

A ONE-STEP SYNTHESIS OF 17 α -HYDROXY CARDENOLIDES AND ISO-CARDENOLIDES FROM C₁₇ STEROIDAL KETONES

Rinaldo Marini-Bettolo, Connie S. J. Tsai, Thomas Y. R. Tsai,
and Karel Wiesner*

Natural Products Research Centre, University of New Brunswick,
Fredericton, New Brunswick, Canada, E3B 5A3

Dedicated to Professor Tetsuji Kametani with best wishes.

Abstract -- The steroidal ketone (3) gave in high yield the cardenolide (4) and iso-cardenolide (6) by treatment with the lithium derivatives prepared from 4-bromo- and 3-bromo-2-trimethylsilyloxyfuran, respectively.

In previous work¹ we have shown that cardenolides and iso-cardenolides may be synthesized by a method which features the reaction of a steroidal ketone with 3-furyl lithium and an oxidative and reductive transformation of the furan ring into a five-membered unsaturated lactone.

We now wish to report a novel and far superior method for the conversion of the appropriate steroidal furan derivative into a cardenolide. We have developed new organometallic reagents of the type I and II. The R group may be any removable blocking group and in this Communication we shall specifically deal with the preparation and use of the trimethylsilyloxy reagents (I and II, R = -Si(CH₃)₃).[†] The known β -bromo-crotonolactone² (mp 77°C) was stirred under nitrogen for 12 h at 65°C in dry tetrahydrofuran with triethylamine, trimethylsilyl chloride and a catalytic amount of ZnCl₂. Distillation of the filtered reaction mixture gave the 4-bromo-2-trimethylsilyloxyfuran III (bp 60°C/0.05 mm Hg) as a colorless oil

[†] The synthetic uses of I and II with various selectively removable alkyl groups as R will be described in separate Communications.

in a yield of 80%. [pmr (CCl_4): τ = 9.74 (s, 9H, $-\text{Si}(\text{CH}_3)_3$), 4.84 (d, J = 1.5 Hz, 1H, $\text{C}_3\text{-H}$), 3.20 (d, J = 1.5 Hz, 1H, $\text{C}_5\text{-H}$).]

The 3-bromo-2-trimethylsilyloxyfuran IV was prepared by the same procedure from the known α -bromo-crotonolactone² (mp 58°C). [pmr (CCl_4): τ = 9.70 (s, 9H, $-\text{Si}(\text{CH}_3)_3$), 3.80 (d, J = 3 Hz, 1H, $\text{C}_4\text{-H}$), 3.25 (d, J = 3 Hz, 1H, $\text{C}_5\text{-H}$).]

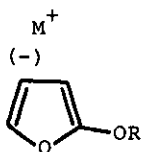
The α,β -unsaturated ketone (1)¹ was heated under reflux with acetone and 3N HCl for 1 h. The β,γ -unsaturated isomer (2) (mp 180-1°C) was isolated in a yield of 90%.^{††} [ir (CHCl_3): 1740 cm^{-1} (C=O); pmr (CDCl_3): τ = 2.66 (s, 5H, aromatic H), 4.50 (dd, J = 2 Hz, 1H, $\text{C}_{15}\text{-H}$), 5.50 (s, 2H, benzylic H), 6.28 (broad s, 1H, $\text{C}_3\text{-H}$), 7.06 (dd, J = 2 Hz, 2H, $\text{C}_{16}\text{-H}$), 8.88 (s, 3H, 19- CH_3), 8.98 (s, 3H, 18- CH_3).] Compound (2) was hydrogenated in a mixture of benzene, ethanol and 0.1 N aqueous KOH over 10% Pd/ CaCO_3 . The dihydro derivative (3) (mp 119-120.5°C) was obtained in a yield of 90%. [ir (KBr): 1740 cm^{-1} (C=O); pmr (CDCl_3): τ = 2.62 (s, 5H, aromatic H), 5.48 (s, 2H, benzylic H), 6.28 (broad s, 1H, $\text{C}_3\text{-H}$), 8.92 (s, 3H, 19- CH_3), 9.05 (s, 3H, 18- CH_3).]

The 4-bromo-2-trimethylsilyloxyfuran III was dissolved in ether and n-butyl lithium was added to the solution stirred under nitrogen at -78°C. A benzene-ether solution of ketone (3) was then added and the stirring was continued at the same temperature. Work-up gave the cardenolide (4) (mp 175-7°C) in a yield of 94%. [ir (CHCl_3): 3600, 3450 (OH), 1785, 1745 cm^{-1} (lactone); pmr (CDCl_3): τ = 2.69 (s, 5H, aromatic), 4.23 (t, J = 1 Hz, 1H, $\text{C}_{22}\text{-H}$), 5.08 (t, J = 2 Hz, 2H, $\text{C}_{21}\text{-H}$), 6.28 (broad s, 1H, $\text{C}_3\text{-H}$), 9.06 (s, 3H, 19- CH_3), 9.16 (s, 3H, 18- CH_3).] The pmr pattern of compound (4) corresponds to a cardenolide with a normal 17- β ,14- β configuration. Also the ORD of compound (4) is superimposable with the ORD of the 17, α -hydroxycardenolides described by Sondheimer.^{3 †††} It is thus clear that the stereochemistry of the nucleophilic attack on the C_{17} -ketone depends on the configuration of the C_{14} -center.

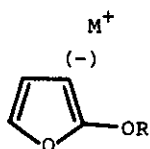
.....

^{††} All compounds gave satisfactory C/H analyses and molecular ions in mass spectrometry.

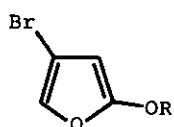
^{†††} An X-ray analysis which corroborated the structure and configuration of compound (6) has just been completed by Drs. F. R. Ahmed and M. Przybylska at the National Research Council Laboratories in Ottawa, Canada.



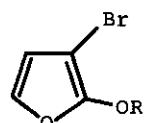
I



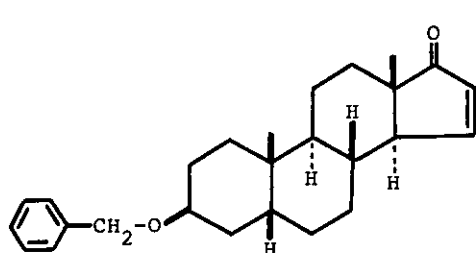
II



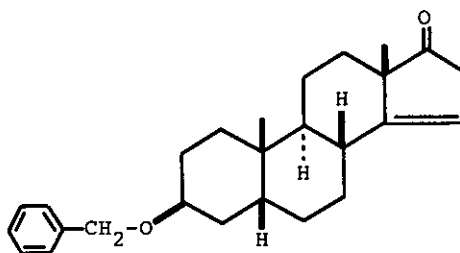
III



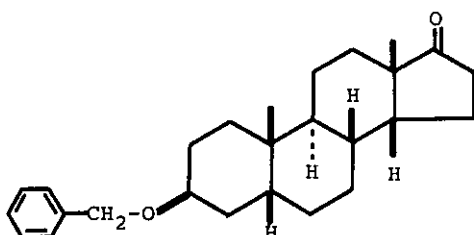
IV



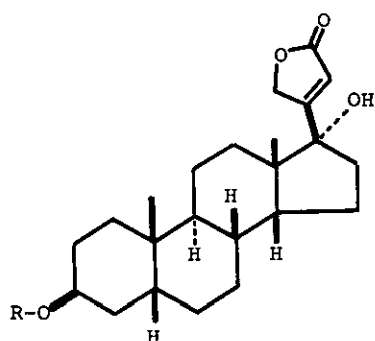
(1)



(2)

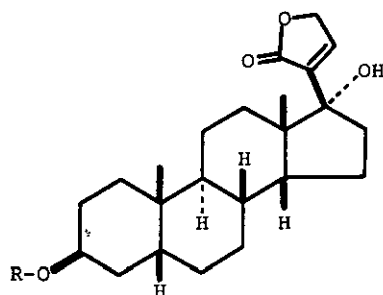


(3)



(4) (R = -CH₂-C₆H₅)

(5) (R = H)



(6) (R = -CH₂-C₆H₅)

(7) (R = H)

Hydrogenolysis of the benzyl group in compound (4) as described previously¹ yielded 90% of compound (5) (mp 209-211°C). [ir (KBr): 3475, 3375 (OH), 1800, 1750 cm^{-1} (C=O); pmr (CDCl_3): τ = 4.20 (t, J = 2 Hz, 1H, $\text{C}_{22}\text{-H}$), 5.06 (t, J = 2 Hz, 2H, $\text{C}_{21}\text{-H}$), 5.86 (broad s, 1H, $\text{C}_3\text{-H}$), 9.06 (s, 3H, 19- CH_3), 9.16 (s, 3H, 18- CH_3).

Compounds (6) and (7) were prepared by the same procedure starting with 3-bromo-2-trimethylsilyloxyfuran IV and the ketone (3). The benzyl derivative (6) (mp 197-8°C) was obtained in a yield of 89%. Finally, hydrogenolysis gave 93% of the iso-cardenolide (7) (mp 228°C). Compound (6): [ir (CHCl_3): 3500 (OH), 1740 cm^{-1} (C=O); pmr (CDCl_3): τ = 2.66 (s, 5H, aromatic H), 2.90 (t, J = 1 Hz, 1H, $\text{C}_{22}\text{-H}$), 5.18 (d, J = 2 Hz, 2H, $\text{C}_{23}\text{-H}$), 5.50 (s, 2H, benzylic H), 6.26 (broad s, 1H, $\text{C}_3\text{-H}$), 9.06 (s, 3H, 19- CH_3), 9.18 (s, 3H, 18- CH_3).] Compound (7): [ir (KBr): 3500 (OH), 1737 cm^{-1} (C=O); pmr (CDCl_3): τ = 2.92 (t, J = 2 Hz, 1H, $\text{C}_{22}\text{-H}$), 5.18 (d, J = 2 Hz, 2H, $\text{C}_{23}\text{-H}$), 5.56 (s, 1H, $\text{C}_{17}\text{-OH}$), 5.88 (broad s, 1H, $\text{C}_3\text{-H}$), 9.06 (s, 3H, 19- CH_3), 9.18 (s, 3H, 18- CH_3).]

The same derivatives (4), (5), (6) and (7) were also obtained by reaction of the ketone (3) with β -furyl lithium followed by the already described oxidation and reduction procedures.¹

ACKNOWLEDGEMENTS

We wish to thank the Canada Council, Ottawa (Izaak Walton Killam Memorial Scholarship to K.W.), the Natural Sciences and Engineering Council, Ottawa, and Advance Biofactures Corporation, New York, for the support of these studies. R.M.-B. thanks the Italian National Research Council for a leave of absence.

REFERENCES

1. T. Y. R. Tsai, A. Minta, and K. Wiesner, Heterocycles, 1979, 12, 1397.
2. Beilstein 17, Erg. III/IV, p. 4295, 4296.
3. N. Danieli, Y. Mazur, and F. Sondheimer, Tetrahedron, 1967, 23, 715.

Received, 26th July, 1980