Cardiotonic Steroids. Part 10.[1] Synthesis of Digitoxigenin from 3β-Acetoxyandrost-5-en-17-one involving Palladium-induced Rearrangement of an Allylic Epoxide[2]

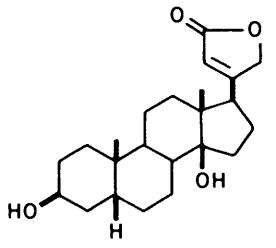
Jerzy Wicha* and Marek. M. Kabat
Institute of Organic Chemistry of the Polish Academy of Sciences, 01–224 Warsaw, Poland

A synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) is presented. In the key step, the allylic epoxide (**8**) was subjected to palladium-induced rearrangement to give the butanolide (**9**).

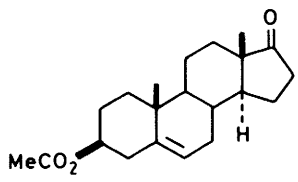
Synthesis of digitoxigenin (**1**) and other cardenolides,[3] which are important heart-stimulating drugs, from readily available 17-oxo-14β-androstane derivatives involves construction of the β-orientated heterocyclic substituent at C-17 and functionalization and inversion of configuration of C-14. Compounds with a hydroxy group at C-15 and side-chain at C-17 are particularly suitable as intermediates in these syntheses,[4] because (a) hydrogenation of the C-6–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 a C-14–C-15 double bond, and (c) the 14β-hydroxy group can be introduced starting from a 14-ene.[5] We report a new synthesis of digitoxigenin (**1**) from 3β-acetoxyandrost-5-en-17-one (**2**) in which formation of the cardenolide ring and the hydroxy group at C-15 proceeds concomitantly by palladium-induced[6] intramolecular rearrangement of the allylic epoxide (**8**).

The unsaturated hydroxy ketone (**3**), obtained[7] from starting compound (**2**) in 40% yield, was oxidized with alkaline hydrogen peroxide in t-butyl alcohol[8] to the 15β,16β-epoxide (**4**) (91% yield).

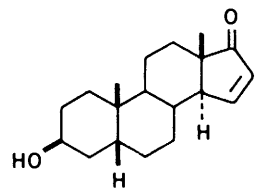
The hydroxy group in compound (**4**) was protected as the tetrahydropyranyl (THP) ether and the derivative (**5**) (90% yield) was subjected to Peterson olefination[9] by means of methyl trimethylsilylacetate and n-butyl-lithium in diethyl ether



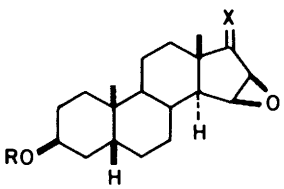
(1)



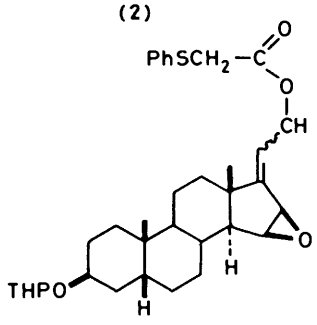
(2)



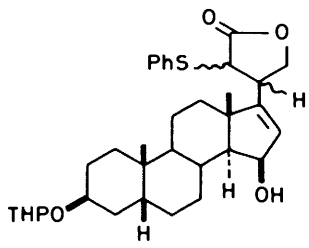
(3)



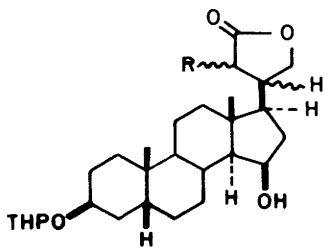
(4) R = H, X = O
(5) R = THP, X = O
(6) R = THP, X = CH~CO_2Me
(7) R = THP, X = CH~CH_2OH



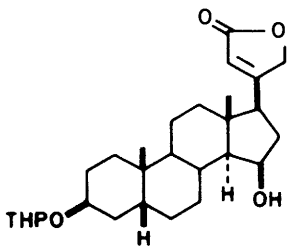
(8)



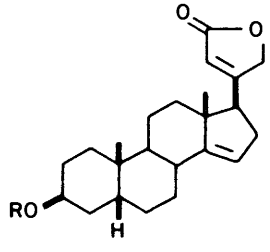
(9)



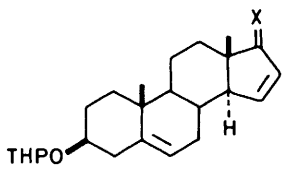
(10) R = SPh
(11) R = S(O)Ph



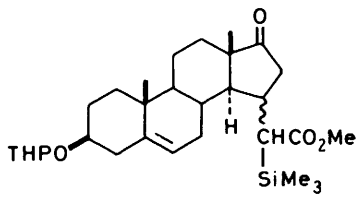
(12)



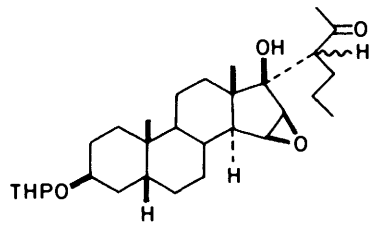
(13) R = THP
(14) R = H



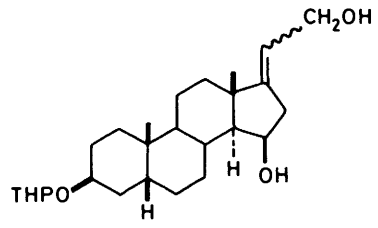
(15) X = O
(16) X = CH~~CO_2Me



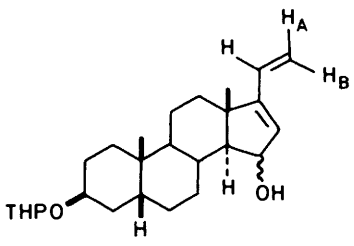
(17)



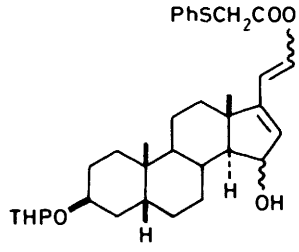
(18)



(19)



(20)



(21)

at −78 °C to room temperature. The product of reaction, isolated in 75% yield, consisted of a mixture of *E* and *Z* isomers of the unsaturated ester (**6**). The ^1H n.m.r. spectrum showed, among other signals, two singlets at δ 5.99 and 5.78, in the ratio 1:3, integrating together for one proton, which were ascribed to the 20-H protons in the isomers.

The required unsaturated esters (**6**) were accompanied by a side-product (5% yield after purification) to which the structure (**18**) was assigned on the basis of its spectral data (i.r., 360 MHz n.m.r., and high-resolution mass spectra; see Experimental section). Product (**18**) arose because of contamination of the methyl trimethylsilylacetate used with methyl acetate. The latter on treatment with n-butyl-lithium gave methyl butyl ketone, which in turn was condensed with the keto epoxide (**5**).

It should be noted that the reaction of the model α,β-unsaturated ketone (**15**) with methyl lithiotrimethylsilylacetate resulted in a mixture of products (**16**) (25% yield) and (**17**) (50% yield), in contrast to the selective 1,2-addition reported[9b] for chalcones.* It is also of interest that an attempt to carry out Wittig–Horner olefination of the keto epoxide (**5**) failed.[10]

The mixture of isomeric esters (**6**) was reduced with lithium aluminium hydride in diethyl ether solution at −40 to −20 °C. The product was separated by chromatography on silica gel to give the alcohols (**7**) (80% yield) and diols (**19**) (10% yield). The alcohols (**7**) were esterified with (phenylthio)acetic acid and dicyclohexylcarbodi-imide (DCC) in diethyl ether.[11] The crude product was carefully purified to give the ester (**8**) (92% yield).

Treatment of compound (**8**) in tetrahydrofuran (THF) solution, at 40 °C, with 10 mol% of tetrakis(triphenylphosphine)palladium(0) in accord with the procedure of Trost and Molander[6a] and Tsuji and co-workers,[6b] followed by chromatography on a silica gel column, afforded the cardenolides (**9**) in 60% yield and two minor products, (**20**) (5% yield) and (**21**) (5% yield). It was observed that the yield of intramolecular alkylation depends dramatically upon the use of freshly prepared catalyst. When commercial or stored palladium complex was used the reaction was sluggish and the yield of compound (**9**) decreased with formation instead of larger quantities of products (**20**) and (**21**).

The diene (**20**) showed, in the vinylic region of its n.m.r. spectrum, 4 signals, each integrating for one proton, which were assigned as follows: 16-H, δ 5.83 (d, *J* 3 Hz); 20-H, δ 6.33 (dd, *J* 17 and 11 Hz); 21-H_A, δ 5.11 (dd, *J* 11 and 2 Hz); and 21-H_B, δ 5.44 (dd, *J* 17 and 2 Hz).

Other spectroscopic data (u.v., i.r., mass spectrum) were in agreement with the proposed structure. H.p.l.c analysis of this product (**20**) revealed that it consists of two compounds, closely related in polarity. Deprotection of compounds (**20**) was attempted in order to clarify whether the chiral centre at C-15 or that in the THP group is responsible for the presence of the isomers; however, rapid dehydration of the allylic hydroxy group on acid treatment was observed. The structure of the product (**21**), which also consisted of two isomers, was elucidated from its ^1H n.m.r. spectrum and other spectral data.

H.p.l.c. analysis of the crude cardenolides (**9**) indicated that the mixture consisted of two isomers in ratio 1:1. It was assumed that in each of these isomers the phenylthio group and the steroidal nucleus are attached *trans* to the butenolide ring. Pyrolysis of the corresponding sulphoxides (**11**), known[12] to proceed predominantly by *cis* elimination of the sulphinyl group and the neighbouring proton, provided evidence for the correctness of this assumption (see below).

Treatment of compound (**9**) with di-imide generated *in situ* from dipotassium azodicarboxylate and acetic acid in pyridine solution,[13] at 60—70 °C, resulted in the saturation of the C-16—C-17 double bond to give compound (**10**) in 70% yield. The sulphide group of (**10**) was oxidized with *m*-chloroperbenzoic acid (MCPBA) to give the sulphoxide (**11**) which was pyrolysed in boiling toluene in the presence of *NN*-dimethylaniline. The elimination of the sulphur moiety was complete in 15 min and the cardenolide (**12**) was obtained in nearly quantitative yield as the single crystalline product.

In the final stages of the synthesis the alcohol (**12**) was dehydrated with methanesulphonyl chloride in pyridine and the unsaturated derivative (**13**) (75% yield) was treated with toluene-*p*-sulphonic acid (PTSA) in methanol to hydrolyse the THP ether. The product obtained in 80% yield showed spectral and analytical properties consistent with the structure of β-anhydrodigitoxigenin (**14**), and its physical constants agreed

* Recently, similar observations on conjugate addition of methyl lithiotrimethylsilylacetate to α,β-unsaturated pentanones have been reported (H. Niskiyama, K. Sakuta, and K. Itoh, *Tetrahedron Lett.*, 1984, **25**, 2487; K. Tomioka and K. Koga, *ibid.*, p. 1599).

with the literature values.[14] Transformation of compound (**14**) to digitoxigenin (**1**) has already been reported.[5a]

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. The spectra were recorded with the following instruments: i.r.—Beckman 4240 or Unicam SP 200 (unless otherwise stated, $CHCl_3$ solutions); ^1H n.m.r.—JEOL JNM-4H-100 (in $CDCl_3$ solutions); u.v.—Beckman MIV (in EtOH solutions); mass—LKB 2091 (at 15 eV ionization potential); high-resolution mass—Varian 731. Chemical shifts are reported in δ units, downfield from Me_4Si. Column chromatography was performed on Kieselgel 60, and t.l.c. on silica gel G (Merck). Organic solutions were dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure on a rotary evaporator. Yields refer to purified crystalline compounds or homogenous products (t.l.c.) which were used for subsequent steps without purification. Microanalyses were performed in our analytical laboratory.

15β,16β-Epoxy-3β-hydroxy-5β-androstan-17-one (**4**).—A mixture of 3β-hydroxy-5β-androst-15-en-17-one (**3**)[7] (3.9 g), t-butyl alcohol (300 ml), 4M-NaOH (3.7 ml), and 30% H_2O_2 (4 ml) was stirred for 16 h at 5 °C. Work-up with Et_2O gave the *epoxy ketone* (**4**) (3.74 g, 91%), m.p. 187—190 °C (from Me_2CO–hexane). After two recrystallizations from the same solvent an analytical sample was obtained, m.p. 189—190 °C: $\nu_{max.}$ 3 400 (OH) and 1 745 cm^{-1} (C=O); δ_H 1.00 and 1.12 (6 H, 2 s, angular CH_3), 3.34 (1 H, d, *J* 3 Hz, 15-H), 3.78 (1 H, d, *J* 3 Hz, 16-H), and 4.12 (1 H, m, 3-H); *m/z* 304 (M^+, 17%), 286 (M^+ − 18, 20), 270 (M^+ − 34, 43), and 120 (100) (Found: C, 74.7; H, 9.5. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27%).

15β,16β-Epoxy-3β-(tetrahydropyran-2′-yloxy)-5β-androstan-17-one (**5**).—A solution of the alcohol (**4**) (3.74 g) in CH_2Cl_2 (50 ml) was treated with dihydropyran (1.12 ml) and PTSA (50 mg) at room temp. for 3 h. Work-up gave the THP-derivative (**5**) (4.34 g, 90%) as an oil; $\nu_{max.}$ 1 745 cm^{-1} (C=O); δ_H 1.01 and 1.14 (6 H, 2 s, angular CH_3), 3.24 (1 H, d, *J* 3 Hz, 15-H), 3.51 (1 H, m, 6′-H_a), 3.80 (1 H, d, *J* 3 Hz, 16-H), 3.96 (2 H, m, 3-H and 6′-H_b), and 4.64 (1 H, br s, 2′-H); *m/z* 388 (M^+, 1%), 287 (M^+ − 101, 40), and 85 (100).

Methyl (E,Z)-*15β,16β-Epoxy-3β-(tetrahydropyran-2′-yloxy)-5β-pregn-17(20)-en-21-oate* (**6**).—To a mixture of methyl trimethylsilylacetate (3.47 g, 23 mmol) and dry Et_2O (80 ml), cooled to −78 °C and stirred under argon, was added a solution of n-butyl-lithium in hexane (1.6M; 14 ml. 23 mmol). After 30 min the resulting mixture was treated dropwise with a solution of compound (**5**) (3.07 g, 7.9 mmol) in Et_2O and the mixture was stirred at −78 °C for 1 h. The mixture was allowed to warm to room temp. during 2 h. Work-up and chromatography of the crude product on a SiO_2 column (150 g) gave (i) on elution with hexane–Et_2O (35:5), compound (**6**) (2.78 g, 79%) as an oil; $\lambda_{max.}$ 223 nm (ε 11 100); $\nu_{max.}$ 1 710 (C=O) and 1 660 cm^{-1} (C=C); δ_H 0.99 and 1.07 (6 H, 2 s, angular CH_3), 3.50 (1 H, d, *J* 3 Hz, 15-H; signal overlaps with 1 H, m, 6′-H_a), 3.69 and 3.74 (3 H, 2 s, OCH_3), 3.96 (2 H, m, 3-H and 6′-H_b), 4.63 (1 H, br s, 2′-H), 4.76 (1 H, d, *J* 3 Hz, 16-H), and 5.78 and 5.99 (1 H, 2 s in the ratio 3:1, 20-H); *m/z* 444 (M^+, 3%), 416 (M^+ − 28, 23), and 85 (100); (ii) on elution with hexane–Et_2O (9:1), a mixture of products (0.7 g) which upon re-chromatography in the same system gave *15β,16β-epoxy-17α 2″-oxohexan-3″-yl)-5β-androstane-3β,17β-diol* 3-(*tetrahydropyran-2′-yl*) *ether* (**18**) (0.23 g, 5%) as an oil; $\lambda_{max.}$ no characteristic absorption; $\nu_{max.}$ 3 480 (OH) and 1 690 cm^{-1} (C=O) δ_H (360 MHz) 0.927 (3 H, t, *J* 7.2 Hz, 6″-H_3), 0.987 and 1.016 (6 H, 2 s, angular CH_3), 2.374 (3 H, s, $COCH_3$), 2.915 (1 H, d, *J* 3.2 Hz, 15-H), 3.262 (1 H, q, J_1 2.9 Hz, J_2 11 Hz, 3″-H), 3.374 [1 H, d, *J* 2.9 Hz (becomes s on decoupling 15-H), 16-H], 3.474 (1 H, m, $w_{\frac{1}{2}}$ 22 Hz, 6′-H_a), 3.898 (1 H, m, $w_{\frac{1}{2}}$ 22 Hz, 6′-H_b), 3.950 (1 H, m, $w_{\frac{1}{2}}$ 7 Hz, 3-H), and 4.626 (1 H, br s, $w_{\frac{1}{2}}$ 20 Hz, 2′-H); high-resolution *m/z* M^+, 488.3464 (2%, $C_{30}H_{48}O_5$ requires *M*, 488.3468), 470.3352 (2, $M^+ - H_2O$. $C_{30}H_{46}O_4$ requires *m/z*, 470.3356), 455.3192 (2, $M^+ - H_2O - CH_3$. $C_{29}H_{43}O_4$ requires *m/z*, 455.3189), 452.3276 (32, $M^+ - 2H_2O$, $C_{30}H_{44}O_3$ requires *m/z*, 452.3277), 388.2604 (2, $M^+ - CH_3COCHCH_2CH_2CH_3 - H$. $C_{24}H_{36}O$ requires *m/z*, 388.2605). 386.2829 (6%, $M^+ - \overline{O{\cdot}CH(OH)[CH_2]_4}$. $C_{25}H_{38}O_3$ requires *m/z*, 386.2828), 286.1902 (30, $M^+ - CH_3COCH_2CH_2CH_2CH_3 - \overline{O{\cdot}CH(OH)[CH_2]_4}$. $C_{19}H_{26}O_2$ requires *m/z* 286.1905), 259.2030 (11, $C_{18}H_{27}O$ requires *m/z*, 259.2033.), 100.0897 (13, $CH_3CO[CH_2]_3CH_3^+$. $C_6H_{12}O$ requires *m/z* 100.0896), and 85.0643 (100, C_5H_9O requires *m/z*, 85.0644). $^+\overline{O{=}CH[CH_2]_4}$.

(E,Z)-15β,16β-Epoxy-5β-pregn-17(20)-ene-3β,21-diol 3-(Tetrahydropyran-2′-yl) Ether (**7**) *and* (E,Z)-*5β-Pregn-17(20)-ene-3β,15β,21-triol 3-(Tetrahydropyran-2′-yl) Ether* (**19**).—A mixture of compound (6) (1.3 g, 2.94 mmol), Et_2O (15 ml), and $LiAlH_4$ (122 mg) was stirred at between −40 and −20 °C for 2 h. Work-up and chromatography of the crude product on a SiO_2 column gave (i) on elution with hexane–Et_2O (85:15), compound (**7**) (0.97 g, 80%) as an oil; $\nu_{max.}$ 3 650 (OH) cm^{-1}; δ_H 1.02 and 1.05 (6 H, 2 s, angular CH_3), 3.41—4.1 (5 H, m, 3-, 15-, and 16-H, and 6′-H_2), 4.30 (2 H, d, *J* 6 Hz, 21-H_2), 4.60 (1 H, br s, 2′-H), and 5.60 (1 H, t, *J* 6 Hz, 20-H); *m/z* 416 (M^+, 5%), 398 (M^+ − 18, 4), and 85 (100); (ii) on elution with hexane–Et_2O (7:3), compound (**19**) (100 mg, 10%) as an oil; $\nu_{max.}$ 3 620 (OH) cm^{-1}; δ_H 0.95 and 1.03 (6 H, 2 s, angular CH_3), 3.96 (1 H, m, 3-H), 4.18 (2 H, d, *J* 6 Hz, 21-H_2), 4.32 (1 H, t, *J* 6 Hz, 15-H), 4.64 (1 H, br s, 2′-H), and 5.22 (1 H, t, *J* 6 Hz, 20-H); *m/z* 316 (M^+ − 84 − 18, 6%), 298 (316 − 18, 11), and 85 (100).

15β,16β-Epoxy-3β-(tetrahydropyran-2′-yloxy)-5β-pregn-17(20)-en-21-yl (Phenylthio)acetate (**8**).—A mixture of the alcohol (**7**) (600 mg, 1.44 mmol), DCC (327 mg, 1.59 mmol), 4-(*NN*-dimethylamino)pyridine (194 mg, 1.59 mmol), (phenylthio)acetic acid (267 mg, 1.59 mmol), and Et_2O (30 ml) was stirred at room temp. for 2 h. After work-up the crude product was filtered through a SiO_2 column [6 g; hexane–Et_2O (95:5)] and crystallized from Et_2O to give *ester* (**8**) (760 mg, 93%), m.p. 124—127 °C; $\lambda_{max.}$ 242.5 nm (ε 9 680); $\nu_{max.}$ 1 700 (C=O), 1 580 (aromatic), and 1 230 cm^{-1} (C–O–C); δ_H 0.98 and 1.01 (6 H, 2 s, angular CH_3), 3.50 (1 H, m, 6′-H), 3.63 (2 H, s, SCH_2), 3.78 (2 H, s, 21-H_2), 3.8—4.3 (4 H, m, 3-, 15-, 16-, and 6′-H), 4.64 (1 H, br s, 2′-H), 5.60 (1 H, t, *J* 6 Hz, 20-H), and 7.3—7.8 (5 H, Ph); *m/z* 374 (M^+ − 192, 28%), 263 (32), 249 (47), and 124 (100), (Found: C, 72.25; H, 8.2. $C_{34}H_{46}O_5S$ requires C, 72.05; H, 8.18%).

Treatment of Compound (**8**) *with Palladium Catalyst.*—A mixture of the ester (**8**) (120 mg, 0.26 mmol), triphenylphosphine (7 mg, 0.03 mmol), freshly prepared tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol), and anhydrous THF (2 ml) was stirred at 40 °C under nitrogen for 90 min. The solvent was evaporated off and the residue was placed on a SiO_2 column (12 g). Elution of the column gave (i) with hexane–Et_2O (93:7), *5β-pregna-16,20-diene-3β,15ξ-diol* 3-(*tetrahydropyran-2′-yl*) *ether* (**20**) (6 mg, 5%) as an oil; $\lambda_{max.}$ 236 nm (ε 6 000); $\nu_{max.}$ 3 620 cm^{-1} (OH); 1.00 and 1.21 (6 H, 2 s, angular CH_3), 3.50 (1 H, m, 6′-H_a), 3.80 (1 H, m, 6′-H_b), 3.98 (1 H, m, 3-H), 4.50 (1 H, m, 15-H), 4.67 (1 H, br s, 2′-H), 5.11 (1 H, dd, $J_{21A.21B}$ 2, $J_{21A.20}$ 11 Hz, 21-H), 5.44 (1 H, dd, $J_{21A.21B}$ 2, $J_{21B.20}$ 17 Hz, 21-H_B),

5.83 (1 H, d, *J* 3 Hz, 16-H), and 6.33 (1 H, dd, $J_{20,21A}$ 11, $J_{20,21B}$ 17 Hz, 20-H); *m/z* 400 (M^+, 5%), 382 ($M^+ - H_2O$, 17), 374 ($M^+ - 26$, 42), 299 (94), and 85 (100); (ii) with hexane–Et_2O (9:1), (*E,Z*)-3β-(Tetrahydropyran-2′-yloxy)-5β-pregna-16,20-diene-15ξ, 21-diol 21-(phenylthio)acetate (**21**) (6 mg, 5%) as an oil; $\lambda_{max.}$ 249 nm (ε 17 400); $\nu_{max.}$ 3 620 (OH), 1 750 (C=O), 1 660 (C=C), and 1 220 cm^{-1} (C–O–C) δ_H 1.02 and 1.13 (6 H, 2 s, angular CH_3), 3.50 (1 H, m, 6′-H_a), 3.68 (2 H, s, SCH_2CO_2), 3.88 (1 H, m, 6′-H_b), 4.46 (1 H, m, 15-H), 4.62 (1 H, br s, 2′-H), 5.79 (1 H, d, *J* 3 Hz, 16-H), 5.98 (1 H, d, $J_{20,21}$ 13 Hz, 20-H), 7.3—7.7 (5 H, m, Ph), and 7.65 (1 H, d, $J_{21,20}$ 13 Hz, 21-H); *m/z* 548 ($M^+ - 18$, 4%), 398 ($M^+ - 168$, 14), 314 ($M^+ - 168 - 84$, 36), 168 (100), 123 (65), and 85 (45); (iii) with hexane–Et_2O (85:15), 15β-*hydroxy*-22ξ-*phenylthio*-3β-(*tetrahydropyran*-2′-*yloxy*)-5β,-14α,20ξ-*card*-16-*enolide* (**9**) (72 mg, 60%), m.p. 77—78 °C (from Et_2O–hexane); $\lambda_{max.}$ 255 nm (ε 2 700); $\nu_{max.}$ 3 620 (OH), 1 785 (C=O), and 1 590 cm^{-1} (phenyl); δ_H 1.00 and 1.09 (6 H, 2 s, angular CH_3), 3.06 (1 H, m, 20-H), 3.53 (1 H, m, 6′-H_a), 3.8—4.2 (4 H, m, 3-H, 21-H_2, and 6′-H_b), 4.35 (1 H, d, $J_{22,20}$ 8 Hz, 22-H), 4.46 (1 H, t, *J* 3 Hz, 15-H), 4.46 (1 H, t, *J* 3 Hz, 15-H), 4.63 (1 H, br s, 2′-H), 5.86 (1 H, d, *J* 3 Hz, 16-H), and 7.3—7.8 (5 H, Ph) (Found: C, 72.05; H, 8.2. $C_{34}H_{46}O_5S$ requires C, 72.05; H, 8.18%).

15β-*Hydroxy*-22ξ-*phenylthio*-3β-(*tetrahydropyran*-2′-*yloxy*)-5β,14α,20ξ-*cardanolide* (**10**).—To a stirred mixture of compound (**9**) (70 mg, 0.12 mmol), dipotassium azodicarboxylate (480 mg, 2.3 mmol), and pyridine (3 ml) at 60 °C was added dropwise acetic acid (144 mg, 2.3 mmol) during 10 h by means of a micro-syringe. The product was isolated with Et_2O and crystallized from Et_2O–heptane to give *compound* (**10**) (50 mg, 70%), m.p. 169–173 °C; $\lambda_{max.}$ 217 (ε 9 800) and 259 nm (3 000); $\nu_{max.}$ 3 640 (OH) and 1 775 cm^{-1} (C=O); δ_H 0.90 and 0.95 (6 H, 2 s, angular CH_3), 3.50 (1 H, m, 6′-H_a), 3.90 (1 H, m, 6′-H_b), 4.00 (1 H, m, 3-H), 4.40 (4 H, m, 21-H_2 and 15- and 22-H), 4.60 (1 H, br s, 2′-H), and 7.20—7.80 (5 H, m, Ph) (Found: C, 72.0; H, 8.4. $C_{34}H_{48}O_5S$ requires C, 71.79; H, 8.51%).

15β-*Hydroxy*-22ξ-*phenylsulphinyl*-3β-(*tetrahydropyran*-2′-*yloxy*)-5β,14α,20ξ-*cardanolide* (**11**).—To a solution of compound (**10**) (65 mg, 0.114 mmol) in CH_2Cl_2 (3 ml) cooled to −78 °C was added MCPBA (19.7 mg, 0.114 mmol). The mixture was stirred for 10 min then washed with aqueous $NaHCO_3$ and filtered through SiO_2 to give the *sulphoxide* (**11**) (65 mg, 97%), m.p. 120—125 °C (from Et_2O–hexane); $\lambda_{max.}$ 252 nm (ε 5 000); $\nu_{max.}$ 3 620 (OH), 1 775 (C=O), 1 580 cm^{-1} (phenyl); δ_H 0.75, 0.90, 0.95, and 1.0 (6 H, 4 s, angular CH_3), 3.5 (1 H, m, 6′-H_a), 3.8—4.6 (5 H, m, 3- and 15 H, 21-H_2, and 6′-H_b), 5.80 (1 H, m, 22-H), and 7.3—7.8 (5 H, m, Ph); *m/z* 552 ($M^+ - 32$, 1%), 374 (20), 356 (29), 217 (93), and 140 (100) (Found: C, 69.8; H, 8.3. $C_{34}H_{48}O_6S$ requires C, 69.83; H, 8.27%).

15β-*Hydroxy*-3β-(*tetrahydropyran*-2′-*yloxy*)-5β,14α-*card*-20(22)-*enolide* (**12**).—A mixture of the sulphoxide (**11**) (65 mg), *NN*-dimethylaniline (100 μl), and toluene (2 ml) was heated under reflux for 15 min. then cooled and placed on a SiO_2 column (2 g). Elution of the column with hexane—Et_2O (4:1) gave *compound* (**12**) (48 mg, 95%), m.p. 145—147 °C (from Et_2O–hexane); $\lambda_{max.}$ 217 nm (ε 13 600); $\nu_{max.}$ 3 620 (OH), 1 790, 1 750, and 1 630 cm^{-1} (butenolide) δ_H 0.85 and 0.95 (6 H, 2 s, angular CH_3), 3.5 (1 H, m, 6′-H_a), 3.85 (1 H, m, 6′-H_b), 4.0 (1 H, m, 3-H), 4.4 (1 H, t, *J* 6 Hz, 15-H), 4.80 (2 H, s, 21-H), and 5.90 (1 H, s, 22-H) (Found: C, 73.2; H, 9.2. $C_{28}H_{42}O_5$ requires C, 73.33; H, 9.23%).

3β-(*Tetrahydropyran*-2′-*yloxy*-5β-*carda*-14,20(22)-*dienolide* (**13**).—A solution of compound (**12**) (40 mg, 0.087 mmol) in pyridine (2 ml) was cooled to 0 °C and treated with methanesulphonyl chloride (43 mg, 0.44 mmol). The resulting mixture was stirred at room temp. for 30 min, then at 60—70 °C for 3 h. Work-up with CH_2Cl_2 gave *compound* (**13**) (29 mg, 75%), m.p. 154—156.5 °C (from Et_2O–hexane); $\lambda_{max.}$ 214 nm (ε 16 700); $\nu_{max.}$ 1 790, 1 750, and 1 630 cm^{-1} (butenolide); δ_H 0.78 and 0.93 (6 H, 2 s, angular CH_3), 3.50 (1 H, m, 6′-H_a), 3.90 (1 H, m, 6′-H_b), 3.93 (1 H, m, 3-H), 4.63 (1 H, br s, 2′-H), 4.73 (2 H, s, 21-H_2), 5.23 (1 H, m, 15-H), and 5.88 (1 H, s, 22-H); *m/z* 440 (M^+, 2%), 356 (31), 339 (100), and 84 (70) (Found: C, 76.2; H, 9.3. $C_{28}H_{40}O_4$ requires C, 76.33; H, 9.15%).

3β-*Hydroxy*-5β-*carda*-14,20(22)-*dienolide* (**14**).—A solution of the THP ether (**13**) (39 mg) in MeOH (4 ml) containing PTSA (4 mg) was kept at room temp. for 2 h. Work-up gave the alcohol (**14**) (30 mg, 94%), m.p. 198—200 °C (from Me_2CO–hexane); $[\alpha]_D^{20}$ − 11° (*c* 0.25 in MeOH); $\lambda_{max.}$ 213 nm (ε 13 900); $\nu_{max.}$ 3 620 (OH), 1 790, 1 750, and 1 630 cm^{-1} (butenolide); δ_H 0.77 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 4.10 (1 H, m, 3-H), 4.74 (2 H, s, 21-H_2), 5.23 (1 H, m, 15-H), and 5.96 (1 H, s, 22-H); *m/z* 356 (M^+, 2%), 338 ($M^+ - H_2O$, 4), and 83 (100) (Found: C, 77.6; H, 9.2 $C_{23}H_{32}O_3$ requires C, 77.49; H, 9.05%) {lit.,[14a] m.p. 202 °C, $[\alpha]_D^{20}$ − 14.4° (*c* 1.3 in MeOH); lit.,[14b] m.p. 195—199 °C, $[\alpha]_D^{20}$ − 9° (*c* 1.5 in MeOH); lit.,[14c] m.p. 191—197 °C, $[\alpha]_D^{24}$ − 15.3° (*c* 0.86 in MeOH)}.

Methyl (E,Z)-3β-(*Tetrahydropyran*-2′-*yloxy*)*pregna*-5,15,17-(20)-*trien*-21-*oate* (**16**) *and Methyl* 17-*Oxo*-3β-(*tetrahydropyran*-2′-*yloxy*)*androsten*-15-*yl*(*trimethylsilyl*)*acetate* (**17**).—To a mixture of methyl trimethylsilylacetate (220 mg, 1.5 mmol) and Et_2O (5 ml), stirred at −78 °C under argon, was added a solution of n-butyl-lithium in hexane (1.6M; 0.94 ml, 1.5 mmol) followed, after 30 min, with a solution of 3β-(tetrahydropyran-2′-yloxy)androsta-5,15-dien-17-one[15] (**15**) (370 mg, 1 mmol) in Et_2O (3 ml). The resulting mixture was stirred at −78 °C for 2 h and was then allowed to warm to room temp. in during 2 h. Work-up and chromatography of the crude product on a SiO_2 column gave (i) on elution with heptane–ethyl acetate (95:5), compound (**16**) (95 mg, 25%); $\lambda_{max.}$ 222 (ε 4 200) and 268 nm (5 200); $\nu_{max.}$ 1 720 (C=O) and 1 630 cm^{-1} (C=C); δ_H 0.91, 0.95, 0.99, and 1.03 (6 H, 4 s, angular CH_3), 3.4—4.2 (3 H, m, 3-H and 6′-H_2), 3.66 and 3.70 (3 H, 2 s, $COCH_3$), 4.75 (1 H, br s, 2′-H), 5.40 (1 H, m, 6-H), 5.52 and 5.66 (1 H, 2 s, 20-H), 6.50 (1 H, m, 16-H), and 7.70 (1 H, m, 15-H); *m/z* 342 ($M^+ - 84$, 5%), 167 (72), and 149 (100); (ii) on elution with heptane–ethyl acetate (9:1), *compound* (**17**) (185 mg, 50%), m.p. 206—209 °C (from Et_2O–hexane); $\nu_{max.}$ 1 730 cm^{-1} (C=O); δ_H 0.18 (9 H, s, $SiMe_3$), 0.88 and 1.03 (6 H, 2 s, angular CH_3), 3.5 (2 H, m, 3-H and 6′-H_a), 3.9 (1 H, m, 6′-H_b), 3.63 (3 H, s, $COCH_3$), 4.7 (1 H, br s, 2′-H), and 5.35 (1 H, m, 6-H); *m/z* 432 ($M^+ - 84$, 3%) and 85 (100) (Found C, 69.9; H, 9.6 $C_{30}H_{48}O_5Si$ requires C, 69.72; H, 9.36%).

Acknowledgements

We thank Dr. E. Baranowska for recording the mass spectra, and Dr. S. Tyrlik and Dr. J. D. Connolly for helpful discussions.

References

1 Part 9. J. Wicha and M. Masnyk, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1985, **33**, 28.
2 Preliminary communication, J. Wicha and M. M. Kabat, *J. Chem. Soc., Chem. Commun.*, 1983, 985.
3 For some recent works, see P. Welzel, H. Stein, and T. Milkova, *Liebigs Ann. Chem.*, 1982, 2119; R. Marini-Bettolo, P. Flecker, T. Y. R. Tsai, and K. Wiesner, *Can. J. Chem.*, 1981, **59**, 1403.
4 T. Y. R. Tsai, A. Minta, and K. Wiesner, *Heterocycles*, 1979, **12**, 1397; U. Stache, W. Fritsch, W. Haede, K. Radscheit, and K. Fachinger, *Justus Liebigs Ann. Chem.*, 1969, **726**, 136.

5 (*a*) Ch. R. Engel and G. Bach, *Steroids*, 1964, **3**, 593; (*b*) M. Heller, F. J. McEvoy, and S. Bernstein, *ibid.*, p. 193.
6 (*a*) B. M. Trost and G. A. Molander, *J. Am. Chem. Soc.*, 1981, **103**, 5969; (*b*) J. Tsuji, H. Kataoka, and Y. Kobayashi, *Tetrahedron Lett.*, 1981, **22**, 2575.
7 R. W. Kelly and P. Sykes, *J. Chem. Soc. C.*, 1968, 416; M. M. Kabat, A. Kurek, and J. Wicha, *J. Org. Chem.*, 1983, **48**, 4248.
8 For epoxidation of androst-15-en-17-one derivatives, see C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, 1965, **87**, 817; J. M. Clark, W. A. Denny, E. R. H. Jones, G. D. Meakins, A. Pendlebury, and J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2765; J. P. Marino and H. Abe, *J. Am. Chem. Soc.*, 1981, **103**, 2907.
9 (*a*) D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 790; (*b*) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 1620.
10 *Cf.* E. G. Baggiolini, J. A. Jacobelli, B. M. Hannessy, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1982, **104**, 2945.
11 F. E. Ziegler and G. D. Berger, *Synth. Commun.*, 1979, **9**, 539.
12 C. A. Kingsbury and D. J. Cram, *J. Am. Chem. Soc.*, 1960, **82**, 1810; for an example of elimination of β-substituted sulphoxides, see M. Hirayama, K. Gamoh, and N. Ikekawa, *Chem. Lett.*, 1982, 491.
13 For an example, see J. W. Hamersma and E. J. Snyder, *J. Org. Chem.*, 1965, **30**, 3985.
14 (*a*) Ch. Tamm and J. P. Rosselet, *Helv. Chim. Acta*, 1953, **36**, 1309; (*b*) P. Hofer, H. Linde, and K. Meyer, *ibid.*, 1962, **45**, 1041; (*c*) P. St. Janiak, Ek. Weiss, and T. Reichstein, *ibid.*, 1967, **50**, 1249.
15 J. Wicha, M. Masnyk, W. Schönfeld, and K. R. H. Repke, *Heterocycles*, 1983, **20**, 231.

Received 14*th August* 1984; *Paper* 4/1439