

## Synthesis of Digitoxigenin from 3 $\beta$ -Acetoxyandrost-5-en-17-one involving Palladium Induced Rearrangement of an Allylic Epoxide<sup>1</sup>

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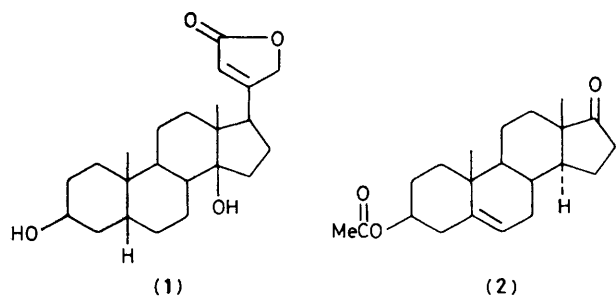
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A synthesis of digitoxigenin (**1**) from 3 $\beta$ -acetoxyandrost-5-en-17-one (**2**) has been developed in which the key step involved a rearrangement of the allylic epoxide (**8**) to the butanolide (**9**) induced by tetrakis(triphenylphosphine)palladium(0).

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Syntheses of digitoxigenin (**1**) and other cardenolides,<sup>2</sup> which are important heart stimulating drugs, from readily available

17-oxo-14 $\alpha$ -androstane derivatives involves construction of the  $\beta$ -oriented heterocyclic substituent at C(17) and functionaliza-



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,<sup>3</sup> because (a) hydrogenation of the C(16)–C(17) or C(17)–C(20) double bonds occurs by  $\alpha$ -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 14 $\beta$ -hydroxy group can be introduced starting from the 14-ene.<sup>4</sup> We report a new synthesis of digitoxigenin (1) from 3 $\beta$ -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<sup>†</sup> from (2) in 40% yield, was oxidized with hydrogen peroxide in alkaline conditions to the 15 $\beta$ ,16 $\beta$ -epoxide<sup>‡</sup> (4) (m.p. 187–190 °C). The hydroxy group in (4) was protected as the tetrahydropyranyl (THP) ether to give compound (5). Peterson olefination<sup>6</sup> 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<sup>§</sup> [75% yield, oil, <sup>1</sup>H n.m.r.  $\delta$  0.99 and 1.07 (2  $\times$  s, angular Me), 3.50 (d, *J* 3 Hz, 1H, epoxide H), 3.69 and 3.74 (2  $\times$  s, 3H, CO<sub>2</sub>Me), 3.96 (m, 1H, 3-H), 4.76 (d, *J* 3 Hz, 1H, epoxide H), 6.05 and 6.20 (2  $\times$  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, <sup>1</sup>H n.m.r.  $\delta$  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<sup>7</sup> 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).

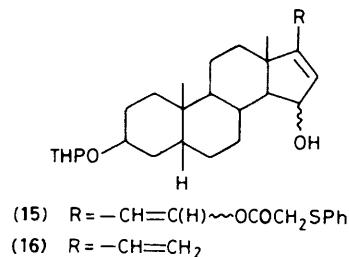
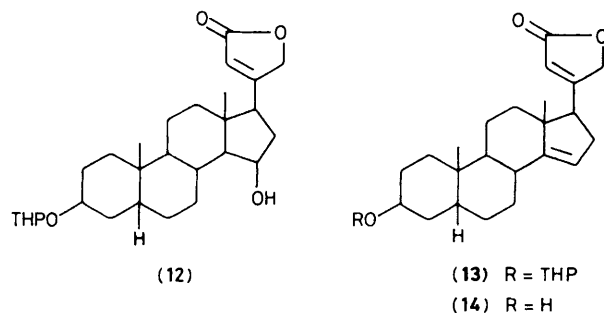
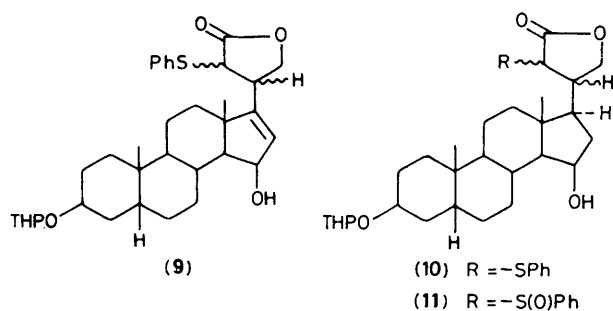
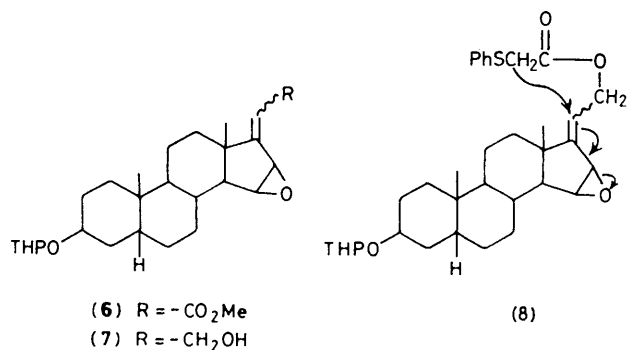
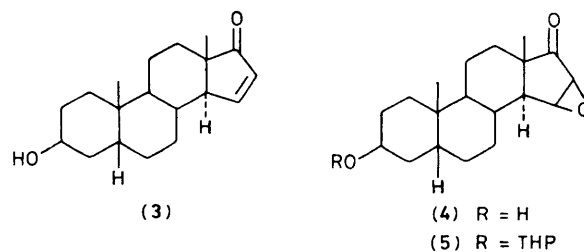
Treatment of compounds (8) in tetrahydrofuran solution with 10 mol% of tetrakis(triphenylphosphine)palladium(0),<sup>¶</sup> in the conditions developed by Trost and Molander<sup>8</sup> for alkylation of allylic epoxides, resulted in the formation of the cardanolide (9) in 60% yield (m.p. 77–78 °C, Et<sub>2</sub>O–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.

<sup>†</sup> The ketone (2) was converted into 3 $\beta$ -acetoxy-17-ethylenedioxy-5 $\beta$ -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).

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

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

<sup>¶</sup> Freshly prepared catalyst was used.



The double bond in (9) was reduced with the di-imide generated<sup>9</sup> 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<sub>2</sub>O–heptane). The product (10) was oxidized with *m*-chloroperbenzoic acid (1 equiv., CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 10 min) to the sulfoxide (11) which was

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<sub>2</sub>O–hexane).

The ease and high yield of the pyrolysis of (**11**) indicated that in each of these diastereoisomeric sulphoxides the benzene-sulphinyl 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  $\alpha$ -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<sub>2</sub>O–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<sup>-1</sup> (butenolide), <sup>1</sup>H n.m.r.  $\delta$  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<sub>2</sub>O–hexane) agreed with the literature value.<sup>10</sup> Transforma-

tion of the intermediate (**14**) to digitoxigenin (**1**) had already been reported.<sup>4</sup>

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