

A Simple and Efficient Synthesis of Bufalin¹

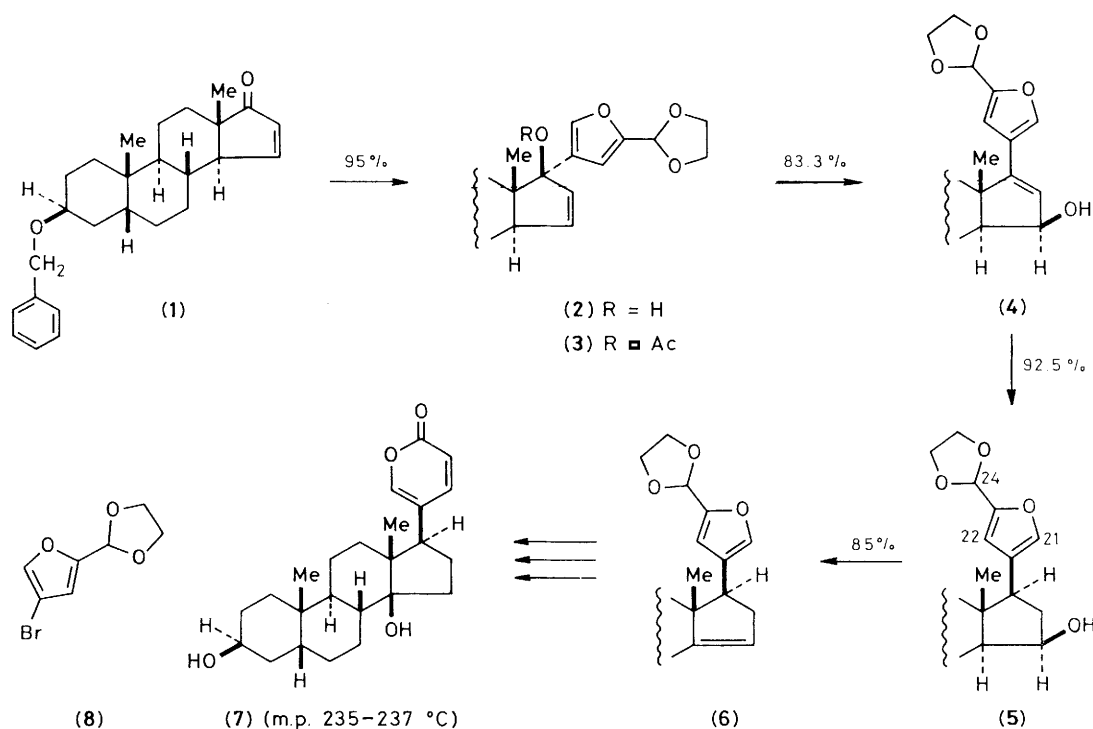
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A simple high-yield preparation of bufalin (**7**) from the steroid (**1**) (derived from testosterone) by an adaptation of our 'furan methodology' for cardenolides is reported.

Some time ago we reported an efficient synthesis of digitoxigenin *via* furyl-containing intermediates.² At an appropriate stage of the synthesis the furyl group was converted into the

unsaturated lactone by a high-yield oxidation reaction. We now disclose a direct preparation of bufalin by an adaptation of this strategy. Lengthy, many-stage syntheses of this natural



product have been reported previously,³ but a truly simple and efficient preparative method does not seem to have been found yet.

Treatment of the bromoacetal (8)⁴ with *n*-butyl-lithium in diethyl ether followed by addition of the protected ketone (1)² at -70°C gave the foamy allylic alcohol (2) in a yield of 95%. Acetylation of (2) with acetic anhydride–pyridine and reflux of the crude acetate (3) in aqueous acetone in the presence of CaCO_3 yielded 83.3% of the allylic rearrangement product (4) (m.p. $140\text{--}141^\circ\text{C}$, recrystallised from ether).

Hydrogenation of (4) (ethanol–Pd/ CaCO_3) gave the pure amorphous dihydro-derivative (5) in a yield of 92.5%. Elimination of the 15β hydroxy-group in (5) with mesyl chloride in pyridine yielded finally 85% of the unsaturated compound (6) (m.p. $141\text{--}142^\circ\text{C}$ from ether–hexane); ^1H n.m.r. (CDCl_3) δ 0.68 [s, 3H, 18-H], 0.97 [s, 3H, 19-H], 3.70 [m, $W_{1/2}$ ca. 7 Hz, 3-H], 3.88–4.20 [m, O–CH₂–CH₂–O], 4.47 [s, –CH₂–Ph], 5.23 [m, $W_{1/2}$ ca. 6 Hz, 1H, 15-H], 5.83 [s, 1H, 24-H], 6.33 [br. s, 1H, 22-H], 7.18 [br. s, 1H, 21-H], and 7.28 [br. s, 5 arom. H].

We prepared compound (6) some time ago from digitoxigenin and converted it into bufalin by a photo-oxidative furan ring opening followed by a modification of the functional

group system.⁵ This simple high-yield process was now repeated and the product was fully verified with the totally synthetic material. The synthetic bufalin (7) was identical in all respects with the natural compound.

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References

- 1 For Part IX of the Series 'On Cardioactive Steroids' see *Can. J. Chem.*, 1982, **60**, 2161.
- 2 T. Y. R. Tsai, A. Minta, and K. Wiesner, *Heterocycles*, 1979, **12**, 1397.
- 3 Cf. F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Am. Chem. Soc.*, 1969, **91**, 1228; G. P. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *Chem. Commun.*, 1970, 93; E. Joshii, T. Oribe, T. Koizumi, I. Hayashi, and K. Tamura, *Chem. Pharm. Bull.*, 1977, **25**, 2249.
- 4 R. Sornay, J.-M. Meunier, and P. Fournari, *Bull. Soc. Chim. Fr.*, 1971, 990.
- 5 T. Y. R. Tsai and K. Wiesner, *Can. J. Chem.*, 1982, **60**, 2161.