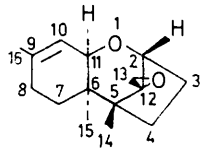
Total Synthesis of (±)-Trichodermin [1]

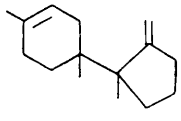
By **Ernest W. Colvin,* Swiatoslaw Malchenko, Ralph A. Raphael,*† and James S. Roberts,** Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

The first total synthesis of a member of the antibiotic trichothecane group of sesquiterpenes, trichodermin (12,13-epoxytrichothec-9-en-4β-yl acetate) (3), is described.

THE trichothecane group of antibiotics constitutes a class of metabolites produced in the main by various species of *Trichothecium, Trichoderma, Myrothecium,* and *Fusarium.*[2] Many of the members show pronounced antifungal, cytotoxic, and phytotoxic effects.[3] Structurally they have all been shown [4] to be derivatives of the tetracyclic 12,13-epoxytrichothec-9-ene skeleton of the stereochemistry indicated (1). The biosynthesis of these highly perverted sesquiterpenes has aroused considerable interest and it is now becoming clearer that they are derived from farnesyl pyrophosphate by a pathway probably implicating the hydrocarbon trichodiene (2), formed by two 1,2-methyl shifts.[5] Hitherto, however, virtually no synthetic attempts on these structures have been reported. We now record the total stereoselective synthesis of a member of this group, trichodermin (3), in racemic form.‡



(1)



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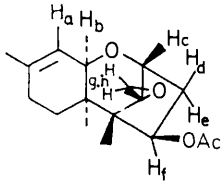


(3)

It was desirable that the potential to attain the desired *cis*-fusion between the two six-membered rings of trichodermin should be built in to the synthetic pathway as early as possible. To that end our first goal was the *cis*-fused bicyclic γ-lactone (13); in systems of this type it has already been established that the *cis*-stereoisomer is the thermodynamically favoured one.[6] The starting material, *p*-methoxytoluene, was subjected to a Birch reduction and the resulting dihydro-compound (4) was transformed into the requisite 4,4-disubstituted cyclohexenones (6; X = CO_2Et or CN) by the following two procedures. In the first, acid-catalysed reaction with methanol gave the corresponding dimethyl acetal, which, by reaction with ethyl diazoacetate, yielded the corresponding cyclopropane ester, readily convertible into the parent ketone (5), by transacetalisation with acetone. Sodium acetate treatment, as already described,[7] effected smooth fragmentation to the cyclohexenone (6; X = CO_2Et). In the second method, low-temperature Diels–Alder reaction of (4) with α-chloroacrylonitrile took place in the expected regioselective manner to give the adduct (7). If the temperature was allowed to rise too high a considerable proportion of secondary product was obtained which proved to be 5-methyl-2-oxobicyclo-[3.2.1]oct-6-ene-1-carbonitrile (8), the formation of which may be rationalised as shown. Reaction of the adduct with sodium sulphide [8] led smoothly to the corresponding bicyclic ketone (9). The crystalline oxime of (9) was then tosylated in the presence of base; the presumed intermediate oxime tosylate underwent ready fragmentation under these conditions to give a high yield of the keto-nitrile (6; X = CN) by an abnormal Beckmann process.

Careful treatment of the unsaturated keto-ester (6; X = CO_2Et) with methylmagnesium chloride gave

† *Present address:* University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

‡ All racemic structures are illustrated by one enantiomer.

[1] Preliminary communication, E. W. Colvin, R. A. Raphael, and J. S. Roberts, *Chem. Comm.*, 1971, 858.

[2] W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971, p. 219; 'Microbial Toxins,' eds. S. Kadis, A. Ciegler, and S. R. Ajl, Academic Press, London, 1971, vol. 7, p. 191.

[3] P. W. Brian, A. W. Dawkins, J. F. Grove, H. G. Hemming, D. Lowe, and G. L. F. Norris, *J. Exp. Bot.*, 1961, **12**, 1; J. F. Grove and P. Mortimer, *Biochem. Pharmacol.*, 1969, **18**, 1473.

[4] W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, 1965, **19**, 1088; J. F. Grove, *J. Chem. Soc.* (*C*), 1970, 378 and references therein; P. Traxler, W. Zurcher, and Ch. Tamm, *Helv. Chim. Acta*, 1970, **53**, 2071 and references therein; W. O. Godtfredsen, J. F. Grove, and Ch. Tamm, *ibid.*, 1967, **50**, 1666; A. T. McPhail and G. A. Sim, *J. Chem. Soc.* (*C*), 1966, 1394; D. Gardner, A. T. Glen, and W. B. Turner, *J.C.S. Perkin I*, 1972, 2576.

[5] Y. Machida and S. Nozoe, *Tetrahedron*, 1972, **28**, 5105, 5113; *Tetrahedron Letters*, 1972, 1969; 1970, 2671; B. A. Achilladelis, P. M. Adams, and J. R. Hanson, *J.C.S. Perkin I*, 1972, 1425; *Chem. Comm.*, 1970, 511; P. M. Adams and J. R. Hanson, *ibid.*, p. 1569; R. Achini, B. Müller, and Ch. Tamm, *ibid.*, 1971, 404; E. R. H. Jones and G. Lowe, *J. Chem. Soc.*, 1960, 3959.

[6] M. S. Newman and C. S. Vanderwerf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.

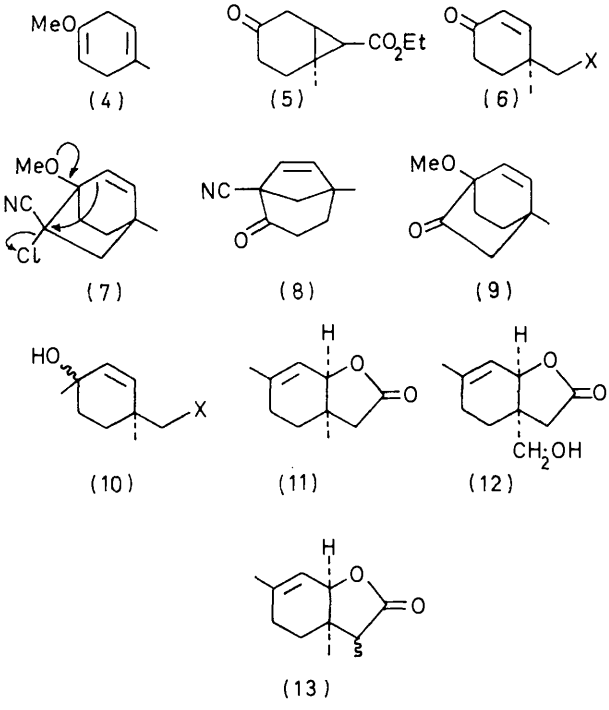
[7] R. D. Stipanovic and R. B. Turner, *J. Org. Chem.*, 1968, **33**, 3261.

[8] D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Letters*, 1972, 121.

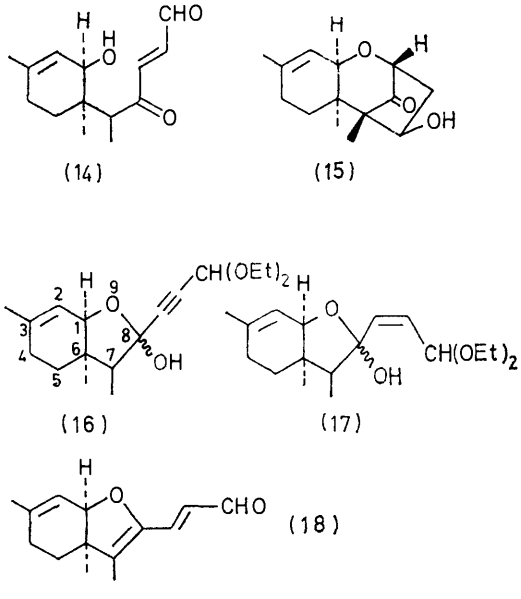
the tertiary alcohol (10; X = CO_2Et), which, without further purification, was hydrolysed with base and the product was acidified. This procedure gave in high yield the crystalline *cis*-fused γ-lactone (11), presumably formed *via* the intermediacy of the allylic carbonium ion [9] derived from (10; X = CO_2H). Similar Grignard treatment of the keto-nitrile (6; X = CN) gave the corresponding tertiary alcohol (10; X = CN) which, by acidic hydrolysis, was converted into the same γ-lactone (11). In this case the apparently possible intramolecular Ritter reaction (to give the corresponding lactam) does not seem to take place. Presumably the amide (10; X = $CO{\cdot}NH_2$) is the intermediate, the consequent formation of the lactone resulting from the greater nucleophilicity of the oxygen centre of an amide group (the exclusive formation of imino-esters by interaction of amides and trialkyloxonium salts is a more familiar example).

The spectroscopic properties of the γ-lactone (11) were consistent with the structure indicated.[10] The vital *cis*-fusion was further demonstrated by the fact that dissolution in aqueous base and reacidification regenerated the starting lactone.[6] An *X*-ray analysis of the closely similar γ-lactone (12) made in these laboratories in exactly analogous fashion shows this stereochemical feature unambiguously.[11] To transform the γ-lactone (11) into the required α-methyl homologue (13) two methods were used. The first involved treatment with methylmagnesium carbonate [12] followed by an excess of methyl iodide. This gave the corresponding α-methyl-α-methoxycarbonyl-γ-lactone, which, by hydrolysis and decarboxylation, produced the γ-lactone (13) as a mixture of the two epimers. The second, more convenient, procedure used lithium diisopropylamide [13] to obtain the carbanion of the γ-lactone (11), direct methylation of which gave a high yield of one epimer of the homologous γ-lactone (13).

The originally planned synthetic sequence towards trichodermin conceived the elaboration of the polyfunctional key compound (14): obvious processes of intramolecular cyclisation followed by an internal aldolisation would then reasonably lead to a manifestly close precursor (15) of trichodermin. This analysis received an independent imprimatur from the Harvard computer.[14] We envisaged that a compound (16) containing in potential form all the functional groupings of (14) might be attainable by interaction of the γ-lactone (13) with the lithium salt of 3,3-diethoxypropyne. In the event this reaction proceeded remarkably smoothly to give the required hemiacetal (16). Partial catalytic reduction of the triple bond of this product produced the unstable *cis*-ethylene (17). Mild acidic hydrolysis of (16) was expected to yield the required unsaturated keto-aldehyde (14), but it produced instead the dihydrofuran (18). This, as an enol ether, was expected to be readily hydrolysable to (14), but it remained obdurately unchanged under more stringent acidic conditions. Finally we admitted



that intermediate (18) was unfruitful, and a detour had to be interposed in the synthetic sequence.



To this end the acetylenic hemiacetal (16) was reduced with sodium borohydride to the corresponding diol (19). Conditions were then found whereby (19) could be smoothly reduced by sodium in liquid am-

[9] *Cf.* J. Meinwald and E. Frauenglas, *J. Amer. Chem. Soc.*, 1960, **82**, 5235.

[10] Since our preliminary note [1] a different route to this lactone has appeared; S. C. Welch and R. Y. Wang, *Tetrahedron Letters*, 1972, 1853.

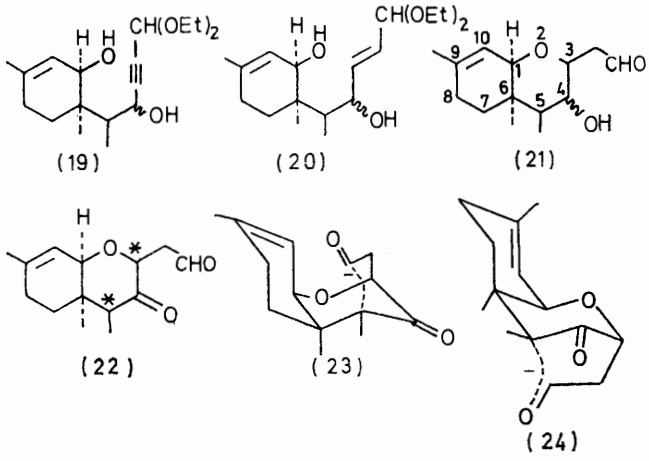
[11] M. Currie, *J.C.S. Perkin II*, 1973, 240.

[12] M. Stiles, *J. Amer. Chem. Soc.*, 1959, **81**, 2598.

[13] P. L. Creger, *J. Amer. Chem. Soc.*, 1970, **92**, 1397.

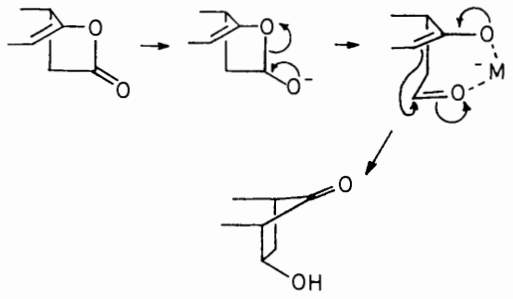
[14] E. J. Corey and W. Todd Wipke, *Science*, 1969, **166**, 187.

monia to give the corresponding *trans*-acetal (20) without the reductive removal of any of the allylic oxygen functions. Mild acidic hydrolysis of (20) not only generated the aldehyde function but also induced an internal nucleophilic attack of the hydroxy-group on the conjugated double bond to give the *cis*-fused bicyclic hydroxy-aldehyde (21). Selective chromium trioxide–pyridine oxidation of (21) in methylene dichloride[15] led to the corresponding keto-aldehyde (22), a compound seemingly ripe for internal aldol condensation to produce the trichodermin precursor (15). At this juncture precise knowledge of the configuration at the two starred chiral centres of (22) was not deemed necessary, as they both flanked the ketonic function. It was reasonable to suppose, therefore, that epimerisation at these two centres would ensue under aldolising conditions to give an equilibrium mixture of the diastereoisomers. Conformational analysis of the possibilities showed that it was sterically feasible for only two of these diastereoisomers to undergo internal aldolisation of the type desired. The requisite transition states are shown as (23) and (24). It is apparent that transition state (23), with its unfavourable



non-bonded interactions, is energetically less favoured than (24). There is thus a good augury for the course of the aldolisation to proceed most rapidly with that component of the equilibrium mixture possessing the stereochemistry of (24); this would lead to a product with a stereochemistry corresponding precisely with that of trichodermin.

In spite of this analysis, extensive experimentation to induce (22) to undergo an intramolecular aldol condensation was unsuccessful. To circumvent this stumbling-block the keto-acid (25) was produced by oxidation[16] of either the keto-aldehyde (22) or, more conveniently, the hydroxy-aldehyde (21). Acetic anhydride treatment converted (25) into a mixture of the two possible racemates of the enol lactone of structure (27); a third product proved to be the acetoxy-lactone (28), formed presumably by addition of acetic acid to either the structurally isomeric enol lactone or its rearrangement product, the conjugated lactone (29). By analogy with the reported highly stereoselective hydride reduction of exocyclic enol δ-lactones[17] it appeared likely that the cognate reduction of similarly constituted enol γ-lactones would take the similar course shown in the Scheme; the configuration-holding property of the co-ordinating metal produces a relative configuration of the newly-formed hydroxy-group precisely that required for trichodermin.



SCHEME

Accordingly the inseparable mixture of the two racemates of (27) was treated with lithium hydridotri-t-butoxyaluminate to give two products. The first was the keto-aldehyde (22) but the second, formed in low yield, was a homogeneous crystalline tricyclic keto-alcohol (30). Consideration of non-bonded interactions in the transition states had already indicated that the one leading to 'trichodermin-like' stereochemistry for the product (30) would be the energetically favoured pathway. This conclusion was encouraged

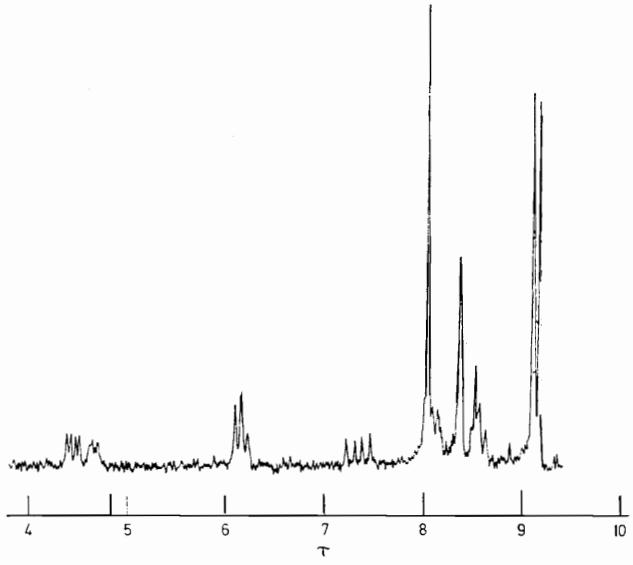


FIGURE 1 N.m.r. spectrum of 12-oxo-13-nortrichothec-9-en-4β-yl acetate (31)

when it was found that the corresponding acetate (31) showed a close correspondence with trichodermin in the relevant regions of the n.m.r. spectra (Figures 1 and 2,

[15] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.

[16] R. H. Cornforth, J. W. Cornforth, and G. Popják, *Tetrahedron*, 1962, **18**, 1351.

[17] J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 1964, 289; J. Martin, W. Parker, B. Shroot, and T. Stewart, *J. Chem. Soc.* (*C*), 1967, 101.

respectively) (a detailed analysis of the n.m.r. spectrum of trichodermin is given in the Experimental section; the assignments were confirmed by double-resonance experiments).

The last stage in the synthesis now seemed to require the application of a methylene-transfer reagent to the tricyclic ketone (31) in order to transform the carbonyl group into the homologous epoxide. To this end the

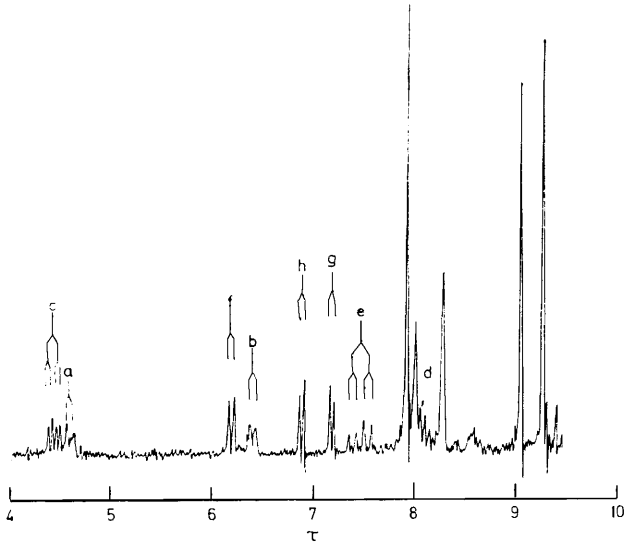
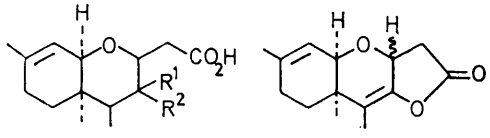


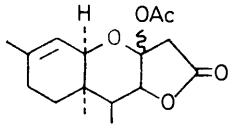
FIGURE 2 N.m.r. spectrum of (−)-trichodermin

ketone (31) was treated with dimethylsulphonium methylide.[18] Only one of the two possible epoxide products was formed and unfortunately this proved to



(25) R^1 R^2= O
(26) R^1 = H, R^2 = OH

(27)



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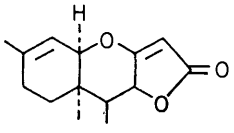

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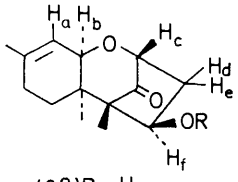


(30) R = H
(31) R = Ac

be an isomer (32) of trichodermin with epimeric stereochemistry of the epoxide ring, formed by exclusive attack from the side of the C-3,C-4 bridge. The n.m.r.

[18] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.

spectrum (Figure 3) closely resembled that of trichodermin itself, but the AB quartet of the epoxide

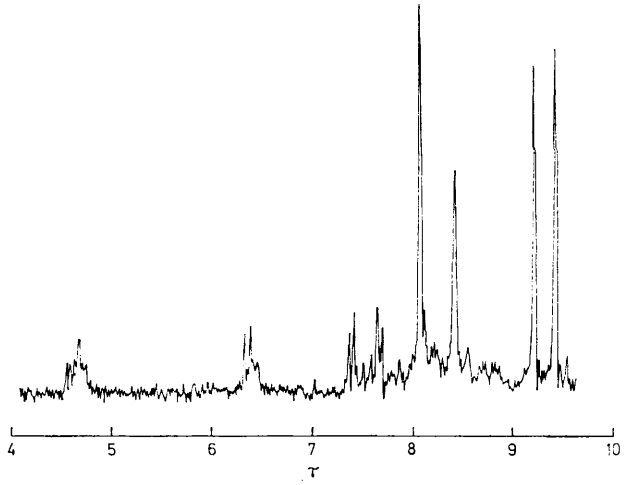
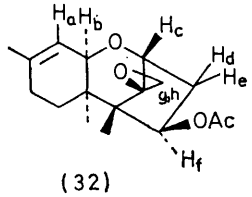
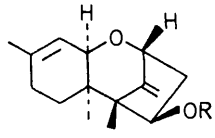


FIGURE 3 N.m.r. spectrum of 12,13-epoxy-12-*epi*-trichothec-9-en-4β-yl acetate (32)

methylene group was appreciably shifted to higher field. The allied reagent, dimethylsulphoxonium methylide,[18] frequently gives stereochemically complementary products,[19] but in this case no reaction could be induced with (31).

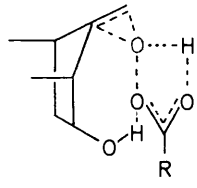


(32)



(33) R = Ac
(34) R = H

trichodermin
(3)



(35)

Accordingly the tricyclic ketone (31) was converted into the corresponding methylene compound (33) by reaction with methylenetriphenylphosphorane followed by reacetylation. It was now reasonable to assume that epoxidation of this methylene function would also take place from the side of the C-3,C-4 bridge to produce the stereochemistry required for trichodermin. However, a final complication presented itself in that the tricyclic diene (33) now contained two sites vulnerable to epoxidation. Of these the 9,10-double bond is trisubstituted and would therefore be expected to undergo epoxidation at least ten times as fast[20] as the disub-

[19] *Cf.* C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Letters*, 1965, 891.

[20] D. Swern, *Chem. Rev.*, 1949, **45**, 49.

stituted methylene double bond. In order to achieve the desired regio- as well as stereo-selectivity the ester (33) was hydrolysed to the parent alcohol (34). The secondary hydroxy-group of this compound is directed precisely towards the double bond of the methylene group and is thus ideally placed to form a hydrogen-bonding 'anchor' for the electrophilic peroxy-acid, giving rise to a transition state of the type (35) previously postulated.[21] In the event, treatment of (34) with 1 equiv. of buffered *m*-chloroperbenzoic acid led to the exclusive production of the desired epoxide. Acetylation of this product finally gave crystalline (±)-trichodermin (3), identical in all respects save rotation with naturally occurring (—)-trichodermin.

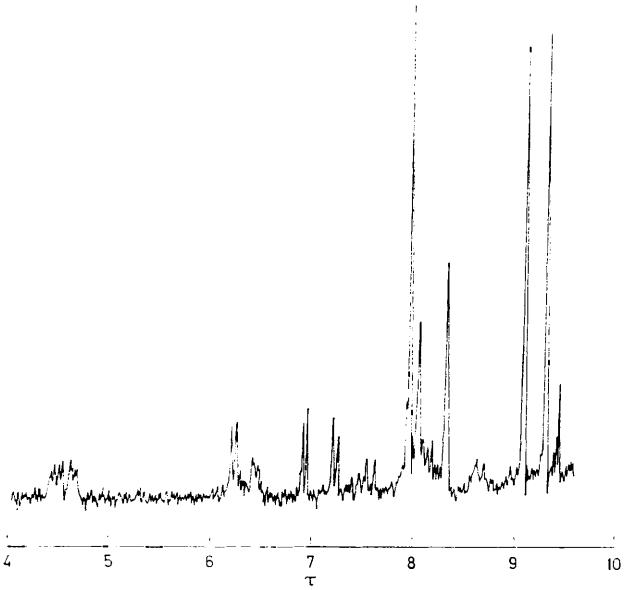


FIGURE 4 N.m.r. spectrum of (±)-trichodermin (3)

As (—)-trichodermin has been oxidised to the corresponding 8-oxo-compound[4] the present work also constitutes a formal synthesis of trichothecolone and the derived trichothecin.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Pye–Unicam SP 1000 or a Perkin-Elmer 225 double-beam spectrophotometer and are for liquid films, unless otherwise stated. ^{1}H N.m.r. spectra were measured on a Varian T-60 (60 MHz) or a Varian HA100 (100 MHz) spectrometer, with tetramethylsilane as internal reference. Mass spectra were determined on an A.E.I.-G.E.C. MS12 spectrometer. Analytical g.l.c. was performed on a Perkin-Elmer F 11 gas chromatograph. U.v. spectra were measured on a Pye–Unicam SP 800A instrument.

Kieselgel G (Merck) was used for analytical t.l.c.; Kieselgel HF_{254} (Merck) was used for preparative t.l.c. Light petroleum refers to that fraction which boils between 60 and 80°. All organic solutions were dried over anhydrous magnesium sulphate.

2-Chloro-1-methoxy-4-methylbicyclo[2.2.2]*oct-5-ene-2-carbonitrile* (7).—1-Methoxy-4-methylcyclohexa-1,4-diene (4) (3·72 g, 0·03 mol) and 2-chloroacrylonitrile (1·75 g, 0·02 mol) were heated under reflux in the presence of hydroquinone (50 mg) for 24 h in an atmosphere of nitrogen. The viscous oil resulting on cooling was diluted with ether, and filtered from the curdy precipitate so formed. Distillation afforded an oil (1·52 g), b.p. 152—162° at 18 mmHg, which was adsorbed on silica gel (45 g) from light petroleum. The fractions eluted with 2% ethyl acetate–light petroleum were combined on the basis of t.l.c. evidence to give the chloro-nitrile (7) (structure assigned according to Alder's rule) as a gum (622 mg, 14%), which slowly crystallised. Recrystallisation from light petroleum furnished *needles*, m.p. 63—64°, $\nu_{max.}$ (Nujol) 2370, 1118, 760, and 705 cm^{-1}, τ ($CDCl_3$) 8·78 (3H, s, MeC), 8·6—7·8 (6H, methylene envelope), 8·23 (1H, d, A of ABq, J_{AB} 14 Hz, C*H*·CCl·CN), 7·45 (1H, d, B of ABq, J_{BA} 14 Hz, C*H*·CCl·CN), 6·67 (3H, s, OMe), 3·9 (1H, d, A of ABq, J_{AB} 9 Hz, C*H*=CH), and 3·71 (1H, d, B of ABq, J_{BA} 9 Hz, CH=C*H*) (Found: C, 62·5; H, 6·55; N, 6·5. $C_{11}H_{14}ClNO$ requires C, 62·5; H, 6·65; N, 6·65%).

Combination of the fractions eluted with ethyl acetate–light petroleum (20—50%) furnished *5-methyl-2-oxobicyclo*[3.2.1]*oct-6-ene-1-carbonitrile* (8) (350 mg), which crystallised from light petroleum as needles, m.p. 95—98°, $\nu_{max.}$ (Nujol) 2340 and 1720 cm^{-1}, τ ($CDCl_3$) 8·68 (3H, s, MeC), 4·05 (1H, d, A of ABq, J_{BA} 5 Hz, C*H*=CH), 3·86 (1H, d, B of ABq, J_{BA} 5 Hz, CH=C*H*) (Found: C, 74·7; H, 6·6; N, 8·9%; M^+, 161. $C_{10}H_{11}NO$ requires C, 74·5; H, 6·9; N, 8·7%; *M*, 161).

A superior method (60% yield) of preparing the chloronitrile (7) involved heating equimolar quantities of the diene (4) and 2-chloroacrylonitrile under reflux in benzene for 9 h.

1-Methoxy-4-methylbicyclo[2.2.2]*oct-5-en-2-one* (9) *and its Oxime*.—According to the method of Evans *et al.*,[8] the chloro-nitrile (7) (20 g, 95 mmol) was refluxed with sodium sulphide (30 g, 125 mmol) in ethanol (150 ml). A yellow precipitate formed during the course of the reaction. The mixture was poured onto ice–water (300 g) and thoroughly extracted with ether. The organic phase was washed with brine and dried. Removal of solvent *in vacuo* afforded a mobile, yellow oil (10·5 g). Fractional distillation furnished the ketone (9) as a colourless oil (8·5 g), b.p. 130—135° at 14 mmHg, $\nu_{max.}$ 3050, 1730, 705, and 670 cm^{-1}, τ ($CDCl_3$) 8·71 (3H, s, MeC), 8·52—7·7 (6H, methylene envelope), 6·45 (3H, s, OMe), and 4·78 (2H, t, *J* 8 Hz). Hydroxylamine hydrochloride (8·4 g, 0·12 mol) and sodium acetate (9·7 g, 0·12 mol) were added to a solution of the ketone (9) (10·5 g, 0·063 mol) in ethanol–water (100 ml; 1 : 2 v/v) and the mixture was heated under reflux for 4 h. The hot mixture was poured onto crushed ice (150 g), then thoroughly extracted with ether. The extracts were combined, washed with water and brine, and dried. Concentration *in vacuo* furnished the crude oxime (10·67 g) of (9); recrystallisation from chloroform–light petroleum gave *plates* (7·31 g), m.p. 127—128·5°, $\nu_{max.}$ (Nujol) 3600, 3280 (absent on high dilution), 1160, and 690 cm^{-1}, τ ($CDCl_3$) 8·75 (3H, s), 8·7—8·0 (4H, methylene envelope), 7·76br (2H, s CH_2–C=N–OH), 6·48 (3H, s, OMe), and 3·97 and 3·67 (2H, ABq, J_{AB} 8·5 Hz, C*H*=C*H*) (Found: C, 66·25; H, 8·35; N, 7·75%; M^+, 181. $C_{10}H_{15}NO_2$ requires C, 66·4; H, 8·25; N, 7·65%; *M*, 181).

1-Methyl-4-oxocyclohex-2-enylacetonitrile (6; X = CN).—

[21] *Cf.* H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.

Sodium hydride (1·425 g, 35·7 mmol; 60% dispersion in mineral oil) was washed three times with light petroleum in a atmosphere of nitrogen. Ether (200 ml) was added, and the oxime of (9) was introduced during 10 min to the stirred suspension. Stirring was continued for 4 h, whereupon the resulting slurry was cooled to −78°, and toluene-*p*-sulphonyl chloride (6·5 g, 33·4 mmol) was added in small portions. The vessel was allowed to warm slowly to room temperature, then left 24 h. Saturated aqueous potassium carbonate solution (30 ml) and ethanol (30 ml) were then added, and the inhomogeneous mixture was stirred for 6 h; a clear solution was obtained. The mixture was extracted with ether; the ethereal solution was washed with water and brine and dried. Concentration under reduced pressure furnished the *enone* (6) as a pale yellow oil (2·78 g, 79%), $\nu_{max.}$ 2240, 1670, and 800 cm^{-1}, τ ($CDCl_3$) 8·62 (3H, s, MeC), 8·2—7·3 (4H, methylene envelope), 7·48 (2H, s, CH_2·CN), and 4·03 and 3·31 (2H, ABq, J_{AB} 11 Hz), $\lambda_{max.}$ (EtOH) 223 nm (ε 9900) (Found: C, 54·85; H, 4·55; N, 21·1%; M^+, 149. $C_9H_{11}NO$ requires C, 54·7; H, 4·6; N, 21·3%; *M*, 149).

Ethyl 4-*Hydroxy*-1,4-*dimethylcyclohex*-2-*enylacetate* (10; X = CO_2Et).—To a stirred, ice-cold solution of the enone ester (6; X = CO_2Et) (7 g, 36 mmol) in ether (100 ml), methylmagnesium chloride solution (12 ml; 3M in tetrahydrofuran; 36 mmol) was added dropwise over 5 min. After a further 10 min, saturated aqueous sulphate solution was added dropwise, and the granular precipitate was filtered off and washed with ether. The combined organic extracts were washed with water and brine and dried, to give, on concentration, the crude tertiary alcohol (10; X = CO_2Et) as an oily epimeric mixture, $\nu_{max.}$ 3450, 1730, 1680, and 1100 cm^{-1}.

Similar treatment of the nitrile (6; X = CN) gave the corresponding tertiary alcohol (10; X = CN) as an oil, $\nu_{max.}$ 3450, 2235, and 1100 cm^{-1}.

2-*Hydroxy*-1,4-*dimethylcyclohex*-3-*enylacetic Acid Lactone* (11).—A solution of the crude tertiary alcohol (10; X = CO_2Et) (7 g) in methanol (10 ml) and sodium hydroxide solution (100 ml; 2N) was stirred for 12 h at room temperature, then extracted with ether. The remaining basic aqueous layer was acidified with dilute sulphuric acid (50 ml; 6N), stirred for 30 min, then extracted with ether (3 × 100 ml). The ethereal extracts were combined, washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried. Removal of solvent under reduced pressure gave the lactone (11) as a solid (3·8 g), which was sublimed to give *plates*, m.p. 47—48°, $\nu_{max.}$ (Nujol) 1775 and 1670 cm^{-1}, τ (CCl_4) 8·82 (3H, s, MeC), 8·2br (3H, s, MeC=C), 7·8 (2H, s, CH_2·CO), 5·75br (1H, s, CH·O), and 4·5br (1H, s, CH=C), (Found: C, 72·1; H, 8·25%; M^+, 166. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%; *M*, 166).

Treatment of the tertiary alcohol (10; X = CN) (350 mg) in methanol (5 ml) with conc. hydrochloric acid (0·5 ml) under reflux for 12 h also produced the γ-lactone (11) (212 mg).

2-(2-*Hydroxy*-1,4-*dimethylcyclohex*-3-*enyl*)*propionic Acid Lactone* (13).—(*a*) A solution of the lactone (11) (240 mg, 1·45 mmol) in dimethylformamide (5 ml) was treated with a solution of methylmagnesium carbonate in dimethylformamide (4 ml; 2·6M; 10·4 mmol), and the mixture was heated under reflux in an atmosphere of nitrogen for 7 h. It was then cooled to room temperature, and methyl iodide (5 ml) was added. The mixture was heated under reflux for a further 4 h, cooled, diluted with water, acidified with dilute aqueous sulphuric acid, and extracted with ether. The extract was washed with water and brine, and dried. Removal of solvent and chromatography gave the corresponding α-methyl-α-methoxycarbonyl-γ-lactone (234 mg).

A solution of this lactone (134 mg) in methanol (5 ml) and dilute aqueous sodium hydroxide solution (10 ml; 2N) was stirred overnight at room temperature. The solution was extracted with ether, the aqueous layer was acidified with dilute aqueous sulphuric acid and extracted with ether, and the ethereal extract was washed with brine and dried. Removal of solvent, followed by heating the residue at 150—160° for 10 min, by which time all effervescence had ceased, then chromatography of the product, afforded the alkylated lactone (13) (68 mg) as a mixture of epimers.

(*b*) To a stirred solution of di-isopropylamine (3·03 g, 30 mmol) in ether (75 ml) under an atmosphere of nitrogen was added n-butyl-lithium (15 ml; 2M in hexane; 30 mmol) at such a rate as to give a gentle reflux. The solution was stirred for a further 5 min. A solution of the lactone (11) (4·5 g, 27 mmol) in ether (25 ml) was added, and stirring was continued for 10 min. Methyl iodide (15 ml) was added, and the mixture was stirred under gentle reflux for 30 min. It was then cooled, water was added, and the mixture was acidified with dilute aqueous sulphuric acid. The layers were separated, the aqueous layer was extracted with ether, and the ethereal extracts were combined, washed with brine, dilute aqueous sodium hydrogen carbonate, and brine, and dried. Removal of solvent followed by distillation afforded the *methylated lactone* (13) (4·4 g), b.p. 104° at 1 mmHg, $\nu_{max.}$ 1765 and 1670 cm^{-1}, τ (CCl_4) 9·0 (3H, s, MeC), 8·98 (3H, d, *J* 8 Hz, CH_3·CH), 8·25br (3H, s, CH_3–C=C), 7·6 (1H, q, *J* 8 Hz, CH_3·C*H*), 5·65 (1H, m, CH·O), and 4·55 (1H, m CH=C) (Found: C, 73·05; H, 8·8%; M^+, 180. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%; *M*, 180).

8-(3,3-*Diethoxyprop*-1-*ynyl*)-3,6,7-*trimethyl*-9-*oxabicyclo*-[4.3.0]*non*-2-*en*-8-*ol* (16).—n-Butyl-lithium (0·51 ml; 2·35M in hexane; 1·2 mmol) was added to a stirred solution of 3,3-diethoxypropyne (155 mg, 1·2 mmol) in ether (5 ml) at −78° in an atmosphere of nitrogen. Stirring was continued at −78° for a further 20 min. A solution of the lactone (13) (180 mg, 1 mmol) in ether (10 ml) was added, the cooling bath was removed, and the mixture was stirred for 1 h. It was then poured into cold water and extracted thoroughly with ether; the extracts were combined, washed with water and brine, and dried. Concentration *in vacuo* afforded the crude hemiacetal (16) as a thermally unstable oil (304 mg), $\nu_{max.}$ 3400, 1665, 1110, 1060, and 1020 cm^{-1}, τ (CCl_4) 9·0 (3H, s, MeC), 9·0 (3H, d, *J* 8 Hz, CH_3·CH), 8·8 (6H, t, *J* 6 Hz, 2 × CH_3·CH_2·O), 8·2br (3H, s, CH_3·C=C), 7·8 (1H, q, *J* 8 Hz, CH_3·C*H*), 6·5 (4H, q, *J* 6 Hz, 2 × CH_3·CH_2·O), 5·85br (1H, s, CH·O), 4·85br (1H, s, C≡C·CH), and 4·6br (1H, s, CH=C).

8-(3,3-*Diethoxy*-cis-*prop*-1-*enyl*)-3,6,7-*trimethyl*-9-*oxabicyclo*[4.3.0]*non*-2-*en*-8-*ol* (17) *and its Hydrolysis Product* (18).—A solution of the acetylenic hemiacetal (16) (100 mg) in ethyl acetate (25 ml) was hydrogenated over 5% palladium–barium sulphate for 3 h. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure. The residue was purified by preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum)

to give the labile *cis*-olefin (17) as an oil (78 mg), τ (CCl_4) 4·5br (3H, s, CH=C, and t, *J* 10 Hz, CH=CH). At ambient temperature this compound rapidly decomposed to a complex mixture.

The *cis*-olefin (17) (150 mg) was treated with acetic acid (5 ml) and sodium acetate (100 mg) for 1 h at room temperature. Normal isolation procedures followed by preparative t.l.c. (developing solvent 20% ethyl acetate–light petroleum) gave a product (118 mg) identified as the dihydrofuran (18), $\nu_{max.}$ 1680, 1630, 1595, and 980 cm^{-1}, $\lambda_{max.}$ (EtOH) 340 (ε 10,000) and 237 nm (6000), τ (CCl_4) 8·95 (3H, s, MeC), 7·2br (6H, s, 2 × CH_3·C=C), 5·75br (1H, s, CH·O), 4·5br (1H, s, CH=C), 3·75 (1H, dd, *J* 15 and 8 Hz, CH=CH CHO), 3·05 (1H, d, *J* 15 Hz, C*H*=CH·CHO), and 0·42 (1H, d, *J* 8 Hz, CHO).

The enol ether system of this dienal was unaffected after stirring with aqueous sulphuric acid (6N) and dioxan for 24 h.

6,6-*Diethoxy*-2-(2-*hydroxy*-1,4-*dimethylcyclohex*-3-*enyl*)*hex*-4-*yn*-3-*ol* (19).—A solution of the acetylenic hemiacetal (16) (250 mg) and sodium borohydride (500 mg) in ethanol (10 ml) and water (10 ml) was stirred at room temperature for 1·5 h. Dilution with water, followed by thorough extraction with ether, washing of the combined extracts with water and brine, and drying gave, on concentration, the diol (19) as an oil (230 mg), $\nu_{max.}$ 3400, 1670. 1110, 1060, and 1020 cm^{-1}, which was used without further purification.

6,6-*Diethoxy*-2-(2-*hydroxy*-1,4-*dimethylcyclohex*-3-*enyl*)-trans-*hex*-4-*en*-3-*ol* (20).—Sodium (310 mg, 13·5 mmol) was added to ammonia (100 ml; distilled from sodium) and the blue solution was stirred for 15 min. A solution of the diol (19) (1·4 g, 4·5 mmol) in ether (25 ml) was added over 5 min, after which stirring was continued for a further 4 min, then absolute ethanol (0·5 ml) was added. Decolourisation ensued rapidly, and the ammonia was allowed to evaporate. The residue was partitioned between ether and water, the aqueous layer was re-extracted with ether, and ethereal extracts were combined, washed with water, and brine, and dried, to give, on concentration *in vacuo*, the *trans*-olefin (20) as a thermally labile oil (1·19 g), $\nu_{max.}$ 3400, 1670, 1660, 1120, 1060, and 980 cm^{-1}, τ (CCl_4) 9·15 (3H, s, MeC), 9·1 (3H, d, *J* 8 Hz, CH_3·CH), 8·8 (6H, t, *J* 6 Hz, 2 × CH_3·CH_2·O), 8·3br (3H, s, CH_3·C=C), 6·5 (4H, q, *J* 6 Hz, 2 × CH_3·CH_2·O), 6·35br [1H, d, *J* 6 Hz, C=C·C*H*·(OH)], 5·6br (1H, s, C*H*·O), 5·25 [1H, d, *J* 3 Hz, C=C·CH·$(OEt)_2$], 4·55br (1H, s, CH=C), 4·45 (1H, dd, *J* 16 and 3 Hz, O·C·C*H*=CH·C·O), and 4·15 (1H, dd, *J* 16 and 3 Hz, O·C·CH=C*H*·C·O).

4-*Hydroxy*-5,6,9-*trimethyl*-2-*oxabicyclo*[4.4.0]*dec*-9-*en*-3-*ylacetaldehyde* (21).—A vigorously stirred mixture of the *trans*-olefin (20) (2 g), sodium acetate (16 g), acetic acid (12 g), and water (40 ml) was heated under reflux for 30 min in an atmosphere of nitrogen. The mixture was cooled, diluted with water, and extracted thoroughly with ether; the extracts were combined, washed well with dilute aqueous sodium hydrogen carbonate and brine, and dried. Removal of solvent under reduced pressure gave the bicyclic hydroxy-aldehyde (21) as an oil (1·68 g). A sample purified by preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum) showed $\nu_{max.}$ 3500, 2750, 1720, and 1670 cm^{-1}, τ (CCl_4), 9·1 (3H, d, *J* 8 Hz, CH_3·CH), 9·05 (3H, s, MeC), 6·25br (1H, s, CH·O), 4·9br (1H, s, CH=C), and 0·25 (1H, t, *J* 2 Hz, CHO) (Found: M^+ 238. Calc. for $C_{14}H_{22}O_3$: *M*, 238).

5,6,9-*Trimethyl*-4-*oxo*-2-*oxabicyclo*[4.4.0]*dec*-9-*en*-3-*yl-acetaldehyde* (22).—To a stirred, ice-cold slurry of the hydroxy-aldehyde (21) (188 mg, 0·8 mmol), barium oxide (200 mg), and methylene chloride (5 ml) was added a slurry of dipyridinechromium trioxide[15] (1·29 g, 4·8 mmol) in methylene chloride (25 ml). Stirring was continued at room temperature for 30 min, then the mixture was filtered through Celite and evaporated to dryness under reduced pressure. The residue was taken up in ether, and the solution was washed with water and brine and dried. Evaporation gave a gum (170 mg), which was purified by preparative t.l.c. to give the pure *keto-aldehyde* (22) (125 mg), b.p. 110° at 0·5 mmHg, $\nu_{max.}$ 2750, 1720, and 1665, τ (CCl_4) 9·1 (3H, s, MeC), 9·05 (3H, d, *J* 8 Hz, CH_3·CH), 8·25br (3H, s, CH_3·C=C), 6·05br (1H, s, CH·O), 5·6 [1H, t, *J* 6 Hz, O·C*H*(CO)(CH_2)], 4·58br (1H, s, CH=C), and 0·25 (1H, t, *J* 1·5 Hz, CHO) (Found: C, 71·3; H, 8·3%; M^+, 236. $C_{14}H_{20}O_3$ requires C, 71·15; H, 8·55%; *M*, 236).

Attempted Aldol Cyclisation of the Keto-aldehyde (22).—Conditions employed included, at room temperature: conc. sulphuric or hydrochloric acid in ether; 6N-sulphuric acid or hydrochloric acid in dioxan or tetrahydrofuran; conc. sulphuric acid in methanol; anhydrous toluene-*p*-sulphuric acid in benzene; trifluoroacetic acid; Amberlite IR120 (H^+) and dioxan; acetic anhydride, acetic acid, and boron trifluoride–ether or conc. sulphuric acid; tin(IV) chloride in pentane; aqueous N-sodium hydroxide and ether or ethanol; aqueous 10% potassium carbonate and ether; 0·01N-potassium hydroxide in methanol; aqueous 0·1N-potassium hydroxide in dioxan; 0·01N-potassium t-butoxide in t-butyl alcohol; 0·05N-sodium t-pentylate in benzene; sodium hydride in dimethylformamide; magnesium methoxide in methanol; lithium di-isopropylamide in ether; Amberlite IR-4A (OH^-) and dioxan; 1,5-diazabicyclo[4.3.0]non-5-ene in dichloromethane with or without acetic anhydride; *N*-trimethylsilyldiethylamine in benzene with or without 1,5-diazabicyclo[4.3.0]non-5-ene; phenyl isocyanate in benzene; *N*-methylanilinomagnesium bromide in benzene and, at reflux temperature, conc. sulphuric acid in methanol; 3N-hydrochloric acid in acetone; Amberlite IRA120 (H^+) or IR-4A (OH^-) and dioxan; triethylamine or pyrrolidine or piperidinium acetate or 0·2N-potassium t-butoxide or barium hydroxide or phenyl isocyanate in benzene.

Such conditions were without effect, or produced useless artefacts, or caused degradation.

5,6,9-*Trimethyl*-4-*oxo*-2-*oxabicyclo*[4.4.0]*dec*-9-*en*-3-*yl-acetic Acid* (25).—(*a*) A solution of the keto-aldehyde (22) (360 mg) was treated with a solution of chromium trioxide (700 mg) in pyridine (7 ml) and water (0·6 ml) at room temperature for 24 h. The mixture was then poured on ice and filtered through Celite. The filtrate was acidified with dilute aqueous sulphuric acid and extracted with ether; the extract was washed with dilute aqueous sulphuric acid and brine and dried. Removal of solvent gave the crude keto-acid (25) (232 mg).

(*b*) A more convenient procedure involved a two-step oxidation of the hydroxy-aldehyde (21). Cornforth[16] oxidation, as in (*a*), gave, unexpectedly, the hydroxy-acid (26), which was then subjected to Jones oxidation to give the keto-acid (25).

A solution of the hydroxy-aldehyde (21) (1·14 g) in pyridine (10 ml) was treated with a solution of chromium trioxide (4·6 g) in pyridine (50 ml) and water (5 ml) for

48 h. The mixture was then poured on ice and filtered through Celite. The filtrate was acidified with dilute aqueous sulphuric acid and thoroughly extracted with ether. The extracts were washed with dilute aqueous sodium hydroxide solution and the washings were acidified with dilute aqueous sulphuric acid and extracted with ether. The ethereal extracts were washed with brine and dried. Concentration under reduced pressure gave the hydroxy-acid (26) (770 mg), characterised as its *methyl ester*, which crystallised from hexane as plates, m.p. 89·5—90·5°, $\nu_{max.}$ (Nujol) 3500, 1735, and 1675 cm^{-1}, τ ($CDCl_3$) 9·05 (3H, d, J 8 Hz, CH_3·CH), 9·02 (3H, s, MeC), 8·35br (3H, s, CH_3·C=C), 7·45 (1H, q, A of ABX, J_{AB} 16, J_{AX} 8 Hz, CH·CO_2Me), 7·25 (1H, q, B of ABX, J_{BA} 16, J_{BX} 8 Hz, CH·CO_2Me), 6·8br (1H, t, X of ABX, J 8 Hz, O·CH·CH_2·CO_2Me), 6·3 (3H, s, CO_2Me), 6·1br (1H, s, CH·O), 5·4 (1H, OH, disappears with D_2O), and 4·75br (1H, s, CH=C) (Found: C, 67·0; H, 9·0%; M^+, 268. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%; M, 268).

A solution of the hydroxy-acid (26) (600 mg) in acetone (10 ml) was treated with Jones reagent at 0° in the usual manner. The solution was diluted with water, then extracted with ether. The extract was extracted with dilute aqueous sodium hydrogen carbonate (3 × 10 ml); the basic solution was carefully acidified with dilute aqueous sulphuric acid, saturated with sodium chloride, and extracted thoroughly with ether. The ethereal extracts were combined, washed with brine, dried, and concentrated to give the keto-acid (25) (520 mg), characterised as its *methyl ester*, which crystallised from hexane as plates, m.p. 72·5—73·5°, $\nu_{max.}$ (Nujol) 1730 and 1675 cm^{-1}, τ ($CDCl_3$) 9·1 (3H, s, MeC), 9·05 (3H, d, J 8 Hz, CH_3·CH), 8·2br (3H, s, CH_3·C=C), 7·3 (1H, q, A of ABX, J_{AB} 15, J_{AX} 6 Hz, CH·CO_2Me), 7·1 (1H, q, B of ABX, J_{BA} 15, J_{BX} 6 Hz, CH·CO_2Me), 6·1br (1H, s, CH·O), 5·5br (1H, t, X of ABX, J 6 Hz, O·CH·CH_2·CO_2Me), and 4·5br (1H, s, CH=C) (Found: C, 67·5; H, 8·6%; M^+, 266. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·35%; M, 266).

In subsequent runs, it proved expedient to take the γ-lactone (13) directly through to the keto-acid (25) with no purification, the final base-acid extraction sequence sufficing to give pure (25); in this way, the conversion (13) ⟶ (25) could be achieved in an overall yield of 20%.

4-*Hydroxy*-5,6,9-*trimethyl*-2-*oxabicyclo*[4.4.0]deca-4,9-*dien*-3-*ylacetic Acid Lactone* (27).—The keto-acid (25) (200 mg) was heated under reflux with acetic anhydride (6 ml) and anhydrous sodium acetate (240 mg) for 1·5 h. The solution was then concentrated *in vacuo* three times with toluene, and the residue was purified directly by preparative t.l.c. (developing solvent 2 × 20% ethyl acetate–light petroleum). This gave two crystalline compounds. One, the desired *enol lactone* (27), was produced as a mixture of epimers (66·6 mg), m.p. 74—76°, $\nu_{max.}$ (Nujol) 1810, 1725, and 1680 cm^{-1}, τ (CCl_4; 100 MHz) 8·72 (3H, s, MeC), 8·34 (3H, d, J 1·5 Hz, CH_3·C=C), 8·25br (3H, s, CH_3·C=C), 7·46 (1H, A of ABX, J_{AB} 16, J_{AX} 10 Hz, CH·CO·O), 7·26 (1H, B of ABX, J_{BA} 16, J_{BX} 8 Hz, CH·CO·O), 5·86br (1H, s, CH·O), 5·40 (1H, dq, J_{AX} 10, J_{BX} 8, $J_{H,Me}$ 1·5 Hz, C=C·CH·CH_2·CO·O), and 4·76br (1H, s, CH=C) (Found: C, 71·5; H, 7·85%; M^+, 234. $C_{14}H_{18}O_3$ requires C, 71·75; H, 7·75%; M, 234).

The second component (120 mg) was the *acetoxy-lactone* (28), which crystallised from ether as plates, m.p. 128—129°, $\nu_{max.}$ (Nujol) 1795, 1725, and 1240 cm^{-1}, τ ($CDCl_3$) 9·05 (3H, s, MeC), 8·98 (3H, d, J 8 Hz, CH_3·CH), 8·25br (3H, s, CH_3·C=C,), 7·98 (3H, s, Ac), 7·4 (1H, d, A of AB, J 11 Hz, CH·CO·O), 7·15 (1H, d, B of AB, J 11 Hz, CH·CO·O), 6·1br (1H, s, CH·O), and 4·75br (1H, s, CH=C) (Found: C, 65·25; H, 7·55. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·55%).

4β-*Hydroxy*-13-*nortrichothec*-9-*en*-12-*one* (30) *and its Acetate* (31).—To a stirred suspension of lithium hydridotri-t-butoxyaluminate [from lithium aluminium hydride (280 mg, 7 mmol) and t-butyl alcohol (1·54 g, 21 mmol)] in ether (15 ml) at −78° in an atmosphere of nitrogen was added a solution of the enol lactone (27) (1·12 g, 4·8 mmol) during 10 min. The cooling bath was removed, and stirring was continued for a further 35 min; the mixture was then poured on brine and extracted twice with ethyl acetate. The organic extracts were combined, washed with brine, and dried. Concentration, followed by preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum) gave the keto-aldehyde (22) (600 mg) and a crude alcohol (30). Treatment of the latter with an excess of acetic anhydride–pyridine for 24 h at room temperature, followed by repeated evaporation to dryness with toluene under reduced pressure, and finally preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum) gave the pure tricyclic *keto-acetate* (31), which crystallised as plates (96·2 mg) from ether, m.p. 131—132°, $\nu_{max.}$ (Nujol) 1760, 1735, 1685, and 1240 cm^{-1}, τ ($CDCl_3$; 100 MHz) (Figure 1) 9·2 (3H, s, MeC), 9·15 (3H, s, MeC), 8·39br (3H, s, CH_3·C=C), 8·1 (1H, m, H_d), 8·07 (3H, s, Ac), 7·32 (1H, dd, J_{ed} 14, J_{ec} 8 Hz, H_e), 6·19br (1H, d, J_{ba} 7 Hz, H_b), 6·14 (1H, J_{fd} 5 Hz, H_f), 4·75br (1H, d, J_{ab} 7 Hz, H_a), and 4·43 (1H, dd, J_{ce} 8, J_{cd} 3 Hz, H_c) (Found: C, 68·85; H, 7·8%; M^+, 278. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·8%; M, 278).

12,13-*Epoxy*-12-epi-*trichothec*-9-*en*-4β-*yl Acetate* (32).—A solution of n-butyl-lithium (0·44 ml; 2·3M in hexane; 1 mmol) was added slowly to a stirred, ice-cold slurry of trimethylsulphonium iodide (204 mg, 1 mmol) in tetrahydrofuran (10 ml; distilled from lithium aluminium hydride) in an atmosphere of nitrogen. Stirring was continued for 5 min at 0°, to give a solution (0·1M) of the requisite ylide.

To an ice-cold solution of the keto-acetate (31) (17 mg, 0·061 mmol) in tetrahydrofuran (2 ml) was added the ylide solution (0·9 ml, 0·09 mmol) *via* a hypodermic syringe, in an atmosphere of nitrogen. Stirring was continued for 30 min at 0°; the mixture was then poured on water and extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. Preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum) gave starting keto-acetate (31) (10 mg) and a more polar compound (4 mg), which was not trichodermin, but in view of both its mode of formation and its physical data, was assigned the structure of the epimer (32), which crystallised from ether as prisms, m.p. 109—110°, $\nu_{max.}$ (Nujol) 1735, 1685, and 1245 cm^{-1}, τ ($CDCl_3$; 100 MHz) (Figure 3) 9·27 (3H, s, MeC), 9·1 (3H, s, MeC), 8·32br (3H, s, CH_3·C=C), 8·07 (1H, m, H_d), 7·99 (3H, s, Ac), 7·56 (1H, d, A of AB, J 6 Hz, H_g), 7·51 (1H, dd, J_{ed} 14, J_{ce} 8 Hz, H_e), 7·3 (1H, d, B of AB, J 6 Hz, H_h), 6·3br (1H, d, J_{ba} 7 Hz, H_b), 6·26 (1H, d, J_{fd} 5 Hz, H_f), 4·6br (1H, d, J_{ba} 7 Hz, H_a), and 4·51 (1H, dd, J_{ce} 8, J_{cd} 3 Hz, H_c) (Found: M^+, 292. Calc. for $C_{17}H_{24}O_4$: M, 292).

A similar reaction sequence with dimethylsulphoxonium methylide left the keto-acetate (31) unchanged.

Trichotheca-9,12-*dien*-4β-*ol* (34).—A solution of potassium

t-butoxide in t-butyl alcohol (1 ml; 0·78N; 0·78 mmol) was added to a stirred suspension of triphenylmethylphosphonium bromide (200 mg, 0·78 mmol) in ether (5 ml), and the mixture was stirred under gentle reflux in an atmosphere of nitrogen for 1 h, then cooled to room temperature. A solution of the keto-acetate (31) (47 mg, 0·175 mmol) in ether (2 ml) was added, and stirring was continued for 1·5 h under gentle reflux in an atmosphere of nitrogen. On cooling, the mixture was poured on water and extracted with ethyl acetate; the extract was washed with brine, dried, and concentrated. The residue was treated with an excess of acetic anhydride–pyridine at room temperature for 24 h (preliminary results indicated that the ylide competitively attacked the acetate carbonyl group, giving as products the desired acetoxy-diene, the hydroxy-diene, and the hydroxy-ketone). Repeated evaporation to dryness *in vacuo* with toluene, followed by preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum) gave the acetoxy-diene (33) (18·2 mg) and the starting keto-acetate (31) (15·3 mg). The acetoxy-diene was stirred with sodium hydroxide (5 ml; N) and methanol (2 ml) at room temperature for 12 h. Normal isolation procedures gave the *tricyclic hydroxy-diene* (34) as plates (14·3 mg) from ether, m.p. 125—126°, $\nu_{max.}$ (Nujol) 3450, 1675, and 880 cm^{-1}, τ ($CDCl_3$; 100 MHz) 5·62 (1H, d, J_{fd} 5 Hz, H_f), 5·3 (1H, s, $=CH_2$), and 4·88 (1H, s, $=CH_2$) (Found: C, 76·65; H, 9·55%; M^+, 234. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·45%; M, 234).

(±)-*Trichodermin* (12,13-*Epoxytrichothec*-9-*en*-4β-*yl Acetate*) (3).—A mixture of the tricyclic diene (34) (16·4 mg, 0·07 mmol), *m*-chloroperbenzoic acid (18 mg, 0·09 mmol), and disodium hydrogen phosphate (100 mg) in methylene chloride (10 ml) was stirred at room temperature for 4 h. It was then poured into water and extracted with ether; the extract was washed with dilute aqueous sodium hydrogen carbonate solution and brine and dried. Concentration and preparative t.l.c. (developing solvent 60% ethyl acetate–light petroleum) gave (±)-trichodermol (8·8 mg), m.p. 124—125°, and unchanged diene (34) (4 mg). Treatment of the (±)-trichodermol with an excess of acetic anhydride–pyridine, followed by normal isolation procedures (see before), gave (±)-trichodermin (3) (7·9 mg), m.p. 58—60°, $\nu_{max.}$ (CCl_4) 1738, 1680, and 1240 cm^{-1}, τ ($CDCl_3$; 100 MHz) (Figure 4) 9·3 (3H, s, CMe), 9·08 (3H, s, CMe), 8·3br (3H, CH_3·C=C), 8·07 (1H, m, H_d), 7·94 (3H, s, Ac), 7·46 (1H, dd, J_{ed} 14, J_{ec} 8 Hz, H_e), 7·18 (1H, d, A of AB, J 4 Hz, H_g), 6·88 (1H, d, B of AB, J 4 Hz, H_h), 6·4br (1H, d, J_{ba} 7 Hz, H_b), 6·18 (1H, d, J_{fd} 5 Hz, H_f), 4·55br (1H, d, J_{ab} 7 Hz, H_a), and 4·4 (1H, dd, J_{ce} 8, J_{cd} 3 Hz, H_c) (Found: M^+, 292. Calc. for $C_{17}H_{24}O_4$: M, 292). The i.r., n.m.r., and mass spectra were identical with those of authentic (−)-trichodermin. Identity was also shown by g.l.c.; coinjection with authentic material on 1½% QF1 at 190°, 1% APL at 180°, and 1% SE30 at 165°, 160°, or 140° showed no peak separation.

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