SELECTIVE CHEMICAL TRANSFORMATIONS OF THE TRICHOTHECENE, 4β-ACETOXYSCIRPENE-3α,15-DIOL

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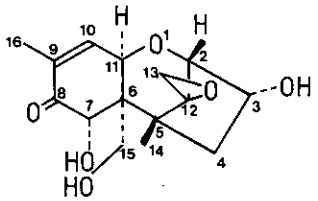
Abstract- The deoxygenated trichothecene derivative (11), suitably functionalised for further selective transformation, has been synthesised efficiently from a naturally occurring trichothecene.

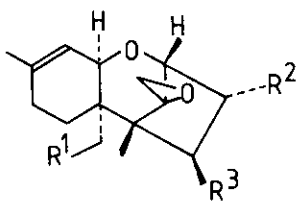
The trichothecenes comprise a group of complex fungal sesquiterpenoids, of which some are phytotoxic and all show some degree of animal toxicity[1]. Their fungal occurrence is so ubiquitous that they have been strongly implicated in natural intoxications of humans and animals. For example, deoxynivalenol (vomitoxin) (1) is produced[2] when cereal grains are infected with Fusarium species: consumption of feedstuffs contaminated with this toxin can cause sub-lethal toxicoses in animals. The tolerance level and biological effects of such compounds are obviously of prime importance. Most, however, are rather difficult to obtain in significant amounts from culture broths. As a group, they present a considerable synthetic challenge, both in terms of need and of the regio- and stereocontrol required for their successful construction.



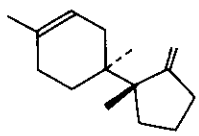
(1)

There are two general approaches to this challenge. The first, that of total synthesis[3], has resulted in syntheses of, inter alia, trichodermin[4] (2), trichodermol[5] (3), verrucarol[6] (4), anguidine[7] (5), calonectrin[8] (6), 12,13-epoxy-trichothec-9-ene[9] (7), and trichodiene[10] (8), the biogenetic precursor of all the

trichothecenes. More complex trichothecenes, such as the Yellow Rain toxins deoxynivalenol[11] and T-2 toxin, have yet to yield to total synthesis.



(2) R^1, R^2 = H, R^3 = OAc
(3) R^1, R^2 = H, R^3 = OH
(4) R^1, R^3 = OH, R^2 = H
(5) R^1, R^3 = OAc, R^2 = OH
(6) R^1, R^2 = OH, R^3 = H
(7) R^1, R^2, R^3 = H



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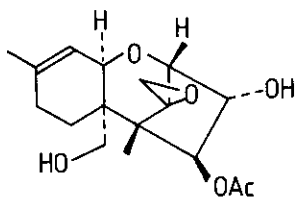
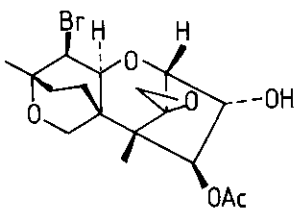
The second approach, one of synthetic manipulation of one of the more readily available trichothecenes, is well exemplified by the conversion[12] of anguidine into verrucarol. Using a suitable Fusarium species[13] and a shake culture procedure, substantial amounts (250-300 mg/l) of anguidine (5) (4β,15-acetoxyscirpene-3-ol) can be obtained. In our hands, an incubation period of 7 days proved ideal for this compound: interestingly, and most usefully, longer periods of incubation, 11 days being optimal, led to production of equal amounts of 4β-acetoxyscirpene-3α,15-diol (9), a compound otherwise obtainable only with difficulty[14]. This communication describes a method for the transformation of (9) into the deoxygenated bromo-ether (11), a compound ideally functionalised for further elaboration.



(9)

The ultimate objective of this research programme is to achieve synthetic manipulation of the 12,13-epoxide moiety, which is demonstrably essential[14] for the biological activity of the trichothecenes in general. The most obvious way of doing this is to deoxygenate the epoxide to produce the corresponding 9,12-diene, but further synthetic operations, such as oxidative cleavage, cannot be achieved selectively at the 12-ene. It is therefore necessary to protect temporarily the 9-ene, using established methodology[16] to form a bromo-ether by intramolecular participation of the C-15 hydroxyl group.

Accordingly, diol (9) (1.43 mmol) was treated with recrystallised N-bromo-succinimide (1.51 mmol) in acetonitrile (45 ml) at room temperature for 1 h. Normal isolation procedures gave the bromo-ether[17] (10), which was acetylated (Ac_2O/pyridine/ether) and purified by suction chromatography to give the corresponding diacetate (82% overall). This diacetate (1.6 mmol) was treated with the Sharpless deoxygenation reagent[18], prepared from WCl_6 (3.3 mmol) and n-BuLi (8.25 mmol) in refluxing tetrahydrofuran for 3.5 h. Normal isolation procedures gave the 12-ene[19] (11) (78%): this method of deoxygenation, which retains the masking of the 9-ene, is superior to that of Roush, where the reductive conditions employed also regenerate this double bond, producing the undifferentiated 9,12-diene[20].



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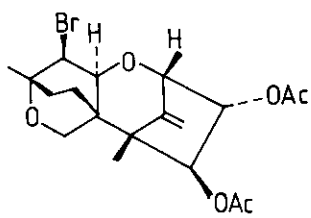
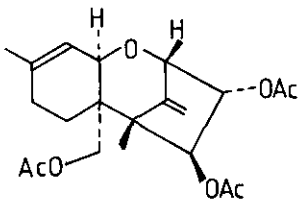


(11)

Under similar conditions, 3,4,15-triacetoxyscirpene and deoxynivalenol 3,7,15-triacetate were deoxygenated[21] to the dienes (12)[22] (97%) and (13)[23] (40%) respectively. Further transformations of the bromo-ether (11) and the dienes (12) and (13) will be reported in due course.



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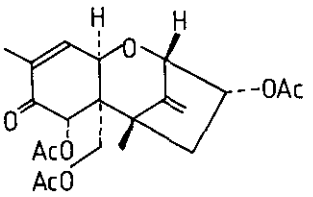

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REFERENCES AND NOTES

1. Trichothecenes, ed. Y. Ueno, Elsevier, Amsterdam, 1984; C.H. Tamm and M. Tori, Trichothecenes, Chapter 8, 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, Agri. Biol. Chem., 1983, 47, 2133 and references within.
3. P.G. McDougal and N.R. Schmuff, Fortschr. Chem. Org. Naturst., 1985, 47, 153; Synform, ed. G. Quinkert, 1984, 4, 2229.
4. E.W. Colvin, S. Malchenko, R.A. Raphael, and J.S. Roberts, J. Chem. Soc., Perkin I, 1973, 1989.
5. W.C. Still and M.-Y. Tsai, J. Amer. Chem. Soc., 1980, 102, 3654.
6. (a) R.H. Schlessinger and R.A. Nugent, J. Amer. Chem. Soc., 1982, 104, 1116; (b) W.R. Roush and T.E. D'Ambra, ibid., 1983, 105, 1058; (c) B.M. Trost, P.G. McDougal, and K.J. Haller, ibid., 1984, 106, 383.
7. D.W. Brooks, P.G. Grothaus, and H. Mazdiyasni, J. Amer. Chem. Soc., 1983, 105, 4472.

8. G.A. Kraus, B. Roth, K. Frazier, and M. Shimagaki, J. Amer. Chem. Soc., 1982, 104, 1114.

9. Y. Fujimoto, S. Yokura, T. Nakamura, T. Morikawa, and T. Tatsuno, Tetrahedron Letters, 1974, 2523; N. Masuoka and T. Kamikawa, ibid., 1976, 1691.

10. S.C. Welch, A.S.C. Prakasa Rao, C.G. Gibbs, and R.Y. Wong, J. Org. Chem., 1980, 45, 4077; M. Suda, Tetrahedron Letters, 1982, 23, 427; R.H. Schlessinger and J.A. Schultz, J. Org. Chem., 1983, 48, 407; K.E. Harding and K.S. Clement, ibid., 49, 3870; G.A. Kraus and P.J. Thomas, J. Org. Chem., 1986, 51, 503.

11. E.W. Colvin and I.G. Thom, Tetrahedron, 1986, 42, in press.

12. D.B. Tulshian and B. Fraser-Reid, Tetrahedron Letters, 1980, 21, 4549.

13. We thank Professor B. Bycroft (Nottingham) for advice and provision of the culture.

14. W.R. Roush and S. Russo-Rodriguez, J. Org. Chem., 1985, 50, 3224.

15. 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, 1181.

16. Refs. 6a, b, 8, 14.

17. 10: m/z 404,0668 and 402.0655 (M^+, $C_{17}H_{23}O_6$ requires 404.0651 and 402.0672). ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 5.03 (1H, d, J 3 Hz, H-4), 4.24 (2H, m, H-10, H-11), 4.21 (1H, dd, J 4.9, 3 Hz, H-3), 3.8 (1H, d, J 4.9 Hz, H-2), 3.82 [1H, dd, J 9.6, 2.7 Hz (W-coupling with H-7β), H-15β], 3.70 (1H, d, J 9.6 Hz, H-15α), 3.05 and 2.75 (2H, ABq, J 14, H-13), 2.1 (3H, s, CH_3CO), 1.3 (3H, s, H-16), 0.6 (3H, s, H-14), ^{13}C n.m.r. ($CDCl_3$, 50 MHz), δ 172.2 (CH_3CO), 83.06 (C-4), 79.7 and 78.1 (C-2 and C-3), 73.74 (C-9), 68.2 (C-11), 65.97 (C-15), 64 (C-12), 54.2 (C-10), 46.4 (C-13), 46.1 (C-5), 41.77 (C-6), 27.9 (C-8), 24.2 (C-16), 20.94 (CH_3CO), 19.2 (C-7), 5.87 (C-14).

18. K.B. Sharpless, M.A. Umbreit, M.T. Nieh, and T.C. Flood, J. Amer. Chem. Soc., 1972, 94, 6538.

19. 11: m/z 430.0810 and 428.0830 (M^+, $C_{19}H_{25}O_6Br$ requires 430.0807 and 428.0828). ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 5.51 (1H, d, J 3.5 Hz, H-4), 5.25 (1H, s, H-13), 4.91 (1H, dd, J 5, 3.5 Hz, H-3), 4.82 (1H, s, H-13), 4.58 (1H, d, J 5 Hz, H-2), 4.25 [1H, dd, J 8.5, 1.6 Hz (W-coupling with H-7α), H-11], 4.14 [1H, dd, J 8.5, 2.4 Hz (W-coupling with H-8α), H-10], 3.98 (1H, dd, J 9.5, 2.7 Hz,

(W-coupling with H-7β), H-15β], 3.7 (1H, d, J 9.5 Hz, H-15α), 2.12, 2.04 2 x CH_3CO), 1.26 (3H, s, H-16), 0.78 (3H, s, H-14).

^{13}C n.m.r. ($CDCl_3$, 50 MHz) δ 170.3, 170 (2 x CH_3CO), 147.25 (C-12), 109.3 (C-13), 78.3, 78.14, 78.09, (C-2, C-3, C-4), 73.3 (C-9), 68.2 (C-11), 66.3 (C-15), 54.8 (C-10), 49.1 (C-5), 41.5 (C-6), 27.8 (C-8), 24.2, 20.97, 20.71 (C-16 + 2 x CH_3CO), 18.7 (C-7), 9.5 (C-14).

20. W.R. Roush and S. Russo-Rodriguez, J. Org. Chem., 1985, 50, 5465.

21. E.W. Colvin and S. Cameron, J. Chem. Soc., Chem. Commun., 1986, in press.

22. 12: m/z 332.1613 (M^+ -AcOH, $C_{19}H_{24}O_5$ requires 332.1842).

^1H n.m.r. ($CDCl_3$, 200 MHz) δ 5.75 (1H, d, J 3 Hz, H-4), 5.42 (1H, dq, J 5, 1.2 Hz, H-10), 5.2 (1H, s. H-13), 4.83 (1H, s, H-13), 4.81 (1H, dd, J 5, 3 Hz, H-3), 4.42 (1H, d, J 5 Hz, H-11), 4.22 and 4.04 (2H, ABq, J 12 Hz, H-15), 4.0 (1H, d, J 5 Hz, H-2), 2.12, 2.05, 2.04 (3 x CH_3CO), 1.66 (3H, bs, H-16), 1.5-1.9 (4H, bm, H-7, H-8), 0.97 (3H, s, H-14).

^{13}C n.m.r. ($CDCl_3$) δ 171, 170 (3 x CH_3CO), 149 (C-12), 140.3 (C-9), 118.5 (C-10), 109 (C-13), 79.4, 78.6, 77.4 (C-3, C-4, C-11), 67.6 (C-2), 63.8 (C-15), 51.6 (C-5), 43.6 (C-6), 27.8 (C-8), 23.2, 21.0, 20.9, 20.7 (C-16 + 3 x CH_3CO), 20.5 (C-7), 10.9 (C-14).

23. 13: m/z 406.1603 (M^+, $C_{21}H_{26}O_8$ requires 406.1620).

^1H n.m.r. ($CDCl_3$, 200 MHz) δ 6.50 (1H, dq, J 5.5, 1.5 Hz, H-10), 5.87 (1H, s, H-7), 5.28 (1H, s, H-13), 4.95 (1H, ddd, J 11, 4.5, 4.5 Hz, H-3), 4.88 (1H, s, H-13), 4.69 (1H, d, J 5.5 Hz, H-11), 4.49 (1H, d, J 4.5 Hz, H-2), 4.37 and 4.25 (2H, ABq, J 12 Hz, H-15), 2.36 (1H, dd, J 15, 4.5 Hz, H-4α), 2.21, 2.15, 1.91 (3 x CH_3CO), 1.83 (3H, bs, H-16), 1.24 (3H, s, H-14).

^{13}C n.m.r. ($CDCl_3$) δ 192.5 (C-8), 170, 169.9, 169 (3 x CH_3CO), 149.9 (C-12), 137 (C-9), 136.7 (C-10), 110 (C-13), 79 (C-7), 74.9, 70.9, 70.4 (C-2, C-3, C-11), 62.4 (C-15), 51 (C-5), 47.8 (C-6), 41.8 (C-4), 20.99, 20.93, 20.63, 19.1 (C-16 + 3 x CH_3CO), 15.5 (C-14).

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