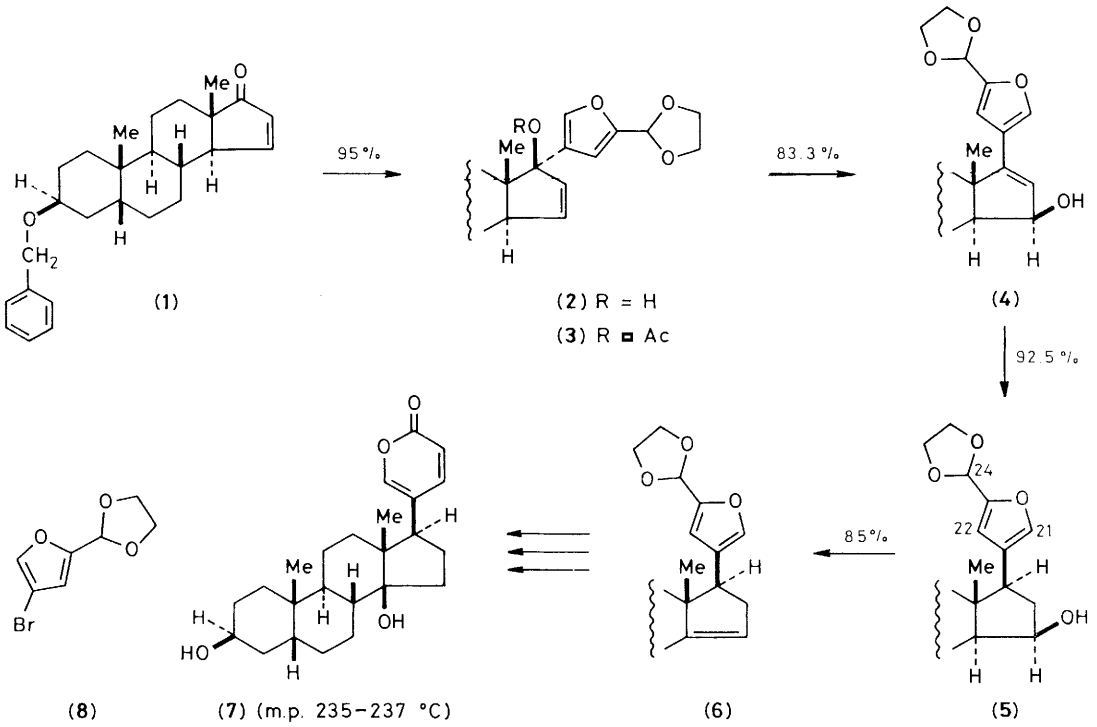
A Simple and Efficient Synthesis of Bufalin[1]

Alina Sen, Franz Josef Jäggi, Thomas Y. R. Tsai, and Karel Wiesner*

Natural Products Research Centre, University of New Brunswick, Bag Service 45222, Fredericton, New Brunswick, Canada E3B 6E2

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—141 °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 15-β hydroxy-group in (**5**) with mesyl chloride in pyridine yielded finally 85% of the unsaturated compound (**6**) (m.p. 141—142 °C from ether–hexane); ^{1}H n.m.r. ($CDCl_3$) δ 0.68 [s, 3H, 18-H], 0.97 [s, 3H, 19-H], 3.70 [m, $W_{\frac{1}{2}}$ *ca.* 7 Hz, 3-H], 3.88—4.20 [m, O–CH_2–CH_2–O], 4.47 [s, –CH_2–Ph], 5.23 [m, $W_{\frac{1}{2}}$ *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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