Synthesis of Digitoxigenin from 3β-Acetoxyandrost-5-en-17-one involving Palladium Induced Rearrangement of an Allylic Epoxide[1]

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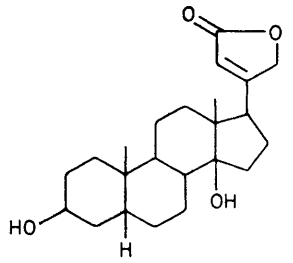
A synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) has been developed in which the key step involved a rearrangement of the allylic epoxide (**8**) to the butanolide (**9**) induced by tetrakis(triphenylphosphine)palladium(0).

Syntheses of digitoxigenin (**1**) and other cardenolides,[2] which are important heart stimulating drugs, from readily available 17-oxo-14α-androstane derivatives involves construction of the β-oriented heterocyclic substituent at C(17) and functionaliza-



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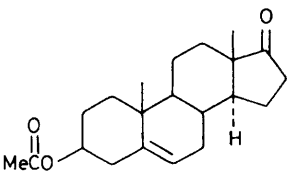
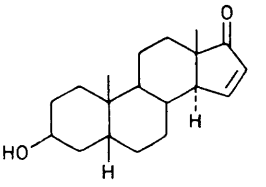


(2)

tion of C(14). Compounds with an hydroxy group at C(15) and a side-chain at C(17) are particularly suitable as intermediates in these syntheses,[3] because (a) hydrogenation of the C(16)–C(17) or C(17)–C(20) double bonds occurs by α-orientated addition of hydrogen, (b) dehydration of C(15) alcohols results in the formation of the C(14)–C(15) double bond, and (c) the 14β-hydroxy group can be introduced starting from the 14-ene.[4] We report a new synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) in which formation of the cardanolide ring and the hydroxy group at C(15) proceeds concomitantly by palladium induced intramolecular rearrangement of the allylic epoxide (**8**).

The unsaturated hydroxy ketone (**3**), obtained† from (**2**) in 40% yield, was oxidized with hydrogen peroxide in alkaline conditions to the 15β,16β-epoxide‡ (**4**) (m.p. 187—190 °C). The hydroxy group in (**4**) was protected as the tetrahydropyranyl (THP) ether to give compound (**5**). Peterson olefination[6] of (**5**) with an anion generated from methyl trimethylsilylacetate and butyl-lithium in diethyl ether, at −78 °C, afforded the unsaturated ester (**6**) as a mixture of *E*- and *Z*-isomers§ [75% yield, oil, ^{1}H n.m.r. δ 0.99 and 1.07 (2 × s, angular Me), 3.50 (d, *J* 3 Hz, 1H, epoxide H), 3.69 and 3.74 (2 × s, 3H, CO_2Me), 3.96 (m, 1H, 3-H), 4.76 (d, *J* 3 Hz, 1H, epoxide H), 6.05 and 6.20 (2 × s, 1H, 20-H)]. The esters (**6**) were reduced with lithium aluminium hydride in diethyl ether, at −40 to −20 °C, to the isomeric alcohols (**7**) [80% yield, ^{1}H n.m.r. δ 4.30 (d, *J* 6 Hz, 2H, 21-H), 5.60 (t, *J* 6 Hz, 1H, 20-H)]. Esterification of (**7**) with phenylthioacetic acid and dicyclohexylcarbodi-imide in diethyl ether[7] and careful purification of the product by chromatography on a silica gel column followed by crystallization from diethyl ether gave (**8**) (92% yield, m.p. 124—127 °C).

Treatment of compounds (**8**) in tetrahydrofuran solution with 10 mol% of tetrakis(triphenylphosphine)palladium(0),¶ in the conditions developed by Trost and Molander[8] for alkylation of allylic epoxides, resulted in the formation of the cardanolide (**9**) in 60% yield (m.p. 77—78 °C, Et_2O–heptane). H.p.l.c. analysis of the product (**9**) indicated that it consisted of two isomers in the ratio 1:1. The major rearrangement product (**9**) was accompanied by two side-products, (**15**) and (**16**). The yields of the side-products increased dramatically when the catalyst was stored before use, even if no visible changes in its appearance occurred.



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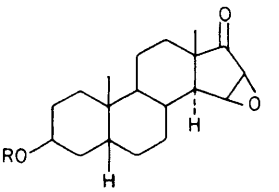
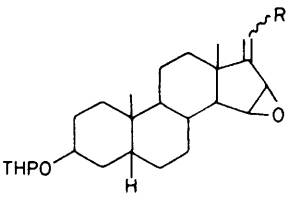
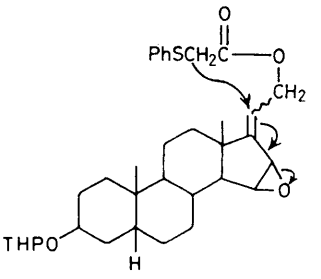


(4) R = H
(5) R = THP



(6) R = -CO_2Me
(7) R = -CH_2OH



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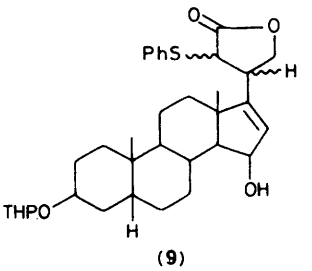
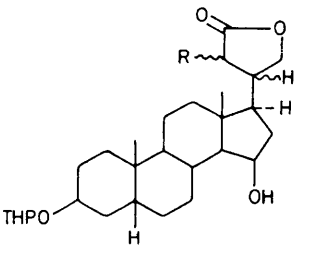
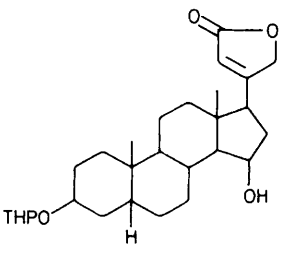


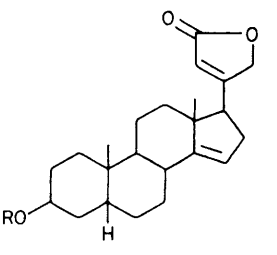
(9)



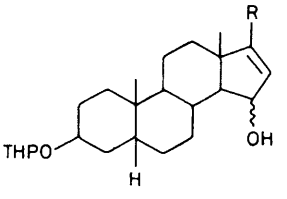
(10) R = -SPh
(11) R = -S(O)Ph



(12)



(13) R = THP
(14) R = H



(15) R = -CH=C(H)~OCOCH$_2$SPh
(16) R = -CH=CH$_2$

The double bond in (**9**) was reduced with the di-imide generated[9] from dipotassium azodicarboxylate and acetic acid in pyridine solution, at 60—75 °C, to give compound (**10**) (70% yield, m.p. 169—173 °C, Et_2O–heptane). The product (**10**) was oxidized with *m*-chloroperbenzoic acid (1 equiv., CH_2Cl_2, −78 °C, 10 min) to the sulphoxide (**11**) which was

† The ketone (**2**) was converted into 3β-acetoxy-17-ethylenedioxy-5β-androstane as described previously (ref. 1). The later compound was transformed into (**3**) (m.p. 123—126 °C) by a procedure in accord with that of Kelly and Sykes (ref. 5).

‡ All new compounds and mixtures of their stereoisomers where applicable gave satisfactory spectral data with appropriate combustion analyses or exact mass data.

§ At this stage a side-product was isolated (*ca.* 20% yield) and its structure is currently under investigation.

¶ Freshly prepared catalyst was used.

pyrolysed in boiling toluene in the presence of dimethylaniline (5—10 equiv., 20 min). The cardenolide (**12**) was so obtained in 95% yield as a single, crystalline product (m.p. 145—147 °C, Et_2O–hexane).

The ease and high yield of the pyrolysis of (**11**) indicated that in each of these diastereoisomeric sulphoxides the benzenesulphinyl group and the proton on C(20) were located on the same side of butanolide ring, in a *cis*-configuration. Since changes in the configuration of chiral centres in subsequent steps is unlikely, this *cis*-geometry can be used to comment on the stereochemistry of the ring closure [(**8**) → (**9**)]. In the two isomeric butanolides (**9**) the phenylthio group and the α-proton were also in a *cis*-configuration. Therefore the cyclisation proceeded in such a way that the phenylthio group and the steroid nucleus were arranged in a *trans*-configuration relative to the plane of the lactone ring.

Compound (**12**) was dehydrated by means of methanesulphonyl chloride in pyridine (3 equiv., 0—60 °C, 3 h) and the unsaturated derivative (**13**) (75% yield, m.p. 154—156.5 °C, Et_2O–hexane) was treated with toluene-*p*-sulphonic acid in methanol to hydrolyse the acetal linkage. The product obtained in 80% yield showed spectral and analytical properties consistent with the structure (**14**) [i.r. 3620 (OH), 1790, 1750, and 1630 cm^{-1} (butenolide), ^1H n.m.r. δ 0.77 and 0.94 (2 × s, angular Me), 4.10 (m, 1H, 3-H), 4.74 (s, 2H, 21-H), 5.23 (br. s, 1H, 15-H), 5.86 (s, 1H, 22-H)] and its m.p. 198—200 °C (Et_2O–hexane) agreed with the literature value.[10] Transformation of the intermediate (**14**) to digitoxigenin (**1**) had already been reported.[4]

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