-dihydroxy-12,13-epoxytrichothec-9-ene (**20**) were obtained from culture as previously described.[3]

Reactions were normally performed in an atmosphere of nitrogen. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from sodium–benzophenone ketyl. Acetonitrile (MeCN) was distilled from blue silica gel. Dichloromethane was distilled from P_2O_5, then filtered through Grade I basic alumina. Light petroleum (b.p. 60—80 °C), hexane, and pentane were distilled from CaH_2. With the exception of THF and ether, all the above were stored over 4Å molecular sieves. 4,4-Dimethylaminopyridine (DMAP) was recrystallised from cyclohexane. *N*-Bromosuccinimide (NBS) was recrystallised from water and dried *in vacuo* over P_2O_5. Organic solutions were dried over $MgSO_4$, and, after filtration, were concentrated under reduced pressure using a Büchi Rotavapor. Dry-column flash chromatography[31] and flash chromatography[32] refer to techniques described elsewhere.

10β-*Bromo*-3α,4β-*bismethylsulphonyloxy*-9α,15;12,13-*diepoxytrichothecane* (**6**).—Aqueous sodium hydroxide (1M; 10 ml) was added to a stirred solution of anguidine (**3**) (374 mg, 1.02 mmol) in THF (8 ml) and MeOH (5 ml), and stirring was continued for 15 min. The solution was then passed down a column of Amberlite IR-120(H) ion exchange resin (10 g), eluting with MeOH–water (1:4). Concentration of the eluate gave the crude triol (**4**), which was used without further purification. NBS (213 mg, 1.22 mmol) was added to a stirred solution of the triol (**4**) (1.02 mmol assumed) in MeCN (20 ml). Stirring was continued for 15 min, after which the mixture was concentrated to give the crude bromo ether (**5**), which was used without further purification. The bromo ether (1.02 mmol assumed) was dissolved in pyridine, and the solution was cooled to 0 °C. To this solution was added methanesulphonyl chloride (3 ml, 38 mmol, excess). The reaction flask was stoppered and kept at 4 °C for 24 h. The mixture was then poured onto ice–water, acidified with dilute HCl (1M; 15 ml), and the resulting mixture was extracted with AcOEt. The organic extracts were dried and concentrated. Purification of the residue by dry column flash chromatography gave the *bismesylate* (**6**) (486 mg, 92% from anguidine) as an off-white amorphous solid; $[\alpha]_D^{20}$ −17.3° (*c* 0.52 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 1 375 and 1 180 cm^{-1}; δ_H 5.36 (1 H, d, *J* 3.3, 4-H), 5.22 (1 H, dd, *J* 4.9 and 3.3, 3-H), 4.25 (1 H, dd, *J* 8.6 and 1.7, 11-H), 4.01 (1 H, d, *J* 4.9, 2-H), 3.99 (1 H, dd, *J* 8.6 and 2.3, 10-H), 3.84 (1 H, dd, *J* 10.0 and 2.6, 15-Hα), 3.73 (1 H, d, *J* 10.0, 15-Hβ), 3.09 and 2.80 (2 H, ABq, $J_{obs.}$ 3.8, 13-H), 3.16 (3 H, s, OSO_2Me), 3.15 (3 H, s, OSO_2Me), 2.22 (1 H, dd, *J* 12.8 and 9.8, 8-Hβ), 2.15—1.96 (1 H, m, 7-Hβ), 1.90—1.70 (1 H, m, 7-Hα), 1.6—1.46 (1 H, m, 8-Hα), 1.27 (3 H, s, 16-H), and 0.75 (3 H, s, 14-H); δ_C 85.0 (C-4), 82.7 (C-3), 78.5 (C-2), 73.8 (C-9), 68.6 (C-11), 65.5 (C-15), 63.1 (C-12), 53.5 (C-10), 46.7 (C-5), 46.5 (C-13), 42.1 (C-6), 39.1 (OSO_2Me), 38.1 (OSO_2Me), 27.7 (C-8), 24.1 (C-16), 19.4 (C-7), and 6.6 (C-14) (Found: M^+, 518.0082 and 516.0149. $C_{17}H_{25}BrO_9S_2$ requires *M*, 518.0104 and 516.0124).

10β-*Bromo*-9α,15;12,13-*diepoxytrichothecan*-3-*one* (**7**).—A solution of the bismesylate (**6**) (214 mg, 0.41 mmol) in MeOH (3 ml) was added to freshly prepared NaOMe in MeOH [from Na (150 mg, 6.5 mmol) and MeOH (12 ml)], and the resulting mixture heated under reflux for 2 h. On cooling, it was diluted with water, then extracted with $CHCl_3$. The organic extracts were dried and concentrated. Purification of the residue by dry-column flash chromatography gave the *ketone* (**7**) (118 mg, 84%) as a white crystalline hygroscopic solid, m.p. 92—94 °C (from ether–light petroleum); $[\alpha]_D^{20}$ −176° (*c* 0.33 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 770 cm^{-1}; δ_H 4.17 (1 H, dd, *J* 8.5 and 1.6, 11-H), 3.98 (1 H, dd, *J* 8.5 and 2.3, 10-H), 3.76 (1 H, d, *J* 9.4, 15-Hβ), 3.61 (1 H, dd, *J* 9.4 and 2.6, 15-Hα), 3.51 (1 H, s, 2-H), 3.22 and 3.02 (2 H, ABq, $J_{obs.}$ 3.8, 13-H), 2.59 and 2.25 (2 H, ABq, $J_{obs.}$ 9.0, 4-H), 2.25—2.01 (2 H, m, 8-H), 1.88—1.55 (2 H, m, 7-H), 1.26 (3 H, s, 16-H), and 0.82 (3 H, s, 14-H); δ_C 210.6 (C-3), 80.2 (C-2), 73.4 (C-9), 69.9 (C-11), 66.0 (C-15), 63.6 (C-12), 53.8 (C-10), 48.0 (C-13), 46.4 (C-4), 43.0 (C-5), 41.2 (C-6), 27.7 (C-8), 24.0 (C-16), 18.5 (C-7), and 11.0 (C-14) (Found: C, 52.7; H, 5.7; Br, 23.6%; M^+, 344.0448 and 342.0471. $C_{15}H_{19}BrO_4$ requires C, 52.5; H, 5.6; Br, 23.3%; *M*, 344.0447 and 342.0467).

10β-*Bromo*-3α-*hydroxy*-9α,15;12,13-*diepoxytrichothecane* (**8**).—A solution of the ketone (**7**) (118 mg, 0.344 mmol) in MeOH (10 ml) and water (4 ml) was cooled to 0 °C, and sodium borohydride (0.5 g, 13.2 mmol) was added. The mixture was stirred at 0 °C for 15 min, then diluted with water and extracted with AcOEt. The organic extracts were dried and concentrated. Purification of the residue by dry column flash chromatography gave the *alcohol* (**8**) (117 mg, 99%) as a white crystalline solid, m.p. 127—130 °C (from AcOEt–hexane); $[\alpha]_D^{20}$ −39.0° (*c* 1.0 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 3 600 cm^{-1}; δ_H 4.45 (1 H, m, 3-H), 4.43 (1 H, dd, *J* 8.6 and 3.2, 10-H), 4.26 (1 H, dd, *J* 8.6 and 2.7, 11-H), 3.67 (2 H, br s, 15-H), 3.62 (1 H, d, *J* 4.6, 2-H), 3.08 and 2.79 (2 H, ABq, $J_{obs.}$ 3.9, 13-H), 2.42 (1 H, br d, *J* 3.3, 8-Hβ), 2.30 (1 H, dd, *J* 12.9 and 10.0, 4-Hα), 2.13—1.90 (3 H, m, 4-Hβ, 7-Hβ, and OH), 1.84—1.65 (1 H, m, 8-Hα), 1.60—1.43 (1 H, m, 7-Hα), 1.27 (3 H, s, 16-H), and 0.64 (3 H, s, 14-H); δ_C 80.7 (C-2), 73.7 (C-9), 69.2 (C-3), 68.6 (C-11), 66.6 (C-15), 65.3 (C-12), 55.0 (C-10), 47.8 (C-13), 43.0 (C-5), 40.8 (C-4 and C-6), 28.1 (C-8), 24.3 (C-16), 19.4 (C-7), and 11.2 (C-14) (Found: C, 52.3; H, 6.15; Br, 23.4%; M^+, 346.0599 and 344.0631. $C_{15}H_{21}BrO_4$ requires C, 52.2; H, 6.1; Br, 23.2%; *M*, 346.0604 and 344.0624).

3α-*Acetoxy*-10β-*bromo*-9α,15;12,13-*diepoxytrichothecane* (**9**).—Acetic anhydride (2 ml) and pyridine (1 ml) were added to a solution of the alcohol (**8**) (130 mg, 0.38 mmol) in ether (5 ml). The mixture was set aside at 20 °C overnight after which excess

of acetic anhydride and pyridine were removed azeotropically under reduced pressure using toluene (× 4) and then CCl_4 (× 2). Purification by dry-column flash chromatography gave the *acetate* (**9**) (136 mg, 93%) as a white crystalline solid, m.p. 119—123 °C (from benzene–light petroleum); $[\alpha]_D^{20}$ −35.6° (*c* 0.62 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 750 cm^{-1}; δ_H 5.20 (1 H, ddd, *J* 10, 5, and 5, 3-H), 4.25 (2 H, br s, 10-H and 11-H), 3.84 (1 H, d, *J* 5, 2-H), 3.69 (1 H, d, *J* 9.3, 15-Hβ), 3.61 (1 H, dd, *J* 9.3 and 2.6, 15-Hα), 3.09 and 2.8 (2 H, ABq, $J_{obs.}$ 3.9, 13-H), 2.10 (3 H, s, MeCO), 2.30—1.35 (6 H, m, 4-H, 7-H, and 8-H), 1.26 (3 H, s, 16-H), and 0.64 (3 H, s, 14-H); δ_C 170.3 (MeCO), 79.0 (C-2), 73.8 (C-9), 70.8 (C-3), 68.6 (C-11), 66.5 (C-15), 64.6 (C-12), 54.8 (C-10), 47.7 (C-13), 42.5 (C-5), 40.8 (C-6), 38.2 (C-4), 28.0 (C-8), 24.2 (C-16), 21.0 (MeCO), 19.0 (C-7), and 11.1 (C-14) (Found: C, 52.9; H, 5.8; Br, 20.6%; M^+, 307.1552. $C_{17}H_{23}BrO_5$ requires C, 52.7; H, 6.0; Br, 20.6%; $C_{17}H_{23}BrO_5$ − Br, 307.1545).

3α,15-*Diacetoxy*-12,13-*epoxytrichothec*-9-*ene* (*Calonectrin*) (**1**).—Zinc powder (21.5 g, 0.32 mol) was added in one portion to a stirred, hot suspension of AgOAc (118 mg) in AcOH (120 ml). After 30 s, the AcOH was removed by decantation, and the Zn/Ag couple[33] washed with AcOH (1 × 55 ml) and ether (5 × 55 ml). Ether (55 ml) was added to the freshly prepared couple, then a solution of the bromo ether (**9**) (531 mg, 1.37 mmol) in THF (105 ml) and EtOH (20 ml) was added. The mixture was heated at 55 °C with stirring for 1.5 h. After being cooled to 20 °C the mixture was concentrated and the residue was taken up in acetone and the solution filtered through a pad of Celite. Concentration of the filtrate, followed by acetylation by the normal procedure and purification by flash chromatography gave calonectrin (**1**) (377 mg, 79%) as a colourless oil which could not be induced to crystallise; $[\alpha]_D^{20}$ +2.9° (*c* 0.76 in $CHCl_3$) [lit.,[6] $[\alpha]_D^{27}$ +5.8° (in $CHCl_3$)]; $\nu_{max.}$(CCl_4) 1 750 cm^{-1}; δ_H 5.42 (1 H, br d, *J* 4.4, 10-H), 5.12 (1 H, ddd, *J* 9.3, 4.8, and 4.8, 3-H), 4.04 and 3.79 (2 H, ABq, $J_{obs.}$ 12.2, 15-H), 3.97 (1 H, br d, *J* 4.4, 11-H), 3.71 (1 H, d, *J* 4.8, 2-H), 3.05 and 2.81 (2 H, ABq, $J_{obs.}$ 4.0, 13-H), 2.07 (3 H, s, MeCO), 2.00 (3 H, s, MeCO), 1.68 (3 H, br s, 16-H), and 0.79 (3 H, s, 14-H); δ_C 170.8 (MeCO), 170.3 (MeCO), 140.2 (C-9), 118.8 (C-10), 77.9 (C-2), 71.1 (C-3), 68.0 (C-11), 64.9 (C-12), 63.5 (C-15), 48.4 (C-13), 45.2 (C-5), 42.8 (C-6), 39.2 (C-4), 28.1 (C-8), 23.1 (C-16), 20.9 (MeCO), 20.8 (MeCO and C-7), and 12.0 (C-14) (Found: M^+, 350.1737. Calc for $C_{19}H_{26}O_6$: *M*, 350.1729).

3α,4β,15-*Triacetoxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (**11**).—A solution of the triacetate (**10**)[3] (175 mg, 0.43 mmol) in dichloromethane (10 ml) was added to a stirred suspension of freshly prepared CrO_3–pyridine complex (7.89 g, 30.6 mmol) in dichloromethane (30 ml), and the resulting slurry was stirred for 2 days at 20 °C. The supernatant liquid was decanted, and saturated aqueous sodium hydrogen carbonate (100 ml) was added to the reaction flask to dissolve the residue. The aqueous solution was extracted with ether (3 × 50 ml), and the organic extracts were combined with the decanted supernatant. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (6 × 50 ml), and the combined aqueous washings were extracted with ether (2 × 50 ml). All the organic extracts were combined, and washed with dilute HCl (1M; 3 × 50 ml), saturated aqueous sodium hydrogen carbonate (2 × 50 ml), brine (3 × 100 ml), and then dried and concentrated. Purification of the residue by dry-column flash chromatography gave recovered starting material (42 mg) and the desired *enone* (**11**) (109 mg, 79% based on consumed starting material) as a white crystalline solid, m.p. 139—140 °C (from AcOEt–light petroleum); $[\alpha]_D^{20}$ +80.4° (*c* 0.56 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 750 and 1 690 cm^{-1}; $\lambda_{max.}$(EtOH) 226 nm (ε 9 000 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H 6.54 (1 H, dq, *J* 5.8 and 1.5, 10-H), 5.71 (1 H, d, *J* 3.3, 4-H), 5.22 (1 H, dd, *J* 4.9 and 3.3, 3-H), 4.37 (1 H, br d, *J* 5.8, 11-H), 4.31 and 4.13 (2 H, ABq, $J_{obs.}$ 12.5, 15-H), 3.94 (1 H, d, *J* 4.9, 2-H), 3.08 and 2.82 (2 H, ABq, $J_{obs.}$ 3.9, 13-H), 2.87 (1 H, d, *J* 15.9, 7-Hβ), 2.45 (1 H, dd, *J* 15.9 and 1.6, 7-Hα), 2.16 (3 H, s, MeCO), 2.10 (3 H, s, MeCO), 1.99 (3 H, s, MeCO), 1.82 (3 H, d, *J* 1.5, 16-H), and 0.72 (3 H, s, 14-H); δ_C 196.3 (C-8), 170.0 (2 × MeCO), 169.7 (MeCO), 138.8 (C-9), 136.4 (C-10), 78.2 (C-2), 78.1 (C-3), 77.6 (C-4), 68.2 (C-11), 64.3 (C-15), 64.1 (C-12), 48.7 (C-5), 47.5 (C-6), 46.8 (C-13), 38.2 (C-7), 20.8 (MeCO), 20.7 (MeCO), 20.6 (MeCO), 15.4 (C-16), and 5.9 (C-14) (Found: C, 59.6; H, 6.1%; M^+, 422.1582. $C_{21}H_{26}O_9$ requires C, 59.7; H, 6.2%; *M*, 422.1577).

3α,15-*Diacetoxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (**12**).—A solution of semi-synthetic calonectrin (**1**) (185 mg, 0.53 mmol) in dichloromethane (5 ml) was added to a stirred suspension of freshly prepared CrO_3–pyridine complex (12.9 g, 49.9 mmol) in dichloromethane (30 ml), and the resulting slurry was stirred for 1 day at 20 °C. Isolation and purification as above gave the *enone* (**12**) (141 mg, 73%) as a white crystalline solid, m.p. 139—140 °C (from ether); $[\alpha]_D^{20}$ +61.6° (*c* 0.54 in $CHCl_3$); $\nu_{max.}$ 1 750 and 1 680 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 8 900 $dm^3\ mol^{-1}\ cm^{-1}$); δ_H 6.54 (1 H, dq, *J* 5.8 and 1.5, 10-H), 5.21 (1 H, ddd, *J* 10.0, 5.0, and 5.0, 3-H), 4.45 (1 H, br d, *J* 5.8, 11-H), 4.11 and 4.02 (2 H, ABq, $J_{obs.}$ 12.0, 15-H), 3.84 (1 H, d, *J* 5, 2-H), 3.11 and 2.88 (2 H, ABq, $J_{obs.}$ 3.9, 13-H), 2.86 (1 H, d, *J* 15.8, 7-Hβ), 2.51 (1 H, dd, *J* 15.8 and 1.4, 7-Hα), 2.30—2.06 (2 H, m, 4-H), 2.13 (3 H, s, MeCO), 1.96 (3 H, s, MeCO), 1.82 (3 H, d, *J* 1.5, 16-H), and 0.81 (3 H, s, 14-H); δ_C 197.1 (C-8), 170.3 (MeCO), 170.2 (MeCO), 138.4 (C-9), 137.1 (C-10), 77.9 (C-2), 70.9 (C-3), 68.6 (C-11), 64.9 (C-12), 64.8 (C-15), 48.2 (C-13), 46.4 (C-5), 45.2 (C-6), 38.4 (C-4), 38.1 (C-7), 20.9 (MeCO), 20.6 (MeCO), 15.5 (C-16), and 11.2 (C-14) (Found: C, 62.6; H, 6.8%; M^+, 364.1520. $C_{19}H_{24}O_7$ requires C, 62.6; H, 6.6%; *M*, 364.1522).

3α,15-*Dihydroxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (**13**).—Potassium carbonate (500 mg, 3.6 mmol) was added to a solution of the diacetate (**12**) (81 mg, 0.22 mmol) in MeOH (10 ml) and water (0.5 ml). The mixture was stirred at 20 °C for 1 h, after which it was concentrated, and the residue was taken up in water and extracted thoroughly with AcOEt. The combined organic extracts were dried and concentrated. Purification of the residue by flash chromatography gave the *diol* (**13**) (56 mg, 90%) as a white solid; $\nu_{max.}$(KBr) 3 600—3 200br, 1 680, and 1 660 cm^{-1}; δ_H($CDCl_3$ + 1 drop MeOD, 90 MHz) 6.65 (1 H, br d, *J* 6, 10-H), 4.7 (1 H, br d, *J* 6, 11-H), 4.5 (1 H, ddd, *J* 11, 6, and 6, 3-H), 3.65 (2 H, br s, 15-H), 3.6 (1 H, d, *J* 6, 2-H), 3.1 and 2.9 (2 H, ABq, $J_{obs.}$ 4, 13-H), 2.9—2.1 (4 H, m, 4-H and 7-H), 1.85 (3 H, br s, 16-H), and 0.85 (3 H, s, 14-H) (Found: M^+, 280.1317. $C_{15}H_{20}O_5$ requires *M*, 280.1311).

3α,15-*Bistrimethylsilyloxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (**14**).—Chlorotrimethylsilane (1 ml, excess) was added to a solution of the diol (**13**) (55 mg, 0.2 mmol) in ether (3 ml) and pyridine (6 ml). The mixture was stirred at 20 °C for 18 h after which it was diluted with ether, washed once with water, dried, and concentrated. Purification of the residue by flash chromatography gave the *bistrimethylsilyl ether* (**14**) (75 mg, 88%) as a colourless oil; $\nu_{max.}$(CCl_4) 1 680 cm^{-1}; δ_H 6.57 (1 H, dq, *J* 5.8 and 1.5, 10-H), 4.75 (1 H, br d, *J* 5.8, 11-H), 4.40 (1 H, ddd, *J* 10.5, 4.6, and 4.0, 3-H), 3.53 (2 H, s, 15-H), 3.47 (1 H, d, *J* 4.6, 2-H), 3.05 and 2.84 (2 H, ABq, $J_{obs.}$ 4.0, 13-H), 2.78 (1 H, d, *J* 15.9, 7-Hβ), 2.37 (1 H, dd, *J* 15.9 and 1.4, 7-Hα), 2.24 (1 H, dd, *J* 14.3 and 4, 4-Hα), 2.04 (1 H, dd, *J* 14.3 and 10.5, 4-Hβ), 1.81 (3 H, d, *J* 1.5, 16-H), 0.77 (3 H, s, 14-H), 0.15 (9 H, s, $SiMe_3$), and 0.01 (9 H, s, $SiMe_3$); δ_C 198.3 (C-8), 138.0 (C-9 and C-10), 79.9 (C-3), 69.5 (C-2), 68.6 (C-11), 66.0 (C-12), 64.1 (C-15), 48.2 (C-13), 47.4 (C-5), 45.2 (C-6), 42.6 (C-4), 38.5 (C-7), 15.5 (C-16), 11.2 (C-14), 0.41 ($SiMe_3$), and −0.99 ($SiMe_3$) (Found: M^+, 424.2126. $C_{21}H_{36}O_5Si_2$ requires *M*, 424.2111).

3α,7α,15-*Tristrimethylsilyloxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (*Deoxynivalenol Tristrimethylsilyl Ether*) (**16**).—A solution of chlorotrimethylsilane (0.6 ml, 4.7 mmol) in THF (5 ml), cooled to −78 °C, was added with stirring to a freshly prepared solution of lithium di-isopropylamide (0.36M) in THF (3.3 ml), also cooled to −78 °C. To this solution was added a solution of the enone (**14**) (165 mg, 0.39 mmol) in THF (5 ml), and stirring was continued for 1 min, when the reaction was quenched by the addition of triethylamine (0.5 ml). The mixture was then diluted with light petroleum, and washed once with water, dried, and concentrated to give the crude *silyl enol ether* (**15**); δ_H(CCl_4, 90 MHz) 5.7 (1 H, br d, *J* 6, 10-H), 4.6 (1 H, br s, 7-H), 4.45 (1 H, br d, *J* 6, 11-H), 4.25 (1 H, ddd, *J* 10, 5, and 5, 3-H), 3.5 and 3.2 (2 H, ABq, $J_{obs.}$ 12, 15-H), 3.1 (1 H, d, *J* 6, 2-H), 2.75 (2 H, ABq, $J_{obs.}$ 4, 13-H), 2.6—1.8 (2 H, m, 4-H), 1.9 (3 H, br s, 16-H), and 0.85 (3 H, s, 14-H).

m-Chloroperbenzoic acid (80%; 85 mg, 3.9 mmol) was added with stirring to a solution of the silyl enol ether (**15**) (0.39 mmol assumed) in hexane (15 ml), cooled to −15 °C. Stirring was continued for 0.5 h at −15 °C and then for 2 h at 30 °C. The mixture was then concentrated, and the residue subjected to flash chromatography to give the desired α′-*trimethylsilyloxy enone* (**16**) (54 mg, 39% based on consumed starting material), recovered enone (**14**) (21 mg), and rearranged by-product (**17**) (51 mg).

The α′-trimethylsilyloxy enone (**16**) was obtained as a colourless oil; $\nu_{max.}$(CCl_4) 1 695 cm^{-1}; δ_H 6.5 (1 H, dq, *J* 6 and 1.4, 10-H), 4.96 (1 H, br d, *J* 6, 11-H), 4.91 (1 H, s, 7-H), 4.38 (1 H, ddd, *J* 10.8, 4.3, and 4.3, 3-H), 3.75 and 3.67 (2 H, ABq, $J_{obs.}$ 10.7, 15-H), 3.53 (1 H, d, *J* 4.3, 2-H), 3.08 and 2.99 (2 H, ABq, $J_{obs.}$ 4.5, 13-H), 2.38 (1 H, dd, *J* 14.5 and 4.3, 4-Hα), 1.95 (1 H, dd, *J* 14.5 and 10.8, 4-Hβ), 1.80 (3 H, d, *J* 1.4, 16-H), 1.00 (3 H, s, 14-H), 0.16 (9 H, s, $SiMe_3$), 0.15 (9 H, s, $SiMe_3$), and 0.00 (9 H, s, $SiMe_3$); δ_C 199.1 (C-8), 137.2 (C-10), 136.3 (C-9), 80.85 (C-7), 76.8 (C-2), 70.6 (C-11), 69.3 (C-3), 65.8 (C-12), 61.0 (C-15), 52.6 (C-5), 47.2 (C-13), 45.8 (C-6), 45.2 (C-4), 15.5 (C-16), 14.0 (C-14), 1.31 ($SiMe_3$), 0.09 ($SiMe_3$), and −0.95 ($SiMe_3$) (Found: M^+, 512.2453. $C_{24}H_{44}O_6Si_3$ requires *M*, 512.2446). This semi-synthetic tristrimethylsilyl ether (**16**) proved identical by both g.l.c. and g.c.-m.s. with a sample prepared by silylation of natural deoxynivalenol.[34]

The ring-opened product (**17**) was also obtained as an oil; $\nu_{max.}$(CCl_4) 3 600, 3 450br, and 1 700 cm^{-1}; δ_H 6.62 (1 H, dq, *J* 5.7 and 1.5, 10-H), 4.52 (1 H, ddd, *J* 10.3, 4.5, and 4.5, 3-H), 4.42 (1 H, br d, *J* 5.7, 11-H), 4.06 (1 H, d, *J* 2.1, 7-H), 3.93 and 3.60 (2 H, ABq, $J_{obs.}$ 11.5, 13-H), 3.87 (1 H, d, *J* 4.5, 2-H), 3.53 and 3.36 (2 H, ABq, $J_{obs.}$ 11.0, 15-H), 2.14 (1 H, dd, *J* 14.5 and 10.3, 4-Hβ), 1.94 (1 H, dd, *J* 14.5 and 4.5, 4-Hα), 1.84 (3 H, d, *J* 1.5, 16-H), 1.12 (3 H, s, 14-H), 0.13 (9 H, s, $SiMe_3$), and −0.02 (9 H, s, $SiMe_3$); δ_C 194.4 (C-8), 139.2 (C-10), 135.6 (C-9), 83.0 (C-7), 75.7 (C-2), 74.6 (C-12), 70.1 (C-11), 68.6 (C-3), 66.8 (C-13), 61.9 (C-15), 45.7 (C-5), 45.5 (C-6), 41.9 (C-4), 15.7 (C-16), 12.2 (C-14), 0.14 ($SiMe_3$), and −1.14 ($SiMe_3$) (Found: M^+, 440.2041. $C_{21}H_{36}O_6Si_2$ requires *M*, 440.2050).

3α,7α,15-*Trihydroxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (*Deoxynivalenol*) (**2**).—To a stirred solution of the tristrimethylsilyl ether (**16**) (25 mg, 0.049 mmol) in MeCN (1 ml) and water (1 ml) was added aqueous HF (40%; 3 drops). After 0.5 h, potassium carbonate (0.5 g) was added; the mixture was then diluted with brine and extracted thoroughly with AcOEt (4 × 15 ml). The combined organic layers were dried and concentrated. Purification of the residue by flash chromatography gave the *triol* (**2**) (14 mg, 99%) as a white solid which could not be crystallised; δ_H 6.57 (1 H, m, 10-H), 4.80 (2 H, s + br d, 7-H and 11-H), 4.51 (1 H, ddd, *J* 10.6, 4.5, and 4.5, 3-H), 3.88 and 3.71 (2 H, ABq, $J_{obs.}$ 11.7, 15-H), 3.61 (1 H, d, *J* 4.5, 2-H), 3.15 and 3.07 (2 H, ABq, $J_{obs.}$ 4.3, 13-H), 2.20 (1 H, dd, *J* 14.7 and 4.5, 4-Hα), 2.05 (1 H, dd, *J* 14.7 and 10.6, 4-Hβ), 1.68 (3 H, d, *J* 1.3, 16-H), and 1.11 (3 H, s, 14-H) (Found: M^+, 296.1250. $C_{15}H_{20}O_6$ requires *M*, 296.1250). The triol was fully characterised as its triacetate (**18**).

3α,7α,15-*Triacetoxy*-12,13-*epoxytrichothec*-9-*en*-8-*one* (*Deoxynivalenol Triacetate*) (**18**).—Excess of triethylamine (1.35 ml), acetic anhydride (1.0 ml), and DMAP (a few crystals, catalytic) were added to a solution of the triol (**2**) (24 mg, 0.81 mmol) in dichloromethane (4 ml). The mixture was stirred for 2 days at 25 °C and then diluted with ether, washed once with saturated aqueous sodium hydrogen carbonate and once with water. The organic extract was dried and concentrated under reduced pressure and the residue purified by flash chromatography to give *deoxynivalenol triacetate* (**18**) (32 mg, 94%) as a white crystalline solid, m.p. 152—156 °C (from ethyl acetate–light petroleum) (lit.,[35] 156—157 °C); $[\alpha]_D^{20}$ +75° (*c* 0.2 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 755 and 1 705 cm^{-1}; δ_H 6.53 (1 H, dq, *J* 5.9 and 1.6, 10-H), 6.03 (1 H, s, 7-H), 5.19 (1 H, ddd, *J* 11, 4.5, and 4.5, 3-H), 4.72 (1 H, d, *J* 5.9, 11-H), 4.37 and 4.26 (2 H, ABq, $J_{obs.}$ 12.2, 15-H), 3.88 (1 H, d, *J* 4.5, 2-H), 3.10 and 2.78 (2 H, ABq, $J_{obs.}$ 3.5, 13-H), 2.34 (1 H, dd, *J* 15.2 and 4.5, 4-Hα), 2.19 (1 H, dd, *J* 15.2 and 11, 4-Hβ), 2.18 (3 H, s, MeCO), 2.12 (3 H, s, MeCO), 1.88 (3 H, s, MeCO), 1.82 (3 H, br s, 16-H), and 0.93 (3 H, s, 14-H); δ_C 191.9 (C-8), 170.1 (MeCO), 170.0 (MeCO), 169.6 (MeCO), 136.9 (C-9), 136.8 (C-10), 78.7 (C-7), 74.6 (C-2), 70.6 (C-11), 70.2 (C-3), 64.5 (C-12), 62.3 (C-15), 50.0 (C-5), 47.6 (C-13), 45.6 (C-6), 40.7 (C-4), 20.8 (2 × MeCO), 20.5 (MeCO), 15.3 (C-16), and 13.6 (C-14) (Found: C, 59.8; H, 6.1%; M^+, 422.1551. $C_{21}H_{26}O_9$ requires C, 59.7; H, 6.2%; *M*, 422.1557). This material proved identical in all respects with authentic triacetate prepared from natural 3-acetyldeoxynivalenol.

4β-*Acetoxy*-10β-*bromo*-3α-*hydroxy*-9α,15;12,13-*diepoxytrichothecane* (**21**).—To a solution of 4β-acetoxy-12,13-epoxytrichothec-9-ene-3α,15-diol (**20**) (203 mg, 0.78 mmol) in dry MeCN (25 ml) was added NBS (146 mg, 0.82 mmol). The mixture was stirred at 20 °C for 1 h and then concentrated. Purification of the residue by dry column flash chromatography gave the *bromo ether* (**21**) (288 mg, 92%) as a white amorphous solid; $[\alpha]_D^{20}$ −29.4° (*c* 0.65 in $CHCl_3$); $\nu_{max.}$(CCl_4) 3 555 and 1 740 cm^{-1}; δ_H 5.04 (1 H, d, *J* 3.2, 4-H), 4.25 (2 H, m, 10-H and 11-H), 4.21 (1 H, dd, *J* 5.0 and 3.2, 3-H), 3.82 (1 H, dd, *J* 9.6 and 2.7, 15-Hα), 3.79 (1 H, d, *J* 5.0, 2-H), 3.70 (1 H, d, *J* 9.6, 15-Hβ), 3.05 and 2.73 (2 H, ABq, $J_{obs.}$ 3.8, 13-H), 2.10 (3 H, s, MeCO), 2.20 (1 H, dd, *J* 12.6 and 10.0, 8-Hβ), 2.15—1.95 (1 H, m, 7-Hβ), 1.85—1.65 (1 H, m, 8-Hα), 1.60—1.40 (1 H, m, 7-Hα), 1.26 (3 H, s, 16-H), and 0.61 (3 H, s, H-14); δ_C 172.2 (MeCO), 83.1 (C-3), 79.7 (C-4), 78.1 (C-2), 73.7 (C-9), 68.3 (C-11), 66.0 (C-15), 64.1 (C-12), 54.2 (C-10), 46.4 (C-13), 46.1 (C-5), 41.8 (C-6), 27.9 (C-8), 24.2 (C-16), 20.9 (MeCO), 19.2 (C-7), and 5.8 (C-14) (Found: M^+, 404.0668 and 402.0655. $C_{17}H_{25}BrO_6$ requires *M*, 404.0659 and 402.0678).

3α,4β-*Diacetoxy*-10β-*bromo*-9α,15;12,13-*diepoxytrichothecane* (**22**).—The bromo-ether (**21**) (278 mg, 0.69 mmol) was acetylated by the normal procedure. Purification by dry column flash chromatography gave the *diacetate* (**22**) (305 mg, 99%) as a white, low-melting amorphous solid; $[\alpha]_D^{20}$ −18.2° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 750 cm^{-1}; δ_H 5.57 (1 H, d, *J* 3.6, 4-H), 5.25 (1 H, dd, *J* 4.9 and 3.6, 3-H), 4.28 (1 H, dd, *J* 8.6 and 1.8, 11-H), 4.12 (1 H, dd, *J* 8.6 and 2.4, 10-H), 3.99 (1 H, dd, *J* 9.8 and 2.8, 15-Hα), 3.96 (1 H, d, *J* 4.9, 2-H), 3.71 (1 H, d, *J* 9.8, 15-Hβ), 3.07 and 2.75 (2 H, ABq, $J_{obs.}$ 3.9, 13-H), 2.30—2.16 (1 H, dd, *J* 12.7 and 7.6, 8-Hβ), 2.10 (3 H, s, MeCO), 2.09 (3 H, s, MeCO), 1.88—1.62 (1 H, m, 7-Hα), 1.60—1.40 (1 H, m, 8-Hα), 1.28 (3 H, s, 16-H), and 0.55 (3 H, s, 14-H); δ_C 170.6 (MeCO), 169.8 (MeCO), 78.4 (C-4), 78.0 (C-2), 77.8 (C-3), 73.7 (C-9), 68.5 (C-11), 66.0 (C-15),

63.8 (C-12), 54.2 (C-10), 46.4 (C-13), 46.1 (C-5), 41.9 (C-6), 27.9 (C-8), 24.2 (C-16), 20.9 (MeCO), 20.7 (MeCO), 19.4 (C-7), and 5.5 (C-14) (Found: M^+, 446.0770 and 444.0794. $C_{19}H_{25}BrO_7$ requires M, 446.0764 and 444.0784).

3α,4β-*Diacetoxy*-10β-*bromo*-9α,15-*epoxytrichothec*-12-*ene* (**23**).—To WCl_6 (802 mg, 2.02 mmol), pre-cooled to −196 °C (liquid nitrogen), was slowly added THF (5.2 ml). After 5 min, butyl-lithium (2.4M) in hexane (2.1 ml) was added. The cooling bath was removed, and the mixture allowed to warm to 20 °C with stirring, when it became dark brown and homogeneous. It was then re-cooled to −78 °C, and a solution of the epoxide (**22**) (300 mg, 0.67 mmol) in THF (8.5 ml) was added. The cooling bath was removed, and the reaction mixture was heated under reflux for 6 h. On cooling to 20 °C, the mixture was diluted with hexane, washed once with an aqueous solution of both NaOH (2M) and sodium tartrate (1.5M) and once with water. The organic solution was dried, concentrated, and the residue purified by flash chromatography, to give the *alkene* (**23**) (285 mg, 98%) as a white crystalline solid, m.p. 102—106 °C (from light petroleum); $[\alpha]_D^{20}$ −18.2° (*c* 0.94 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 745 and 910 cm^{-1}; δ_H 5.53 (1 H, d, *J* 3.5, 4-H), 5.25 (1 H, s, 13-H_a), 4.91 (1 H, dd, *J* 5.0 and 3.5, 3-H), 4.82 (1 H, s, 13-H_b), 4.57 (1 H, d, *J* 5.0, 2-H), 4.25 (1 H, dd, *J* 8.6 and 1.6, 11-H), 4.14 (1 H, dd, *J* 8.6 and 2.4, 10-H), 3.98 (1 H, dd, *J* 9.7 and 2.7, 15-Hα), 3.71 (1 H, d, *J* 9.7, 15-Hβ), 2.28—2.16 (1 H, m, 8-Hβ), 2.13 (3 H, s, MeCO), 2.04 (3 H, s, MeCO), 1.92—1.65 (2 H, m, 7-H), 1.42—1.20 (1 H, m, 8-Hα), 1.26 (3 H, s, 16-H), and 0.79 (3 H, s, 14-H); δ_C 170.3 (MeCO), 170.1 (MeCO), 147.3 (C-12), 109.3 (C-13), 78.3 (C-2), 78.1 (C-4), 73.3 (C-9), 68.2 (C-11), 66.3 (C-15), 54.8 (C-10), 49.1 (C-5), 41.5 (C-6), 27.8 (C-8), 24.2 (C-16), 21.0 (MeCO), 20.7 (MeCO), 18.7 (C-7), and 9.48 (C-14) (Found: M^+, 430.0810 and 428.0830. $C_{19}H_{25}BrO_6$ requires M, 430.0815 and 428.0830).

3α,4β-*Diacetoxy*-10β-*bromo*-9α,15-*epoxynortrichothecene*-12-*one* (**24**).—Ozone was bubbled through a solution of the alkene (**23**) (530 mg, 1.24 mmol) in dichloromethane (50 ml), cooled to −78 °C, until the blue colour of excess ozone appeared. The solution was kept at −78 °C for 15 min; if the blue colour had been discharged by this time, the above procedure was repeated until the blue colour persisted. The solution was then purged with nitrogen, and the ozonide was reduced by the addition of triethylamine (0.34 ml, 2.47 mmol) at −78 °C followed by stirring overnight at 20 °C. The solution was filtered through a short column of chromatographic silica gel and concentrated to give the *nor-ketone* (**24**) (462 mg, 87%) as a white crystalline solid, m.p. 187—190 °C (from ether–light petroleum); $[\alpha]_D^{20}$ +65° (*c* 0.36 in $CHCl_3$); $\nu_{max.}$(CCl_4) 1 770 and 1 750 cm^{-1}; δ_H 5.71 (1 H, d, *J* 3.8, 4-H), 5.08 (1 H, dd, *J* 5.0 and 3.8, 3-H), 4.37 (1 H, dd, *J* 8.6 and 2.1, 10-H), 4.27 (1 H, dd, *J* 8.6 and 1.6, 11-H), 4.22 (1 H, d, *J* 5, 2-H), 4.06 (1 H, dd, *J* 9.5 and 2.6, 15-Hα), 3.67 (1 H, d, *J* 9.5, 15-Hβ), 2.3–2.0 (1 H, m, 8-Hβ), 2.18 (3 H, s, MeCO), 2.06 (3 H, s, MeCO), 1.9—1.5 (3 H, m, 7-H and 8-Hα), 1.28 (3 H, s, 16-H), and 0.76 (3 H, s, 14-H); δ_C 207.8 (C-12), 170.0 (MeCO), 169.6 (MeCO), 77.2, 75.8, and 73.8 (C-2, C-3, and C-4), 73.8 (C-9), 68.2 (C-11), 65.4 (C-15), 55.6 (C-5), 53.5 (C-10), 48.2 (C-6), 27.5 (C-8), 24.0 (C-16), 20.8 (MeCO), 20.6 (MeCO), 18.7 (C-7), and 6.4 (C-14) (Found: C, 50.0; H, 5.4; Br, 18.5%; M^+, 390.0500 and 388.0524. $C_{18}H_{23}BrO_7$ requires C, 50.1; H, 5.4; Br, 18.5%; $C_{18}H_{23}BrO_7 - C_2H_2O$ requires M, 390.0502 and 388.0522).

10β-*Bromo*-9α,15;12,13-epi-*diepoxytrichothecane*-3α,4β-*diol* (**25**).—(a) *From the ketone* (**24**). To a stirred suspension of trimethylsulphonium iodide (560 mg, 2.75 mmol) in THF (11 ml), cooled to 0 °C, was added butyl-lithium (2.4M) in hexane (1.15 ml), and the resulting clear solution was stirred at 0 °C for 1 h. A solution of the ketone (**24**) (148 mg, 0.34 mmol) in THF (5.5 ml) was added, the cooling bath was removed, and stirring was continued for 1 h. The mixture was diluted with ether, washed successively with saturated aqueous ammonium chloride and brine, and then dried. Concentration followed by purification by flash chromatography gave the epi-*epoxide* (**25**) (43 mg, 35%) as a white crystalline solid, m.p. 207—208 °C (from ethyl acetate–light petroleum); $[\alpha]_D^{20}$ −51.6° (*c* 0.51 in MeOH); $\nu_{max.}$(KBr) 3 600—3 200br cm^{-1}; δ_H 4.22 (1 H, dd, *J* 8.6 and 1.4, 11-H), 4.14 (1 H, dd, *J* 8.6 and 1.8, 10-H), 4.05 (1 H, d, *J* 2.9, 4-H), 3.97 (1 H, dd, *J* 4.7 and 2.9, 3-H), 3.72 (1 H, d, *J* 9.3, 15-Hβ), 3.70 (1 H, d, *J* 4.7, 2-H), 3.62 (1 H, dd, *J* 9.3 and 1.5, 15-Hα), 2.70 and 2.40 (2 H, ABq, $J_{obs.}$ 4.5, 13-H), 2.37—2.10 (2 H, m, 7-Hβ and 8-Hβ), 1.80—1.45 (2 H, m, 7-Hα and 8-Hα), 1.22 (3 H, s, 16-H), and 0.56 (3 H, s, 14-H); δ_C 79.6 (C-4), 78.4 (C-3), 78.0 (C-2), 74.0 (C-9), 68.4 (C-11), 66.3 (C-15), 62.6 (C-12), 54.5 (C-10), 45.5 (C-13), 45.2 (C-5), 39.8 (C-6), 28.0 (C-8), 24.3 (C-16), 19.4 (C-7), and 7.1 (C-14) (Found: C, 49.8; H, 5.9; Br, 21.9%; M^+, 362.0545 and 360.0570. $C_{15}H_{21}BrO_5$ requires C, 49.9; H, 5.9; Br, 22.1%; M, 362.0553 and 360.0573).

(b) *From bistriethylsilyl ether* (**28**). To a stirred suspension of trimethylsulphonium iodide (141 mg, 0.7 mmol) in THF (10 ml), cooled to 0 °C, was added butyl-lithium (2.4M) in hexane (0.305 ml), and the resulting clear solution was stirred at 0 °C for 1 h. A solution of the ketone (**28**) (290 mg, 0.5 mmol) in THF (6 ml) was added, the cooling bath was removed, and stirring was continued for 1 h. Product isolation as before gave the epi-*epoxide* (**29**) (191 mg, 65%) as a colourless oil; $[\alpha]_D^{20}$ −27.1° (*c* 0.35 in $CHCl_3$); δ_H 4.24 (1 H, dd, *J* 8.7 and 2.1, 10-H), 4.15 (1 H, dd, *J* 8.7 and 1.5, 11-H), 4.05 (1 H, d, *J* 2.5, 4-H), 3.96 (1 H, dd, *J* 4.8 and 2.5, 3-H), 3.75 (1 H, d, *J* 9.1, 15-Hβ), 3.63 (2 H, d and dd, *J* 4.8 and *J* 9.1 and 2.6, 2-H and 15-Hα), 2.66 and 2.38 (2 H, ABq, $J_{obs.}$ 4.6, 13-H), 2.42—2.12 (2 H, m, 7-Hβ and 8-Hβ), 1.80—1.61 (1 H, m, 7-Hα), 1.60—1.44 (1 H, m, 8-Hα), 1.25 (3 H, s, 16-H), 0.95 (6 H, 2 × t, CH_3CH_2), 0.60 (4 H, 2 × q, CH_3CH_2), and 0.55 (3 H, s, 14-H); δ_C 80.9 (C-3), 80.7 (C-4), 79.7 (C-11), 73.8 (C-9), 68.0 (C-2), 66.5 (C-15), 62.6 (C-12), 54.4 (C-10), 45.5 (C-13), 45.4 (C-5), 39.9 (C-6), 28.0 (C-8), 24.5 (C-16), 19.7 (C-7), 7.6 (C-14), 6.8 (2 × CH_3CH_2), 4.9 (CH_3CH_2), and 4.8 (CH_3CH_2) (Found: M^+, 561.1891 and 559.1913. $C_{27}H_{49}BrO_5Si_2 - C_2H_5$ requires M, 561.1891 and 559.1911).

To a solution of the *epi*-epoxide (**29**) (114 mg, 0.194 mmol) in THF (6 ml), cooled to 0 °C, was added tetrabutylammonium fluoride (1M) in THF (0.78 ml). The mixture was stirred at 0 °C for 2 h, diluted with ethyl acetate, washed with brine, dried, and concentrated. Purification of the residue by flash chromatography gave the epi-*epoxide* (**25**) (61 mg, 87%), identical in all respects with that prepared above.

3α,4β-*Dihydroxy*-10β-*bromo*-9α,15-*epoxytrichothec*-12-*ene* (**26**).—Potassium carbonate (2 g) was added to a solution of the diacetate (**23**) (151 mg, 0.35 mmol) in MeOH (9 ml) and water (1 ml) and the mixture was stirred for 2 h at 20 °C. It was then concentrated and the residue was taken up in water and extracted with AcOEt (×3). The combined organic extracts were dried and concentrated. Purification of the residue by flash chromatography gave the *diol* (**26**) (103 mg, 85%) as a white crystalline solid, m.p. 122—123 °C (from ether–hexane); $[\alpha]_D^{20}$ −34.6° (*c* 0.78 in MeOH); $\nu_{max.}$(CCl_4) 3 600—3 200br and 910 cm^{-1}; δ_H 5.17 (1 H, s, 13-Ha), 4.78 (1 H, s, 13-Hb), 4.4—3.6 (9 H, m, 2-H, 3-H, 4-H, 10-H, 11-H, 15-H, and 2 × OH), 2.25—1.25 (4 H, 7-H and 8-H), 1.25 (3 H, s, 16-H), and 0.86 (3 H, s, 14-H); δ_C 148.6 (C-12), 108.7 (C-13), 81.1, 79.9, and 79.5 (C-2, C-3, and C-4), 73.5 (C-9), 68.1 (C-11), 66.5 (C-15), 55.1 (C-10), 49.9 (C-5), 40.8 (C-6), 27.8 (C-8), 24.3 (C-16), 18.7 (C-7), and 10.0 (C-14) (Found: C, 52.2; H, 6.1; Br, 23.35%; M^+, 346.0596 and 344.0633. $C_{15}H_{21}BrO_4$ requires C, 52.2; H, 6.1; Br, 23.15%; M, 346.0604 and 344.0624).

3α,4β-*Bistriethylsilyloxy*-10β-*bromo*-9α,15-*epoxytrichothec*-12-*ene* (**27**).—To a solution of the diol (**26**) (225 mg, 0.65 mmol)

in pyridine (15 ml) were added chlorotriethylsilane (0.44 ml, 2.62 mmol) and DMAP (32 mg, 0.26 mmol). The mixture was stirred for 24 h at 20 °C before being diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried and concentrated. Purification of the residue by dry-column flash chromatography gave the *bistriethylsilyl ether* (**27**) (327 mg, 88%) as a white crystalline solid, m.p. 51—52 °C (from AcOEt–MeOH); $[\alpha]_D^{20}$ −33° (*c* 1.09 in $CHCl_3$); δ_H 5.10 (1 H, s, 13-Ha), 4.70 (1 H, s, 13-Hb), 4.20 (1 H, d, *J* 4.8, 2-H), 4.16 (2 H, m, 10-H and 11-H), 4.09 (1 H, d, *J* 2.5, 4-H), 3.80 (1 H, dd, *J* 4.8 and 2.5, 3-H), 3.72 (2 H, br s, 15-H), 2.25—1.2 (4 H, m, 7-H and 8-H), 1.25 (3 H, s, 16-H), 0.95 [6 H, 2 × t (overlapping), *J* 8, 2 × CH_3CH_2], 0.77 (3 H, s, 14-H), and 0.64 [4 H, 2 × q (overlapping), *J* 8, 2 × CH_3CH_2]; δ_C 149.7 (C-12), 107.6 (C-13), 83.2, 81.6, and 80.1 (C-2, C-3, and C-4), 73.3 (C-9), 67.6 (C-11), 66.7 (C-15), 55.0 (C-10), 41.0 (C-6), 27.8 (C-8), 24.4 (C-16), 18.9 (C-7), 10.3 (C-14), 6.9 (2 × CH_3CH_2), 5.0 and 4.9 (2 × CH_3CH_2) (Found: C, 56.3; H, 8.4; Br, 13.45%; M^+, 574.2317 and 572.2342. $C_{27}H_{49}BrO_4Si_2$ requires C, 56.5; H, 8.6; Br, 13.45%; *M*, 574.2333 and 572.2353).

3α,4β-*Bistriethylsilyloxy*-10β-*bromo*-9α,15-*epoxynortrichothecan*-12-*one* (**28**).—A solution of the alkene (**27**) (327 mg, 0.57 mmol) in dichloromethane (30 ml) was treated with an excess of ozone, and the ozonide was reduced with triethylamine (0.25 ml, 1.79 mmol) as before. Purification of the product by dry-column flash chromatography gave the *nor-ketone* (**28**) (275 mg, 84%) as a white crystalline solid, m.p. 90—91 °C (from ether–MeOH); $[\alpha]_D^{20}$ +33.3° (*c* 0.63 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 1 765 cm^{-1}; δ_H 4.4 (1 H, dd, *J* 8.8 and 2.2, 10-H), 4.26 (1 H, d, *J* 2.6, 4-H), 4.18 (1 H, dd, *J* 8.8 and 1.6, 11-H), 3.92 (1 H, dd, *J* 5.0 and 2.6, 3-H), 3.85 (1 H, d, *J* 5.0, 2-H), 3.76 (1 H, dd, *J* 9.2 and 2.4, 15-Hα), 3.67 (1 H, d, *J* 9.2, 15-Hβ), 2.27—2.10 (1 H, m, 8-Hβ), 1.84—1.45 (3 H, m, 8-Hα and 7-H), 1.26 (3 H, s, 16-H), 0.96 [6 H, 2 × t (overlapping), *J* 8.3, 2 × CH_3CH_2], 0.78 (3 H, s, 14-H), and 0.64 [4 H, 2 × q (overlapping), *J* 8.3, 2 × CH_3CH_2]; δ_C 211.2 (C-12), 80.0, 79.3, and 79.0 (C-2, C-3, and C-4), 73.8 (C-9), 67.5 (C-11), 65.8 (C-15), 57.2 (C-5), 53.6 (C-10), 47.3 (C-6), 27.5 (C-8), 24.2 (C-16), 19.0 (C-7), 7.0 (C-14), 6.8 (2 × CH_3CH_2), and 4.9 and 4.8 (2 × CH_3CH_2) (Found: C, 54.1; H, 8.1; Br, 13.7%; M^+, 576.2148 and 574.2155. $C_{26}H_{47}BrO_5Si_2$ requires C, 54.2; H, 8.2; Br, 13.9%; *M*, 576.2126 and 574.2146).

3α,4β-*Diacetoxy*-10β-*bromo*-9α,15;12,13-epi-*diepoxytrichothecane* (**30**).—The diol (**25**) (87 mg, 0.24 mmol) was acetylated by the normal procedure. Purification by flash chromatography gave the *diacetate* (**30**) (103 mg, 96%) as a white crystalline solid, m.p. 160—161 °C (from ether–light petroleum); $[\alpha]_D^{20}$ −42.2° (*c* 0.45 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 1 755 cm^{-1}; δ_H 5.50 (1 H, d, *J* 3.5, 4-H), 5.12 (1 H, dd, *J* 4.8 and 3.5, 3-H), 4.29 (1 H, dd, *J* 8.5 and 1.7, 11-H), 4.19 (1 H, dd, *J* 8.5 and 2.2, 10-H), 4.0 (1 H, d, *J* 4.8, 2-H), 3.93 (1 H, dd, *J* 9.7 and 2.8, 15-Hα), 3.75 (1 H, d, *J* 9.7, 15-Hβ), 2.75 and 2.54 (2 H, ABq, $J_{obs.}$ 4.5, 13-H), 2.47—2.17 (2 H, m, 7-Hβ and 8-Hβ), 2.14 (3 H, s, MeCO), 2.07 (3 H, s, MeCO), 1.85—1.45 (2 H, m, 7-Hα and 8-Hα), 1.28 (3 H, s, 16-H), and 0.54 (3 H, s, 14-H); δ_C 170.0 (2 × MeCO), 77.7 (C-2), 77.5 (C-3), 75.5 (C-4), 73.9 (C-9), 68.8 (C-11), 66.2 (C-15), 62.3 (C-12), 54.2 (C-10), 45.3 (C-13), 44.6 (C-5), 40.5 (C-6), 28.0 (C-8), 24.3 (C-16), 20.9 (MeCO), 20.7 (MeCO), 19.6 (C-7), and 7.23 (C-14) (Found: C, 51.1; H, 5.6; Br, 17.6%; M^+, 446.0748 and 444.0781. $C_{19}H_{25}BrO_7$ requires C, 51.2; H, 5.7; Br, 17.95%; *M*, 446.0764 and 444.0784).

3α,4β,15-*Triacetoxy*-12,13-epi-*epoxytrichothec*-9-*ene* (**31**).—Zinc powder (4.16 g, 0.064 mol) was added in one portion to a stirred, hot suspension of AgOAc (23 mg) in AcOH (23 ml). After 30 s, the AcOH was removed by decantation, and the Zn/Ag couple was washed with AcOH (1 × 10 ml) and ether (5 × 10 ml). Ether (11 ml) was added to the freshly prepared couple, and this was followed by a solution of the bromo ether (**30**) (118 mg, 0.265 mmol) in THF (21 ml) and EtOH (4 ml). The mixture was heated at 55 °C with stirring for 2 h, cooled to 20 °C, and concentrated. The residue was taken up in acetone and the solution filtered through a pad of Celite. Concentration of the filtrate, followed by acetylation by the normal procedure and purification by flash chromatography, gave the *triacetate* (**31**) (87 mg, 80%) as a white crystalline solid, m.p. 169—170 °C (from benzene–hexane); $[\alpha]_D^{20}$ +7.9° (*c* 0.81 in $CHCl_3$); $\nu_{max.}(CCl_4)$ 1 750 cm^{-1}; δ_H 5.71 (1 H, d, *J* 3.2, 4-H), 5.47 (1 H, br d, *J* 5.8, 10-H), 5.02 (1 H, dd, *J* 4.8 and 3.2, 3-H), 4.20 and 4.06 (2 H, ABq, $J_{obs.}$ 12.4, 15-H), 4.05 (1 H, br d, *J* 5.8, 11-H), 3.83 (1 H, d, *J* 4.8, 2-H), 2.81 and 2.50 (2 H, ABq, $J_{obs.}$ 4.6, 13-H), 2.14 (3 H, s, MeCO), 2.08 (3 H, s, MeCO), 2.06 (3 H, s, MeCO), 1.71 (3 H, br s, 16-H), and 0.76 (3 H, s, 14-H); δ_C 170.6 (MeCO), 170.1 (MeCO), 169.9 (MeCO), 140.6 (C-9), 118.2 (C-10), 78.5 (C-2), 76.6 (C-3), 76.1 (C-4), 68.1 (C-11), 63.8 (C-15), 62.7 (C-12), 47.1 (C-5), 45.7 (C-13), 42.8 (C-6), 27.8 (C-8), 23.2 (C-16), 21.1 (C-7), 21.0 (MeCO), 20.9 (MeCO), 20.7 (MeCO), and 8.13 (C-14) (Found: C, 61.8; H, 6.7%; M^+, 348.1579. $C_{21}H_{28}O_8$ requires C, 61.7; H, 6.9%; $C_{21}H_{28}O_8$ − AcOH requires *M*, 348.1573).

Table 2. Non-hydrogen atom co-ordinates in 3α,4β,15-triacetoxy-12,13-*epi*-epoxytrichothec-9-ene (**31**)

	x	*y*	*z*
O(1)	0.385 46(18)	0.011 08(13)	0.793 07(10)
O(2)	0.242 26(19)	0.190 35(12)	0.763 27(11)
O(3)	0.340 6(3)	0.205 8(2)	0.638 5(1)
O(4)	−0.072 18(19)	0.077 36(16)	0.754 70(12)
O(5)	−0.188 3(3)	0.122 3(3)	0.869 8(2)
O(6)	0.110 8(3)	0.084 9(2)	0.983 1(1)
O(7)	−0.058 6(3)	0.057 6(2)	1.077 0(2)
O(8)	0.211 6(3)	−0.165 5(2)	0.720 2(1)
C(2)	0.280 3(3)	0.013 5(2)	0.730 4(1)
C(3)	0.176 7(3)	0.100 3(2)	0.736 5(2)
C(4)	0.062 0(3)	0.069 2(2)	0.798 6(2)
C(5)	0.094 9(3)	−0.040 9(2)	0.821 1(2)
C(6)	0.205 2(3)	−0.045 7(2)	0.894 5(1)
C(7)	0.265 2(3)	−0.151 1(2)	0.904 3(2)
C(8)	0.383 2(3)	−0.160 9(2)	0.969 1(2)
C(9)	0.483 0(3)	−0.076 2(2)	0.972 5(2)
C(10)	0.458 4(3)	0.006 7(2)	0.931 2(2)
C(11)	0.332 1(3)	0.023 4(2)	0.876 2(1)
C(12)	0.172 5(3)	−0.067 7(2)	0.741 1(2)
C(13)	0.109 6(4)	−0.114 9(3)	0.668 8(2)
C(14)	−0.037 6(4)	−0.102 4(2)	0.836 8(3)
C(15)	0.136 7(3)	−0.018 7(2)	0.977 4(2)
C(16)	0.615 9(5)	−0.090 0(3)	1.022 8(2)
C(17)	0.324 7(3)	0.236 0(2)	0.706 6(2)
C(18)	0.392 5(3)	0.325 6(2)	0.741 6(2)
C(19)	−0.188 8(3)	0.105 9(2)	0.797 4(2)
C(20)	−0.315 3(3)	0.111 2(3)	0.741 6(3)
C(21)	0.006 7(4)	0.113 2(3)	1.035 3(2)
C(22)	−0.007 2(6)	0.222 2(3)	1.034 9(3)

Crystal Data for Compound (**31**).—$C_{21}H_{28}O_8$, *M* = 408.5. Orthorhombic, *a* = 9.375(1), *b* = 13.682(2), *c* = 16.207(2) Å, *V* = 2 078.6 Å^3, Cu-K_α, λ = 1.5418 Å, space group $P2_12_12_1$, *Z* = 4, D_x = 1.30 g cm^{-3}, *F*(000) = 872, *T* = 291 K, final *R* = 0.053 for 2 343 observed reflections. A large, cube-shaped colourless crystal, grown from benzene–hexane. μ = 7.61 cm^{-1}. For non-hydrogen atoms co-ordinates, see Table 2.

Crystallographic Measurements.—Cell dimensions were derived by least-squares treatment of the setting angles of 25

reflections on an Enraf–Nonius CAD-4 diffractometer with Cu-K_α radiation. 2 435 Observed intensities were collected in the range $\theta \leqslant 75°$ and of these 2 343 satisfied the criterion $I \geqslant 3\sigma_I$.

Structure Analysis.—The crystal structure was solved using the direct phasing procedure MITHRIL.[36] Refinement with anisotropic thermal parameters for the C and O atoms with H atoms included, but not refined, in the final two cycles of least-squares converged at R 0.053, R_w 0.078 with weights $w_\alpha 1/\sigma^2(F)$.

Thermal parameters, hydrogen atom co-ordinates, bond angles, and bond distances are available on request from the Cambridge Crystallographic Data Centre.*

Testing Methods.[30]—*Tissue culture*: human epithelial cells (HEp-2 line) were maintained in Hank's-based modified Eagles medium supplemented with 15% donor calf serum, sodium hydrogen carbonate (0.43mM), HEPES (20mM), and glutamine (2mM) (Flow Laboratories, Rickmansworth, U.K.).

Cytotoxicity. The assay was carried out in a 96-well microtitre plate. Maintenance medium (40 μl) was placed in the top row of wells, together with test compound dissolved in acetone (10 μl). Medium (50 μl) was added to the remaining wells, and a two-fold serial dilution of each test compound was carried out down the column of wells. A suspension of cells was prepared containing 2—3 × 10^5 cells ml^{-1} and 100 μl was added to each well. The plates were sealed, incubated at 37 °C, and examined by microscope after 24 and 48 h. The lowest concentration of test compound completely inhibiting cell division was recorded. Solvent blanks and assays were performed in duplicate on each plate.

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* For details see 'Instructions for Authors (1989)' in *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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