The Preparation of Furano-steroid Analogues of Demethoxyviridin

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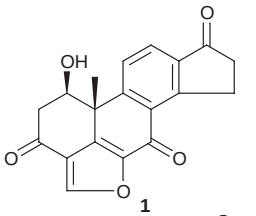
The syntheses of a C-4:C-6 furano-steroid by the base-catalysed cyclization of 6α-acetoxyandrost-4-ene-3,17-dione and of a C-4:C-6 tetrahydrofuran by the cyclization of 3β,6β-dihydroxy-4β-hydroxymethyl-androstan-17-one, are described.

Demethoxyviridin **1** has been reported[1] to be a potent inhibitor of the formation of inositol 1,4,5-triphosphate which is an important messenger in the cell regulatory process. The viridin family of steroidal antibiotics are characterized by the presence of a furan ring bridging C-4 and C-6.[2] It has been suggested[3] that their biological activity is associated with the presence of this moiety. Despite the fact that in the biosynthesis of the steroids, the C-4 methyl groups are removed by an oxidative process, C-4′–C-6 furano-steroids are relatively rare as natural products. We have therefore explored some methods for the introduction of a furan and a tetrahydrofuran ring between C-4 and C-6 in the androstane series.



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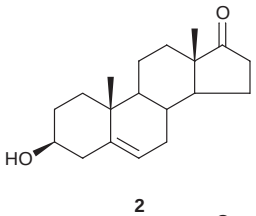

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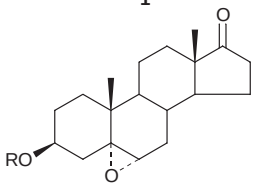
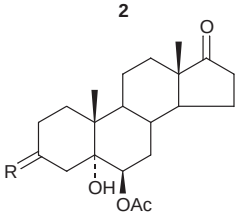
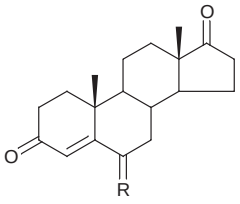


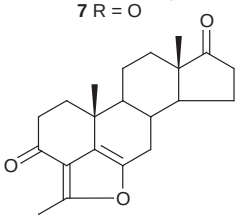
3 R = Ac
4 R = H



5 R = α-H, β-OAc
6 R = α-H, β-OH
7 R = O



8 R = α-H, β-OAc
9 R = α-OAc, β-H
10 R = α-OH, β-H
11 R = α-H, β-OH



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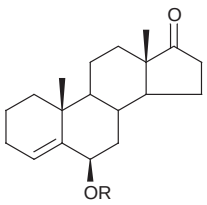
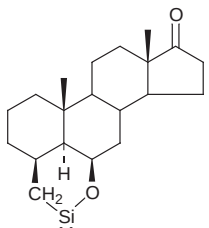
The furan **12** was prepared as a simple demethoxyviridin model from the readily available dehydroisoandrosterone **2** following a method described previously[4] for testosterone acetate. In our case the furan ring was formed by the intramolecular base-catalysed cyclization of 6α-acetoxy-androst-4-ene-3,17-dione **9**. Acetolysis of 3β-acetoxy-5α,6α-epoxyandrostan-17-one **3** gave the 3β,6β-diacetate **5**.[5] Selective hydrolysis of the more exposed equatorial 3β-acetate with tetracyanoethylene in methanol[6] and oxidation of the 3β-hydroxy group in **6** afforded the 3-ketone **7**. Dehydration of the 5α-hydroxy group with thionyl chloride afforded 6β-acetoxyandrost-4-ene-3,17-dione **8**.[7] Epimerization of the 6β-acetate with hydrobromic acid in acetic acid gave the equatorial 6α-acetate **9**.[8] A more direct method involved the Swern oxidation[9] of the epoxide **4** of dehydroisoandrosterone which gave, *inter alia*, a mixture of the 6α- and 6β-hydroxyandrost-4-ene-3,17-diones **10** and **11**. This crude mixture was acetylated and isomerized to afford the 6α-acetate **9**. Cyclization to form the furan **12** was achieved by treatment of **9** with sodium hydride in refluxing xylene.



14 R = Ac
15 R = H
16 R = $Si(Me)_2CH_2Br$



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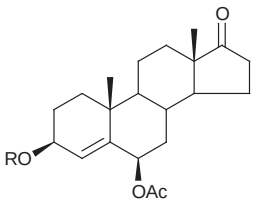
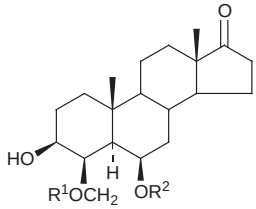
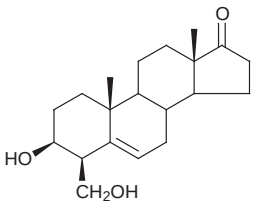


18 R = Ac
19 R = H
20 R = $Si(Me)_2CH_2Br$



21 $R^1 = R^2 = H$
22 R^1 = Ac, R^2 = H
23 R^1 = H, R^2 = Ac



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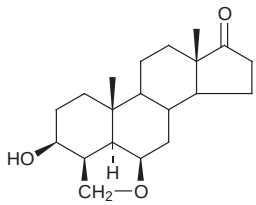

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The C-4′–C-6 tetrahydrofuran ring was constructed *via* a 4-hydroxymethyl derivative using the Stork procedure.[10,11] Androst-5-en-17-one was converted to 6β-hydroxyandrost-4-en-17-one **15** *via* the 5α,6α-epoxide, acetolysis, elimination and hydrolysis of the 6β-acetate **14**.[12] Although radical cyclization of the 6β-(bromomethyl)dimethylsilyl ether **16** led to the formation of the cyclic silyl ether **17** on treatment with tri-*n*-butyltin hydride and AIBN, the oxidative removal of the silicon was unsuccessful. However substitution at C-4 was achieved from the 3β-alcohol **19** which was obtained by the selective hydrolysis of the diacetate **18**. Treatment of the 3β-(bromomethyl)dimethylsilyl ether **20** with tri-*n*-butyltin hydride and AIBN followed by oxidative hydrolysis of the silyl ether led to the triol **21**. The major product of this

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reaction sequence was the 4β-acetoxymethyl derivative **22** in which an acyl migration from C-6 in **23**, has occurred. Although dehydration of the 6β-alcohol occurred in the presence of toluene-*p*-sulfonic acid to form **24**, the triol was cyclized to form the tetrahydrofuran **25** using toluene-*p*-sulfonyl chloride in pyridine.

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Techniques used: ^{1}H NMR, IR, chromatography

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