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PARTIAL SYNTHESES OF THE TRICHOTHECENE MYCOTOXINS, CALONECTRIN AND DEOXYNIVALENOL

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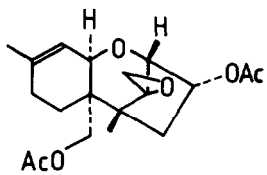
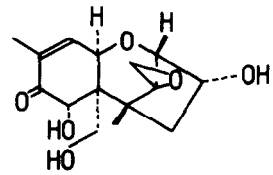
Summary: The partial syntheses of two trichothecenes, calonectrin (1) and deoxynivalenol (2), from a readily available derivative of the trichothecene, anguidine, are described. The methodology used should be applicable to the provision of other less abundant trichothecenes.

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 additional possibilities of specific isotopic labelling and of analogue synthesis.



(1)

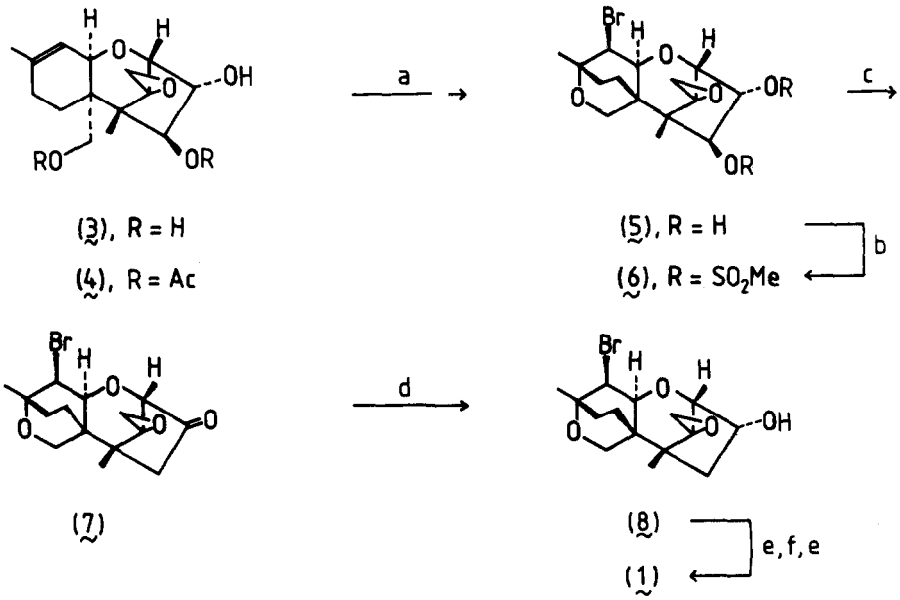


(2)

Continuing our studies on the synthesis[2] and synthetic transformations[3] of the trichothecene mycotoxins, we wish to communicate the partial syntheses of two natural trichothecenes, calonectrin (1), and deoxynivalenol (2), from a common precursor, 3α,4β,15-trihydroxy-12,13-epoxytrichothec-9-ene (3). The total synthesis of calonectrin has been reported[4], as has its partial synthesis[5] from anguidine (4). Deoxynivalenol (vomitoxin) is produced[6] when cereal grains suffer natural contamination of Fusarium species: consumption of feedstuffs so contaminated induces feed refusal and sub-lethal toxicoses. Deoxynivalenol has not hitherto succumbed to either partial or total synthesis.

The synthetic sequence is outlined in Scheme I. The triol (3) was converted quantitatively[7] into the bridged bromoether[8] (5), thus selectively protecting the C-15 hydroxyl group. Reaction of the diol (5) with methanesulphonyl chloride in the presence of pyridine provided the bis-mesylate (6), which, on treatment with sodium methoxide in refluxing methanol, underwent

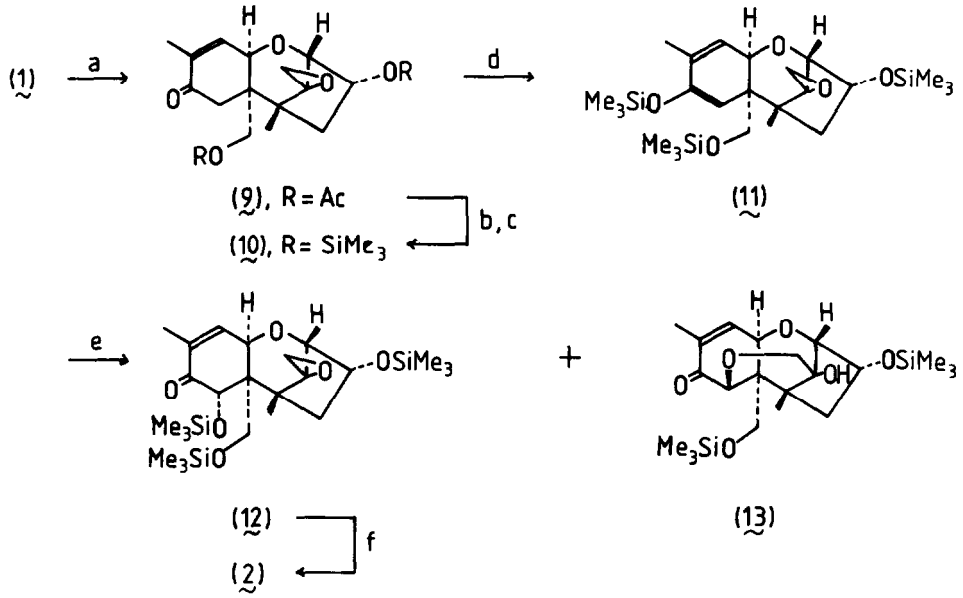
regiospecific elimination[9] to an enol mesylate and thence to the ketone (7), in 80% yield. Stereospecific hydride reduction[4] to the 3α-alcohol, followed by acetylation, regeneration of the 9,10-double bond[6] and acetylation of the so-produced C-15 alcohol gave calonectrin (1), in an overall yield of 55% from the triol (3). Calonectrin obtained in this way possessed spectral data identical with those reported[10].



Scheme I: (a) N-Bromosuccinimide, MeCN; (b) $MeSO_2Cl$, pyridine (py); (c) NaOMe, MeOH, reflux, 1.5 h; (d) $NaBH_4$, MeOH, H_2O, 0°C, 15 min; (e) Ac_2O, py, ether; (f) Zn(Ag), tetrahydrofuran (THF), EtOH, ether, reflux, 2 h.

Having thus established the correct level of oxygenation in the right-hand part of the molecule, it remained to oxidise the cyclohexene ring to achieve the functionality possessed by deoxynivalenol (2). This required selective allylic oxidation, and introduction of the 7α-hydroxyl group. The best allylic oxidant proved to be freshly prepared dipyridine chromium trioxide[11], which gave the desired enone directly and in 73% yield (Scheme II) Methanolysis of the diacetate (9) gave the diol, and thence the bis(trimethylsilyl) ether (10), in a combined yield of 81%. Kinetic deprotonation and *in situ* silylation[12] gave the silyloxydiene (11), which on treatment with one equivalent of *m*-chloroperbenzoic acid[13] gave a 1:2 mixture of the tris(trimethylsilyl) ether (12) of deoxynivalenol (2) and the rearranged alcohol (13) in a combined yield of 75%. This outcome can be understood by consideration

of the rearrangement of the two epimeric silyloxyoxiranes involved as intermediates[14], with the β-alcohol epimer attacking the proximal 12,13-epoxide function. The ether (12) 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 to give deoxynivalenol itself.



Scheme II: (a) $py_2.CrO_3$, dichloromethane, 24 h; (b) K_2CO_3, MeOH, H_2O, 1 h; (c) Me_3SiCl, py, ether; (d) $LiNPr^i_2$, Me_3SiCl, THF, -78°C; (e) m-chloroperbenzoic acid, hexane, -15°C → 30°C; (f) HF, MeCN, H_2O.

Application of similar methodology should provide access to useful amounts of less abundant trichothecenes, and when combined with an epoxide deoxygenation protocol[3] could provide them in specifically labelled form[15]. Such studies are currently in progress.

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