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THE READY CONVERSION OF ANGUIDINE INTO VERRUCAROL AND TRICHODERMOL[1]

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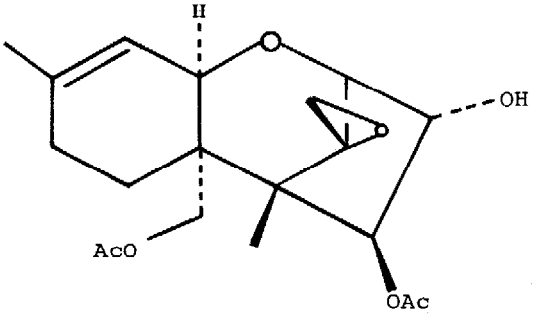
Summary: *Anguidine, 1, is readily converted into verrucarol diacetate, 2d, in 85 percent yield by application of the Barton-McCombie deoxygenation procedure. To enable conversion into trichodermol, 3a, the primary hydroxyl group of verrucarol, 2a, is selectively acetylated or preferably silylated, thereby paving the way for its deoxygenation in three simple, high-yield reactions.*

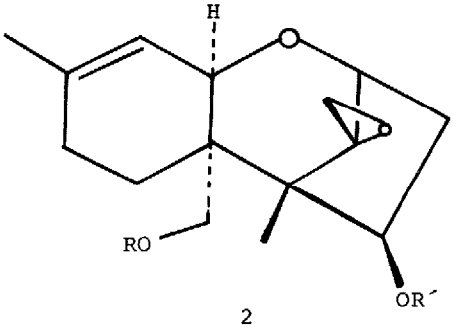
The trichothecene group of antibiotics currently attract considerable attention owing, in part, to the wide range of biological activities which they display.[3] Activity may reside in the sesquiterpene backbone as in the case of anguidine[4] 1, but examination of the various roridins and verrucarins indicates that the heavily functionalized "ribbons" which connect the C4 and C15 hydroxyl groups of verrucarol 2a, profoundly influence biological activity.[3]

Recently Jarvis and co-workers[5] have isolated novel trichothecene specimens in which (a) the "ribbon" is "broken", with the esters pendant at C4 and C15 (as in trichoverrin 2b), and (b) in which the C15 hydroxyl is esterfied (as in trichoverrol 2c, and trichodermadiene 3b). These substances are undoubtedly of interest from the standpoints of biosynthesis and pharmacology, and for such investigations ready supplies of verrucarol, 2a, and trichodermol, 3a, are required. Unfortunately these substances are not directly accessible, and their isolation requires elaborate protocols and hydrolysis of chromatography.[2,6] On the other hand, anguidine 1, is obtained directly from fermentation broths in crystalline form, and its attractiveness is enhanced by the fact that two of the hydroxyl groups are conveniently protected. In this communication we outline simple routes from anguidine (1) to verrucarol (2a) and trichodermol (3a).

Anguidine, 1, was deoxygenated by the procedure of Barton and McCombie[7] to give an 85 percent yield of diacetyl verrucarol, 2d, which was quantitatively deacetyated to verrucarol, 2a with sodium methoxide.

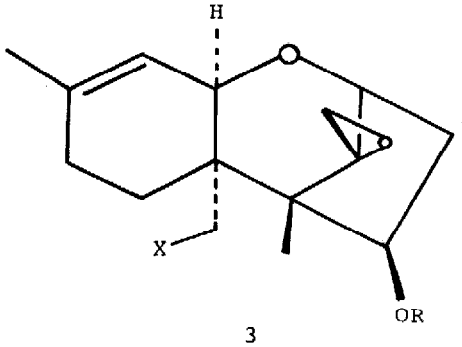


1



2

	R	R´
a	H	H
b	COCH=C(CH$_3$)-(CH$_2$)$_2$OH (E)	COCH=CH-CH=CH-CH(OH)-CH(OH)-CH-CH$_3$ (c, t)
c	H	Ditto
d	Ac	Ac
e	H	Ac
f	Ac	H
g	TBDMSi	H
h	H	TBDMSi



3

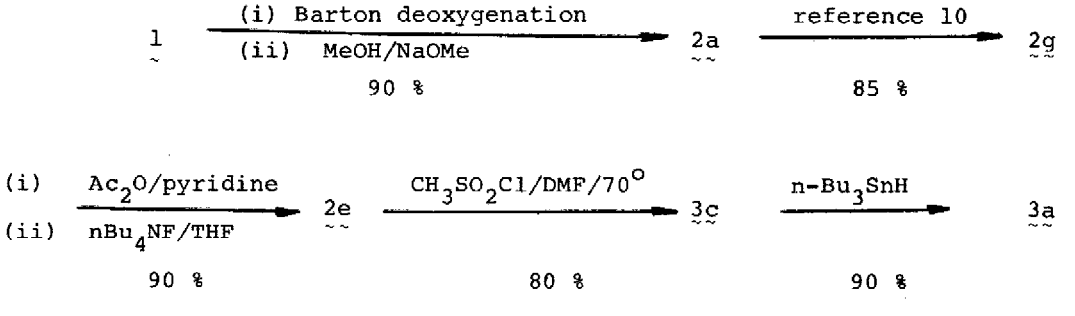
	X	R
a	H	H
b	H	COCH=CH-CH=CH-CH(O)-CH-CH$_3$ (c, t, t)
c	Cl	Ac
d	Cl	TBDMSi

Conversion into trichodermol (3a) now required selective access to the primary hydroxyl group. Breitenstein and Tamm had actually prepared the secondary acetate 2e by treating verrucarol, 2a, with acetyl chloride[8], but the low yield (∿40 percent) prompted us to seek an alternative approach. Attempts to selectively deesterify the diacetate 2d were unsuccessful. On the other hand, the primary hydroxyl group of 2a could be selectively acetylated[9] giving 2f in 70 percent yield, or better still, be selectively silylated[10] giving crystalline 2g[11] (m.p. 145-146°) virtually uncontaminated. The former (2f) was then silylated (TBDMSiCl/DMF) and deacetylated to give 2f[11], whereas the latter (2g) was acetylated (Ac_2O/pyridine) and then desilylated (nBu_4NF/THF) to give known[8] 2e.

For both 2e or 2h, application of the Barton procedure led, as expected[7], only to partial deoxygenation. The alcohols were therefore converted into the chlorides[11] 3c and 3d, respectively, by reaction with methanesulfonyl chloride in dimethylformamide at 70° [12]. Reduction with tri-n-butyltin hydride in the presence of benzoyl peroxide was virtually quantitative, and removal of the acetate or silyl protecting group then led to trichodermol 3a.

The summary shown is Scheme 1 outlines our preferred routes from anguidine, 1, to 2a and 3a, and it is seen that these may be carried out readily in high yields.

SCHEME 1



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REFERENCES AND NOTES

1. This investigation was supported in part by Grant Number CA-28192-01 awarded by the National Cancer Institute, DHEW.
2. Holder of a Graduate Fellowship in Chemistry awarded by The Upjohn Company, Kalamazoo, Michigan.
3. J. R. Bamburg and F. M. Strong, In "Microbial Toxins," S. Kadis, A. Ciegler, S. J. Ajl, Ed.; Vol VII, Academic Press: New York, Chapter 7, 1971. Ch. Tamm, Progr. Chem. Org. Natural Prod., 31, 63, 1974.
4. T. W. Doyle, W. T. Bradner, in "Anticancer Agents Based on Natural Product Models," J. M. Cassidy, J. D. Douros, Ed.; Academic Press, New York, Chapt. 2, 1980.
5. B. B. Jarvis, J. O. Midiwo, G. P. Stahly, G. Pavanasasivam, E. P. Mazzola, Tetrahedron Lett., 787, 1980.
6. G. Pavanasasivam, Ph.D. Thesis, University of Maryland, 1980.
7. D. H. R. Barton and S. W. McCombie, J. C. S. Perkin I, 1574 (1975).
8. W. Breitenstein and Ch. Tamm, Helv. Chim. Acta., 61, 1975 (1978).
9. To 2a dissolved in methylene chloride was added 1.2 equivalents of Ac_2O and 6 equivalents of pyridine and stirred at room temperature (8-10 hours). Standard work-up afforded 2e[8] in 70% yield.
10. To a solution of 2a and tert-butyldimethylsilyl chloride (1.2 equivalents) in methylene chloride were added triethylamine (1.3 equivalents) and 4-dimethylaminopyridine (0.04 equivalent) and stirred at room temperature for 4 days. Standard work-up afforded 2g in 85% yield.
11. This substance gave satisfactory spectroscopic features, and elemental analsis and/or mass spectral data.
12. M. E. Evans and F. W. Parrish, Methods Carbohyd. Chem. 6, 193 (1972).

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