Chemical Deoxygenation of the Trichothecenes, Diacetoxyscirpenol and Deoxynivalenol

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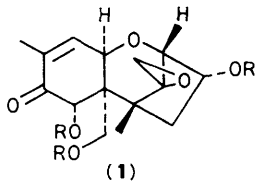
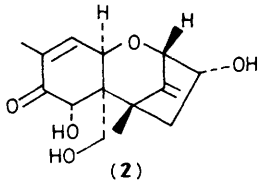
Based on a model study using the bicyclic epoxides (**9**) and (**10**), an efficient one-step procedure for the selective removal of the 12,13-epoxide ring of the trichothecene toxins has been devised.

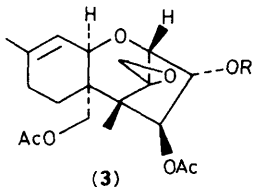
The trichothecenes[1] are a group of complex fungal sesquiterpenoids which can act as antibacterial, antiviral, and cytostatic agents; some are phytotoxic, and all show some degree of animal toxicity. Deoxynivalenol (**1**, R = H) is a major trichothecene mycotoxin[2] associated with infection of cereal grains by *Fusarium* species; consumption of such contaminated feed-stuffs can cause sub-lethal toxicoses in animals. The exact metabolic fate of the toxin when ingested is as yet unknown, although there is good evidence[3] to suggest that the toxicity of the trichothecenes in general requires the presence of the 12,13-epoxide group. Indeed, limited studies with rumen micro-organisms *in vitro*,[4] and with rats *in vivo*,[2] have demonstrated that the predominant biological transformation of deoxynivalenol, and hence its detoxification, is one of deoxygenation of the epoxide moiety to form the 9,12-diene (**2**).



(**1**)



(**2**)



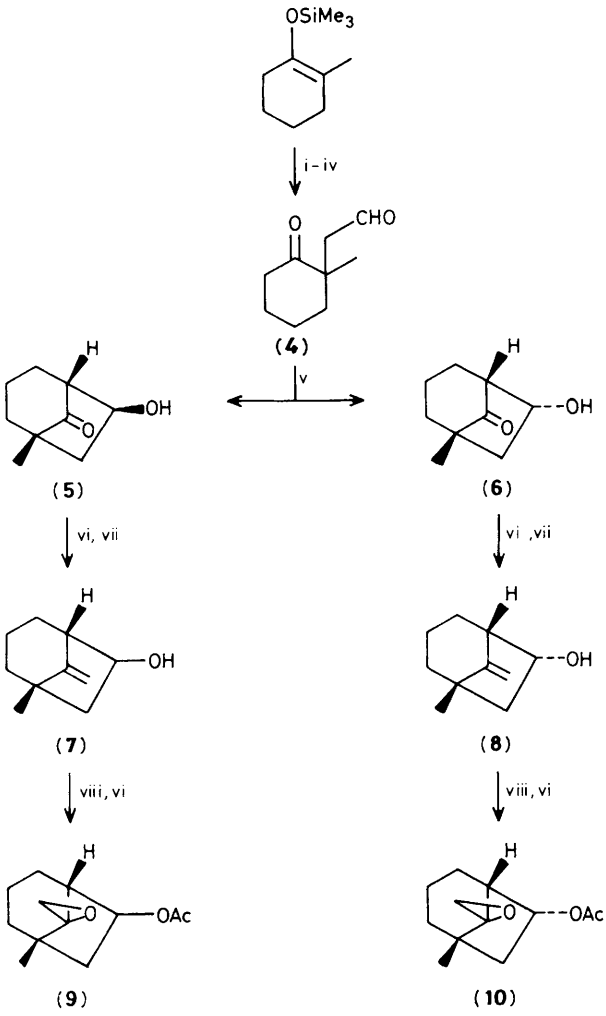
(**3**)

It was therefore of interest to explore general methods for the selective chemical deoxygenation of the trichothecenes; if successfully achieved, the so-created dienes would offer manifold possibilities for further chemical modification and metabolic study. This communication describes an efficient method for the selective deoxygenation of deoxynivalenol and of diacetoxyscirpenol (**3**, R = H), the latter being readily available[5] from appropriate *Fusarium* cultures.

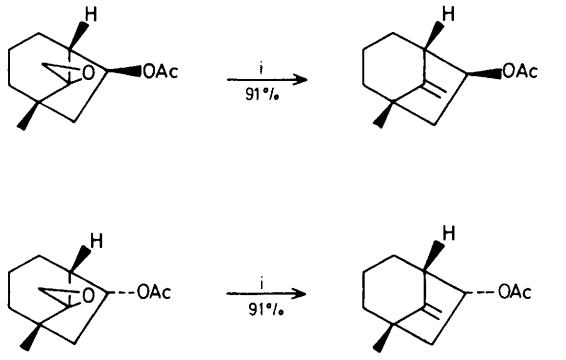
Model studies were carried out on the epimeric bicyclo[3.2.1]octane epoxides (**9**) and (**10**), prepared† as shown (Scheme 1). Aldol cyclisation of the keto-aldehyde (**4**) gave the epimeric alcohols (**5**) and (**6**), in a ratio of 2 : 1 in favour of the β-epimer (**5**). Chromatographic separation, acetylation, and treatment with excess of methylenetriphenylphosphorane gave the unsaturated alcohols (**7**) and (**8**). Subsequent epoxidation with *m*-chloroperbenzoic acid and acetylation gave in each case a single epoxyacetate, (**9**) and (**10**), the rigid geometry of the bicyclo-octane framework ensuring attack by the oxidant from the side of the two-carbon bridge.

Preliminary investigations on these acetates using, *inter alia*, dimethyl diazomalonate with rhodium catalysis[6] proved unpromising. However, employment of the lower-valent tungsten method of Sharpless[7] proved highly successful (Scheme 2).

† All reported compounds were fully characterised by elemental analysis and/or high resolution mass spectrometry, and i.r., and ^1H and ^{13}C n.m.r. spectroscopy.

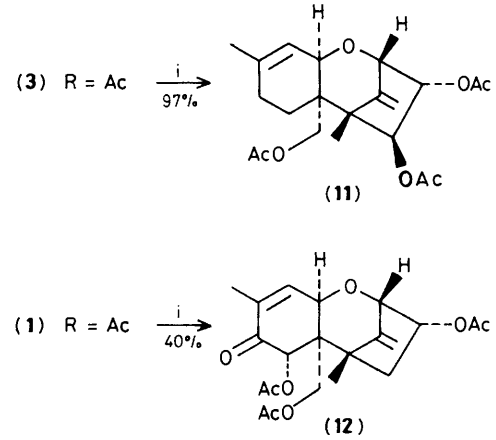


Scheme 1. *Reagents:* i, LiMe; ii, CH_2=$CHCH_2Br$; iii, O_3, CH_2Cl_2; iv, Et_3N; v, NaOMe, MeOH; vi, Ac_2O, pyridine; vii, Ph_3P=CH_2 (4 equiv.); viii, *m*-chloroperbenzoic acid.



Scheme 2. *Reagents:* i, Bu^nLi (6 equiv.), WCl_6 (2 equiv.), tetrahydrofuran (THF), reflux, 6 h.

Turning to diacetoxyscirpenol (**3**, R = H), this was first converted into the triacetate (**3**, R = Ac) (Ac_2O, pyridine, Et_2O). Similar treatment with the Sharpless reagent resulted in clean and selective deoxygenation to afford the diene (**11**) (Scheme 3). Even more remarkably, reaction of deoxynivalenol triacetate (**1**, R = Ac) (Ac_2O, 4-*N*,*N*-dimethylaminopyridine, Et_3N, CH_2Cl_2) under the same conditions gave the diene (**12**). These deoxygenations can be performed on a reasonable scale (100—200 mg). Further synthetic transformations of the dienes (**11**) and (**12**) will be reported in due course.



Scheme 3. *Reagents:* i, Bu^nLi (6 equiv.), WCl_6 (2 equiv.), THF, reflux, 6 h.

A three-step procedure[8] for the deoxygenation of protected forms of diacetoxyscirpenol and verrucarol has been reported recently. The vigorous conditions necessary for this deoxygenation, based on nucleophilic opening of the 12,13-epoxide ring with benzenethiolate ion, are unlikely to be compatible with the sensitive enone functionality of deoxynivalenol, or with the various trichothecene ester groupings. A reported chemical method[9] for the 12,13-epoxide deoxygenation of deoxynivalenol, involving Zn/AcOH reduction of the derived bromohydrin, proceeds in an overall yield of only 9%, and cannot be applied to triacetoxyscirpenol.[10]

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References

1 'Trichothecenes,' ed. Y. Ueno, Elsevier, Amsterdam, 1984; Ch. Tamm and M. Tori, 'Trichothecenes,' ch. 8 in 'Mycotoxins—Production, Isolation, Separation and Purification,' ed. V. Betina, Elsevier, Amsterdam, 1984; R. J. Cole and R. H. Cox, 'Handbook of Toxic Fungal Metabolites,' Academic Press, New York, 1981.
2 T. Yoshizawa, H. Takeda, and T. Ohi, *Agric. Biol. Chem.*, 1983, **47**, 2133 and references therein.
3 J. F. Grove and P. H. Mortimer, *Biochem. Pharmacol.*, 1969, **18**, 1473; M. D. Grove, H. R. Burmeister, S. L. Taylor, D. Weisleder, and R. D. Plattner, *J. Agric. Food Chem.*, 1984, **32**, 541.
4 R. R. King, R. E. McQueen, D. Levesque, and R. Greenhalgh, *J. Agric. Food Chem.*, 1984, **32**, 1181.
5 We thank Professor B. Bycroft (Nottingham) for advice and provision of the culture; in our hands, prolonged periods of incubation gave large amounts of 4β-acetoxyscirpene-3α,15-diol; *cf.* W. R. Roush and S. Russo-Rodriguez, *J. Org. Chem.*, 1985, **50**, 3224.
6 M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **25**, 251.
7 K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, 1972, **94**, 6538.
8 W. R. Roush and S. Russo-Rodriguez, *J. Org. Chem.*, 1985, **50**, 5465.
9 R. R. King and R. Greenhalgh, *Can. J. Chem.*, 1985, **63**, 1089.
10 Ref. 8, footnote 24.