The Total Synthesis of (±)-Trichodermin

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Summary The first total synthesis of a member of the phytotoxic trichothecane group of sesquiterpenes, trichodermin (**16**), is described.

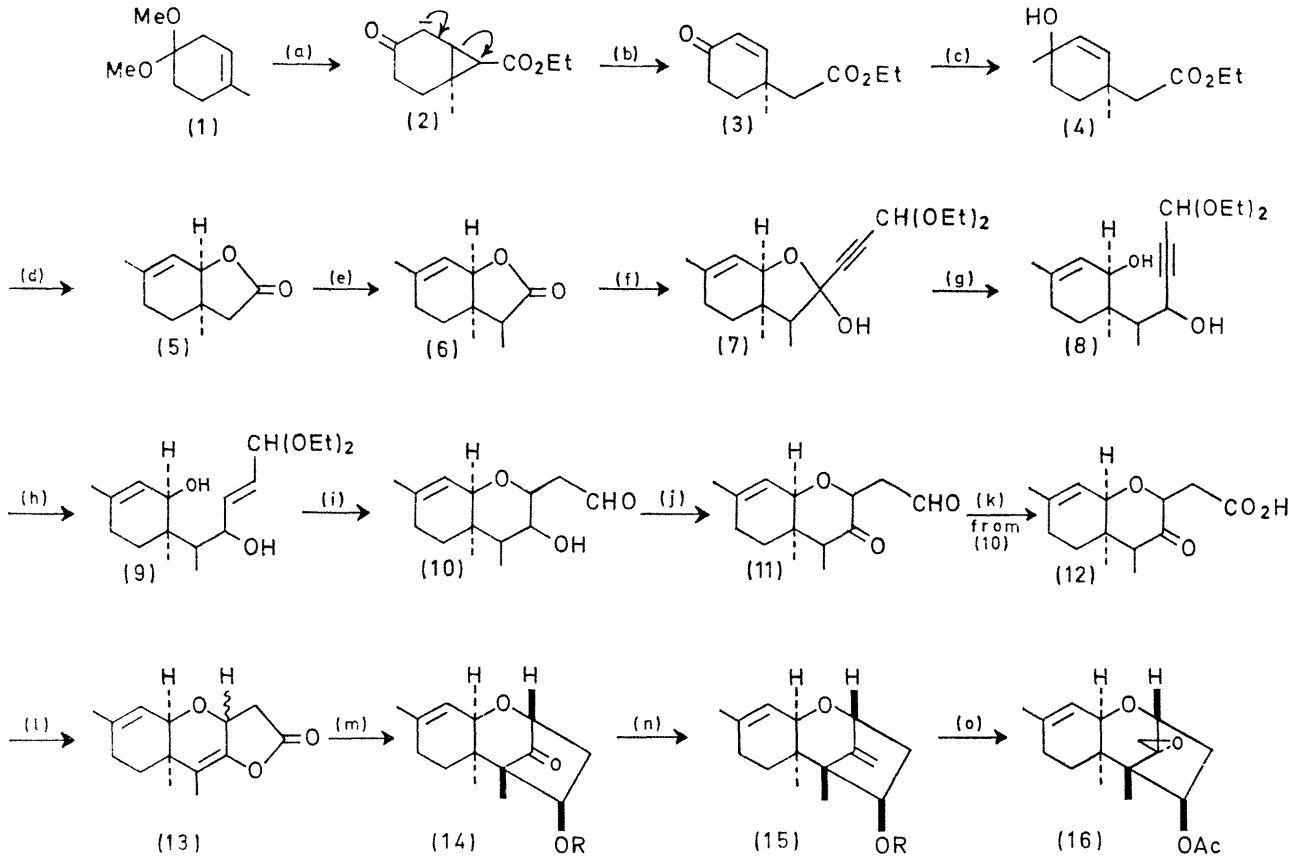
THE trichothecane group of modified sesquiterpenes constitutes a steadily growing class comprising metabolites of various species of *Trichothecium, Trichoderma, Myrothecium,* and *Fusarium*. Its members have aroused considerable interest because of their novel structural framework,[1] their pronounced phytotoxic activity,[2] and their biogenetic elaboration.[3] Hitherto, however, no synthetic ventures in the field have been reported. We now record the total stereoselective synthesis in racemic form of a member of this class, trichodermin (**16**).

Birch reduction of *p*-methoxytoluene, followed by treatment of the resulting dihydro-compound with methanolic toluene-*p*-sulphonic acid gave the acetal (**1**) which, by reaction with ethyl diazoacetate, yielded the corresponding cyclopropane ester, readily convertible to the parent ketone (**2**) by trans-acetalization with acetone. Mild base treatment of (**2**) effected smooth fragmentation as indicated (see Scheme) in quantitative yield to the unsaturated keto-ester (**3**).[4] Selective attack by methylmagnesium chloride produced the tertiary hydroxy-ester (**4**) which without purification was hydrolysed to the free acid. This latter spontaneously underwent an acid-catalysed anionotropic rearrangement to give in high yield the crystalline *cis*-fused γ-lactone (**5**), m.p. 47—48°. Monomethylation to the corresponding homo-lactone (**6**) was readily achieved by lithium di-isopropylamide and methyl iodide. Interaction of (**6**) and one equiv. of the lithium salt of 3,3-diethoxypropyne gave the hemi-acetal (**7**) which was then reduced to the diol (**8**) with borohydride. Selective partial reduction with sodium in ammonia of the triple bond of (**8**) furnished the corresponding *trans*-ethylenic acetal (**9**). Mild acid treatment of this product not only induced hydrolysis of the acetal but also brought about intramolecular cyclisation involving the suitably disposed hydroxy-group and the conjugated double bond to produce the *cis*-fused bicyclic hydroxy-aldehyde (**10**). Selective chromium trioxide–pyridine oxidation[5] then led to the keto-aldehyde (**11**); extensive experimentation to induce this product to undergo an intramolecular aldol condensation was uniformly unsuccessful. The hydroxy-aldehyde (**10**) was therefore oxidised by a two-step process to the corresponding keto-acid (**12**) which was then converted into a mixture of the two possible racemates of the enol-lactone (**13**). This inseparable mixture was then reduced by lithium hydridotri-t-butoxyaluminate[6] to give in low yield a homogeneous crystalline tricyclic keto-alcohol (**14**; R=H), m.p. 150—150·5°.

Consideration of non-bonded interactions in the possible transition states had already suggested that the one leading to a "trichothecane-like" stereochemistry for the product (**14**; R = H) would be the energetically favoured path. The close resemblance in the relevant regions of the n.m.r. spectra between the corresponding acetate (**14**; R = Ac) and trichodermin encouraged this conclusion.

Reaction of the acetoxyketone (**14**; R = Ac) with the methylene-transfer reagent dimethylsulphonium methylide[7] gave an isomer of trichodermin with epimeric stereochemistry at the epoxide ring (dimethylsulphoxonium methylide[7] did not react). This difficulty was overcome by transforming the acetoxyketone (**14**; R = Ac) by means

of a Wittig reaction into the corresponding methylene compound (**15**; R = Ac). Regio- and stereo-selective epoxidation of the methylene double bond was achieved by treating the corresponding alcohol (**15**; R = H) with *m*-chloroperbenzoic acid. Hydrogen bonding between the strategically placed hydroxy-group and the peracid[8] presumably "anchored" the electrophile in the required manner with the exclusive production of the desired epoxy-alcohol, (±)-trichodermol. Acetylation of this product finally gave crystalline (±)-trichodermin, m.p. 58—60°, identical in all respects save rotation (n.m.r., i.r., mass spectrum, t.l.c., and g.l.c. behaviour under a wide variety of conditions) with the naturally-occurring (−)-trichodermin. Resolution of the intermediate lactone (**5**) is under active study.



SCHEME

Reagents: (a) $CHN_2{\cdot}CO_2Et$–CuBr; Me_2CO–TsOH; (b) NaOAc–EtOH; (c) MeMgCl; (d) NaOH; H_2SO_4; (e) $LiNPr^i{}_2$–MeI; (f) $Li^+{}^-C{\equiv}C{\cdot}CH(OEt)_2$; (g) $NaBH_4$; (h) Na-NH_3–EtOH; (i) AcOH–NaOAc–H_2O; (j) CrO_3–py–CH_2Cl_2; (k) CrO_3–py–H_2O; CrO_3–H_2SO_4–Me_2CO; (l) NaOAc–Ac_2O; (m) $LiAl(OBu^t)_3H$; Ac_2O–py; (n) $CH_2{=}PPh_3$; (o) NaOH; *m*-chloroperbenzoic acid–Na_2HPO_4–CH_2Cl_2; Ac_2O.

Analytical and spectroscopic data for all compounds were in full accordance with the structures assigned.

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