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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 trichothecenes¹ 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 mycotoxin² 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 evidence³ 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).

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 available⁵ 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 catalysis⁶ proved unpromising. However, employment of the lower-valent tungsten method of Sharpless⁷ proved highly successful (Scheme 2).

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



Scheme 1. *Reagents:* i, LiMe; ii, CH₂=CHCH₂Br; iii, O₃, CH₂Cl₂; iv, Et₃N; v. NaOMe, MeOH; vi, Ac₂O, pyridine; vii, Ph₃P=CH₂ (4 equiv.); viii, *m*-chloroperbenzoic acid.



Scheme 2. Reagents: i, BuⁿLi (6 equiv.), WCl₆ (2 equiv.), tetrahydrofuran (THF), reflux, 6 h.

Turning to diacetoxyscirpenol (3, R = H), this was first converted into the triacetate (3, R = Ac) (Ac₂O, pyridine, Et₂O). 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) (Ac₂O, 4-N,N-dimethyl-





(3) R = Ac

Scheme 3. Reagents: i, BuⁿLi (6 equiv.), WCl₆ (2 equiv.), THF, reflux, 6 h.

aminopyridine, 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.

A three-step procedure⁸ 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 method⁹ 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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