202. On Cardioactive Steroids. VIII. The Synthesis of Bufalin and Resibufogenin Isomers[1])

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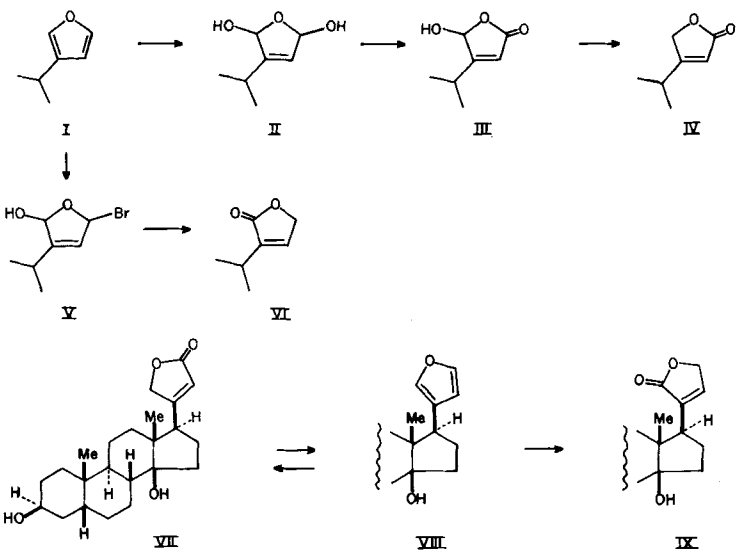
Summary

α-Isobufalin[1]) (**1**) and β-isoresibufogenin[1]) (**3**) have been synthesized from testosterone by a method which features a novel oxidative furan to pyrone transformation.

Introduction. – Some years ago one of us *(K. W.)* has initiated [1] [2] a systematic study of furan oxidation as a tool in organic synthesis in general, and in the synthesis of cardioactive steroids in particular. It was found in model experiments that the

Scheme 1



[1]) Systematic names are given at the titles of the *Exper. Part.*

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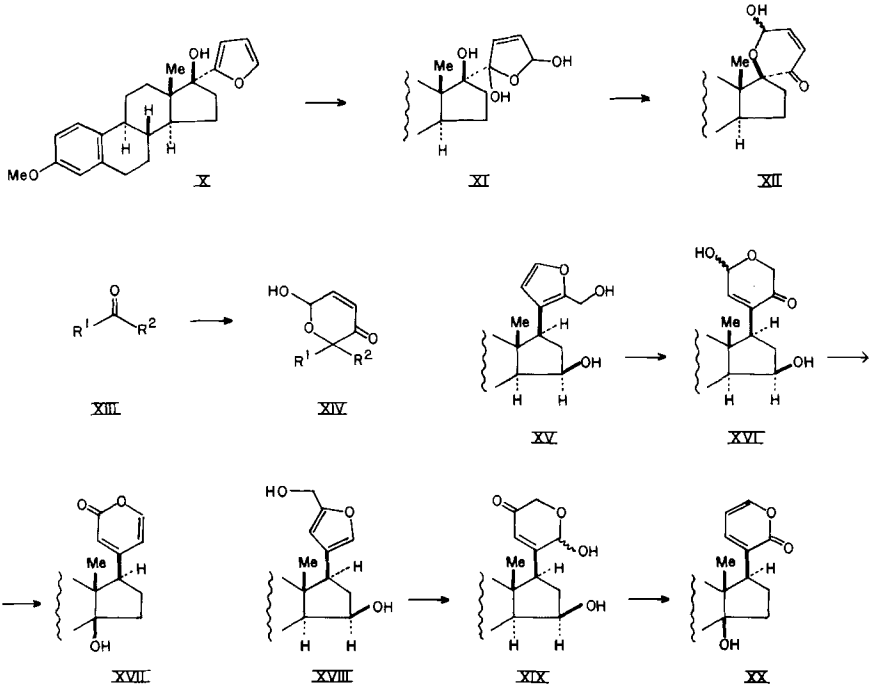
oxidation of furan derivatives was initiated by an attack of an electrophile in the less hindered α-position, followed by a nucleophilic attack at the other α-site. Thus, if the oxidizing agent was a peracid, the primary oxidation product of the isopropylfuran **I** was the diol **II** and this was immediately oxidized further to **III** *(Scheme 1)*. Borohydride reduction of **III** yielded smoothly the butenolide **IV**. When *N*-bromosuccinimide (NBS) was used as oxidizing agent, the primary bromoalcohol **V** eliminated hydrobromic acid and the isomeric butenolide **VI** resulted.

These findings were immediately utilized [1] in the following manner. Digitoxigenin (= 3β,14β-dihydroxy-5β,14β-card-20(22)-enolide; **VII**) was reduced with lithium aluminum hydride to the furyl derivative **VIII**, and this material was readily converted by *N*-bromosuccinimide to the isomeric lactone **IX** *(Scheme 1)*. The glucoside of **IX** was subjected to extensive pharmacological studies which have revealed a high level of inotropic activity combined with a greater margin of safety and reversibility of toxic effects in comparison with the naturally occurring glycosides of *Digitalis* currently used in therapy [3]. Later, when the programme was reactivated in Fredericton we developed also a very efficient synthesis of the isomeric lactone **IX** and of digitoxigenin (VII) from testosterone *via* oxidation of furyl-containing intermediates [4].

Among the various substituted furan derivatives which we have subjected to oxidation in the course of our initial studies at *Ayerst Laboratories* was also the steroid derivative **X** *(Scheme 2)*. On oxidation with peracid compound **X** gave an excellent yield of a product, the structure of which was predictable, and it was immediately

Scheme 2

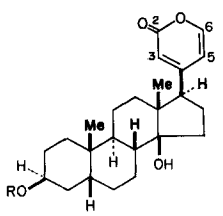


postulated [2a] to be represented by **XII**. Oxidation of the furan was assumed to proceed *via* the dihydroxy derivative **XI** which rearranged to the ketohemiacetal **XII**. The correctness of the formula **XII** was indeed later corroborated by chemical transformations, and a number of ketones **XIII** was converted to the corresponding dihydropyran derivatives **XIV** in excellent yield [2b].

In our later synthesis of digitoxigenin from testosterone [4] we have developed an efficient method for the introduction of a furyl group at C(17) with a simultaneous creation of the correct configuration and substitution at C(14). Immediately at the conclusion of this work, it was clear that if we could duplicate this process with properly substituted furans (*i. e.*, **XV** and **XVIII**) we might achieve an unusually facile synthesis of the bufadienolide isomers **XVII** and **XX** *via* the intermediates **XVI** and **XIX**. Compounds **XVII** and **XX** appeared to be very attractive synthetic targets, if we recall the above-mentioned remarkable pharmacologic properties of the isocardenolide **IX**.

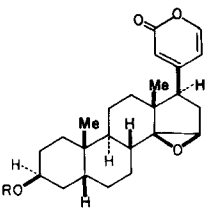
We wish to disclose in the present paper an efficient stereospecific synthesis of α-isobufalin[1]) (**1**), α-isoresibufogenin[1]) (**2**) and β-isoresibufogenin[1]) (**3**) from testosterone *(Scheme 3)*. The modified methodology which is required for the synthesis of the α'-isobufalin system **XXI** and of natural bufalin (**XXII**) will be the subject of a separate communication.

Scheme 3[1])



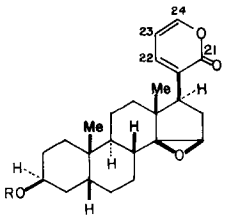
1 α-Isobufalin R=H

19 R = $CH_2C_6H_5$



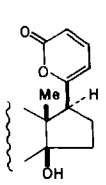
2 α-Isoresibufogenin R=H

20 R = $CH_2C_6H_5$



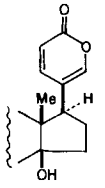
3 β-Isoresibufogenin R=H

31 R = $CH_2C_6H_5$



XXI

α'-Isobufalin

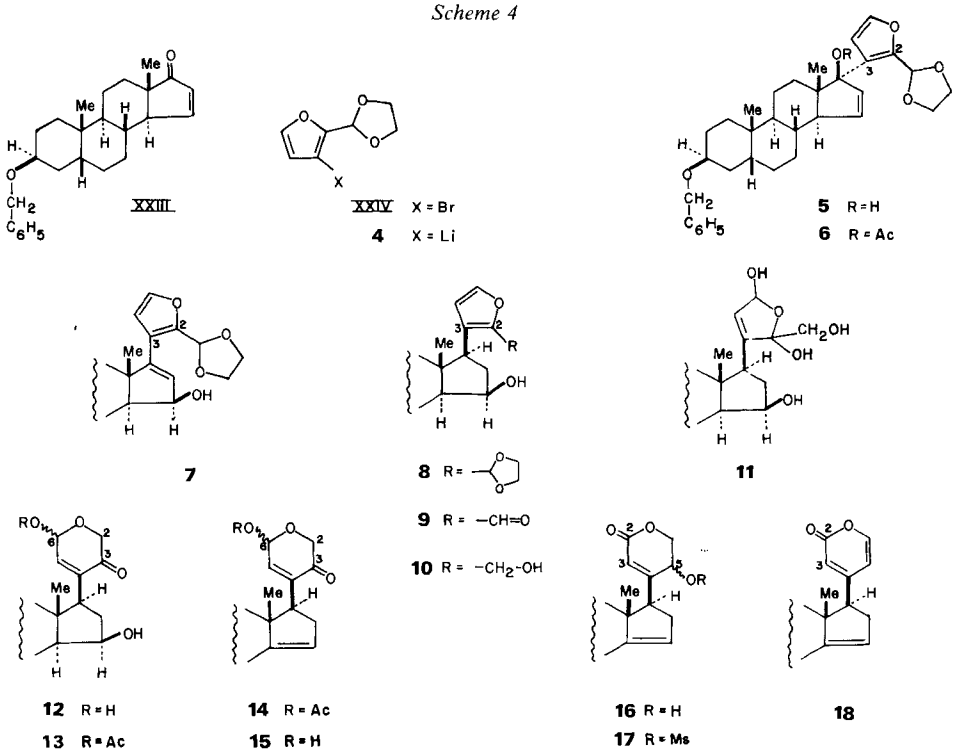


XXII

Bufalin (natural)

Discussion. – The steroid starting material for all of the synthetic work to be described in the sequel was the α,β-unsaturated ketone **XXIII**, which can be readily prepared from testosterone [4] *Scheme 4*. The second component for the synthesis of the α-derivatives **1** and **2** was provided by the bromoacetal **XXIV** [5] which contains the five C-atoms destined to form the 2-pyrone ring.

Scheme 4



Compound **XXIV** was first converted to the lithium derivative **4** by treatment with butyllithium at low temperature in ether, and this material was immediately allowed to react with the steroid **XXIII**. The tertiary alcohol **5** was obtained in a yield of 95%. Compound **5** was now acetylated, and the crude acetyl derivative **6** was subjected to an allylic rearrangement in refluxing aqueous acetone in the presence of calcium carbonate. In agreement with our previous experience [4], the product **7** of the stereospecific rearrangement was obtained in a yield of 83% over the two steps. Hydrogenation of compound **7** with $Pd/CaCO_3$ in ethanol gave 92% of the 17β-derivative **8**, and the subsequent deprotection and $NaBH_4$ reduction of the aldehyde group (intermediates **9** and **10**) proceeded practically quantitatively. Thus it was possible to set up the correct β-configuration at C(17) and at the same time provide the 15β-hydroxy group as a handle for the future inversion and functionalization of the C(14) position exactly as in our above-mentioned cardenolide synthesis [4].

The stage was now set for the oxidative conversion of furan to pyrane. Treatment of the alcohol **10** with *m*-chloroperbenzoic acid yielded 90% of the crystalline epim-

eric hemiacetals **12**, presumably by rearrangement of the primary oxidation product **11**. The UV. and IR. spectra of compound **12** showed the presence of an α,β-unsaturated ketone [UV. (EtOH): 237 nm (log $\varepsilon = 3.85$); IR.: 1690, 1640 cm^{-1}]. Also the ^{1}H-NMR. spectrum was in agreement with the structure **12** [^{1}H-NMR.: 6.74 (*d*, $J = 4$ Hz, H–C(5)); 5.70 (*d*, $J = 4$ Hz, H–C(6)); 4.61, 4.12 and 4.57, 4.03 ppm (2*d* for each epimer, $J = 17$ Hz, H–C(2))].

With the obtention of compound **12** the synthetic problem was practically solved since the functionality and configuration of this material is eminently suited for an uneventful conversion to the final products **1** and **2** as follows. The hemiacetal OH-group of **12** was first blocked by a selective monoacetylation with sodium acetate/acetic anhydride in benzene, and the epimeric monoacetates **13** were obtained in a yield of 90%. The ^{1}H-NMR. spectrum of **13** showed the H-atom unshielded by the acetoxy group as two doublets (6.57 and 6.60 ppm, $J = 4$ Hz), one for each of the epimers.

A fully regioselective elimination of the 15β-hydroxy group with thionyl chloride in pyridine followed, and yielded 88% of the $\Delta^{14,15}$-derivative **14** which was saponified to the hemiacetal **15**. Both these materials displayed in the ^{1}H-NMR. spectrum the additional vinylic H–C(15) signal as a broad unresolved peak at 5.23 ppm.

The hemiacetal OH-group was now oxidized with the chromic acid dipyridine complex, and the quite unstable ketolactone which resulted was immediately reduced with zinc borohydride in ether. The epimeric hydroxylactones **16** were obtained in a yield of 80% over the two steps. The alcohols **16** were converted to the corresponding methanesulfonates **17** with mesyl chloride and triethylamine in methylene chloride (in a yield of 80%), and this material was heated under reflux with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene. The $\Delta^{14,15}$-pyrone **18** was obtained in a yield of 86%, and it was purified by crystallization from ether/chloroform. The spectral properties *(vide infra)* of compound **18** clearly indicated that the assembly of the pyrone system was now completed, and the last stage of the synthesis, the introduction of the 14β-hydroxy group, could begin.

The $\Delta^{14,15}$-derivative **18** was now treated with *N*-bromosuccinimide (NBS) in aqueous acetone, and the intermediate bromohydrin was debrominated by stirring with *Raney* nickel. The crystalline 3-*O*-benzyl-α-isobufalin (**19**) (s. *Scheme 3*) was obtained in a yield of 72%. For the debenzylation of this material we have used the method described by *Hanessian et al.* [6] since hydrogenolysis with Pd/C frequently resulted in a partial reduction of the pyrone system. Compound **19** was heated under reflux in benzene/ethanol with $Pd(OH)_2$/C and cyclohexene. The final product α-isobufalin (**1**) was obtained in a yield of 87%, and it crystallized in beautiful prisms from ether/chloroform. The spectral data of compound **1** were entirely consistent with the structure assigned to it[2]) [UV. (EtOH): 289 nm (log $\varepsilon = 3.73$); IR.: 3610, 3450

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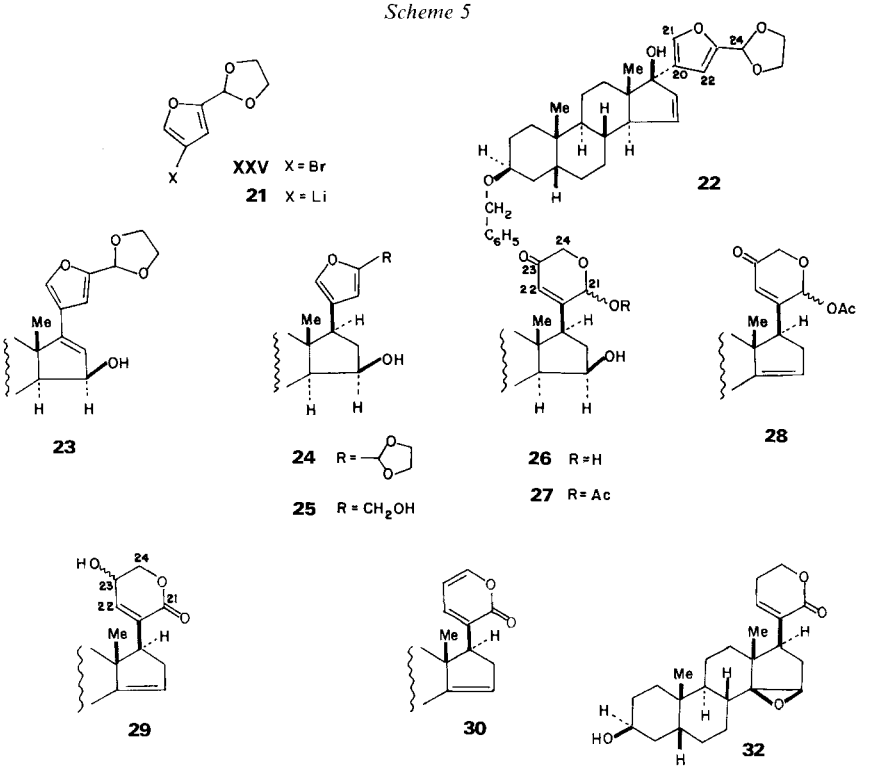
[2]) The conversion of digitoxigenin into α-isobufalin (**1**) has been very recently accomplished in our laboratories. In this process the configuration at C(14) and C(17) remained undisturbed, and consequently the identity of the product with the same derivative described in the present paper constitutes additional support for the structural assignment. The digitoxigenin → isobufalin conversion will be described in a separate communication. The crystal and molecular structure of the 5,6-dihydro derivative of **1** has just been solved by Dr. *Peter S. White* at the Chemistry Department of our University and it was found to be in agreement with our formulation.

(OH), 1715 (C=O), 1635 cm^{-1} (C=C); ^{1}H-NMR.: 7.35 (*d*, *J*=6 Hz, H–C(6)); 6.68 (*d*×*d*, *J*=2,6 Hz, H–C(5)); 6.10 (*d*, *J*=2 Hz, H–C(3)) ppm].

When the intermediate bromohydrin, which was produced by the action of NBS on compound **18**, was stirred with basic alumina, the epoxide **20** was obtained in a yield of 85%. Debenzylation by the *Hanessian* technique [6] yielded 84% of α-isoresibufogenin (**2**) which crystallized in beautiful rosettes of needles from ether/hexane. For pharmacological testing both compounds **1** and **2** were converted to glucosides[3]).

For the entry into the β-series, the starting materials were the protected steroid ketone **XXIII** and the reagent **21** obtainable by lithiation of the bromoacetal **XXV** [5]. The synthesis proceeded in a precisely analogous manner, and the description of the intermediates **22–29** *(Scheme 5)* can be found in the *Experimental Part.* A major difference in reactivity was, however, encountered when the $\Delta^{14,15}$-derivative **30** was reached. The bromohydrin obtained from this material by NBS in acetone gave, under all conditions we have tried, on treatment with *Raney* nickel exclusively 3-*O*-benzyl-β-isoresibufogenin (**31**; s. *Scheme 3*). To date we have failed to synthesize the corresponding β-isobufalin derivative[4]).

Scheme 5



[3]) The pharmacology of all our compounds will be reported in due course by Prof. *Rafael Mendez* and his colleagues.

[4]) Recently we have prepared β-isobufalin from digitoxigenin.

For the debenzylation of **31** we have used hydrogenolysis with Pd/C. This method yielded approximately equal quantities of the crystalline β-isoresibufogenin (**3**) and its dihydro derivative **32**. The spectral properties of β-isoresibufogenin (**3**) were in full agreement with the α-series [UV. (EtOH): 295 nm (log ε=3.75); IR.: 3605, 3350 (OH), 1700 (C=O), 1630 cm^{-1} (C=C); ^{1}H-NMR.: 7.53 (*d*× *d*, *J*=2,7 Hz, H–C(22)); 7.35 (*d*× *d*, *J*=2,5 Hz, H–C(24)); 6.20 (*d*× *d*, *J*=5,7 Hz, H–C(23)); 3.58 (br. *s*, H–C(15))[5]].

We wish to thank the *Natural Sciences and Engineering Research Council*, Ottawa, Canada, and the *Canadian Heart Foundation* for the support of these studies.

Experimental Part

General. Melting points were measured on a *Reichert* instrument and are uncorrected. – UV. spectra (λmax [nm] (log ε)) were recorded on a *Beckman 25*. – IR. spectra were measured on *Perkin Elmer 727B* or *598* instruments and characteristic absorption maxima are given in cm^{-1}. – 60-MHz-^{1}H-NMR. spectra were recorded on a *Varian T-60* instrument, chemical shifts are given in ppm downfield from TMS (= 0 ppm), *J*=spin-spin coupling constant (Hz). – Mass spectra (MS.; low-resolution) were recorded on a *Hitachi Perkin-Elmer RMU-6D*. High-resolution MS. (HR.-MS.) and elementary analyses were measured at the facilities of the *University of Alberta*, Chemistry Department, Edmonton, and at *Canadian Microanalytical Service Ltd.*, Vancouver, or at *Mikroanalytisches Laboratorium*, Bonn, respectively.

Synthesis of 3-(3'β-benzyloxy-17'β-hydroxy-5'β-androst-15'-en-17'α-yl)furan-2-carbaldehyde ethylene acetal (**5**). A solution of butyllithium in ether (2.74 ml, 2.1M) was added to a stirred ether solution of **XXIV** (1.32 g/20 ml) at –70°. The ketone **XXIII** (1.87 g in 10 ml benzene and 20 ml ether) was then added, and the mixture was stirred for 30 min at –70°. Then the mixture was washed with water, dried over anh. $MgSO_4$ and evaporated to dryness. The crude product was purified by chromatography on silicagel with ether/$CHCl_3$ 5:95 yielding 2.48 g (95%) of pure, foamy **5**. – IR. ($CHCl_3$): 3600 (OH). – ^{1}H-NMR. ($CDCl_3$): 1.00 (*s*, 3 H–C(19')); 1.03 (*s*, 3 H–C(18')); 3.70 (*m*, $W_{1/2}\approx 7$, H–C(3')); 3.97–4.30 (*m*, OCH_2CH_2O); 4.50 (*s*, CH_2Ph); 5.78 (*d*× *d*, *J*=6 and 2, H–C(15')); 6.13 (*d*, *J*=2, H–C(4)); 6.15 (*d*, *J*=6, H–C(16')); 6.29 (*s*, HC–C(2)); 7.38 (br. *s*, H-C(5) and 5 arom. H). – MS.: 518 ($C_{33}H_{42}O_5^+$). – HR.-MS. for M^+: Found 518.3033; Calc. 518.3032.

Synthesis of 3-(3'β-benzyloxy-15'β-hydroxy-5'β-androst-16'-en-17'-yl)furan-2-carbaldehyde ethylene acetal (**7**). Compound **5** (2.46 g) was acetylated with 15 ml of acetic anhydride/pyridine 1:2 in the presence of 4-dimethylaminopyridine (116 mg) at RT. for 3 days. The mixture was worked up by the usual method, and the crude acetyl derivative **6** was heated under reflux in acetone/H_2O 4:1 (300 ml) in the presence of $CaCO_3$ (1.45 g) for 4 days. Workup and chromatography on *silicagel G* with hexane/acetone 4:1 yielded 1.77 g (83%) of **7** which was recrystallized from ether, m.p. 140–141°. – IR. ($CHCl_3$): 3605 (OH). – ^{1}H-NMR. ($CDCl_3$): 1.06 (*s*, 3 H–C(19')); 1.24 (*s*, 3 H–C(18')); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3')); 3.95–4.28 (*m*, OCH_2CH_2O); 4.51 (*s*, CH_2Ph); 4.58 (br. *t*, *J*=7, H–C(15')); 5.87 (*d*, *J*=2, H–C(16')); 5.90 (*s*, HC–C(2)); 6.37 (*d*, *J*=2, H–C(4)); 7.34 (br. *s*, H–C(5) and 5 arom. H). – MS.: 518 ($C_{33}H_{42}O_5^+$).

$C_{33}H_{42}O_5$ (518.67) Calc. C 76.41 H 8.16% Found C 76.14 H 8.52%

Synthesis of 3-(3'β-benzyloxy-15'β-hydroxy-5'β-androstan-17'β-yl)furan-2-carbaldehyde ethylene acetal (**8**). Compound **7** (1.76 g) was hydrogenated in ethanol (50 ml) with 10% Pd/$CaCO_3$ (176 mg) at RT. The product was purified by chromatography on *silicagel G* with acetone/hexane 15:85 giving TLC.-pure amorphous **8** (1.54 g; 92%). – IR. ($CHCl_3$): 3610, 3450 (OH). – ^{1}H-NMR. ($CDCl_3$): 0.85 (*s*, 3 H–C(18')); 1.00 (*s*, 3 H–C(19')); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3')); 3.92–4.26 (*m*, OCH_2CH_2O); 4.35 (br. *t*, *J*=7, H–C(15')); 4.50 (*s*, CH_2Ph); 5.89 (*s*, HC–C(2)); 6.37 (*d*, *J*=2, H–C(4)); 7.33 (br. *s*, H–C(5) and 5 arom. H). – MS.: 520 ($C_{33}H_{44}O_5^+$). – HR.-MS. for M^+: Found 520.3184; Calc. 520.3188.

Synthesis of 3-(3'β-benzyloxy-15'β-hydroxy-5'β-androstan-17'β-yl)furan-2-carbaldehyde (**9**). The acetal **8** (1.54 g) was dissolved in 20 ml of THF/1N HCl 9:1, and the solution was stirred for 1 h. Then the solution was neutralized with aq. $NaHCO_3$-solution and extracted with ether. The ether solution was

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[5]) Compound **3** was found identical with the same derivative prepared recently in our laboratories from digitoxigenin. In this work the *Hanessian* technique [6] was used for the debenzylation instead of hydrogenolysis with Pd/C.

dried over anh. $MgSO_4$ and evaporated to dryness giving oily, practically pure **9** in quantitative yield. It was immediately used for the next reacti on. – IR. ($CHCl_3$): 3650, 3530 (OH), 1690 (C=O). – ^{1}H-NMR. ($CDCl_3$): 0.87 (*s*, 3 H–C(18′)); 1.00 (*s*, 3 H–C(19′)); 3.75 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.42 (br. *t*, $J=7$, H–C(15′)); 4.50 (*s*, CH_2Ph); 6.60 (*d*, $J=2$, H–C(4)); 7.34 (br. *s*, 5 arom. H); 7.58 (*d*, $J=2$, H–C(5)); 9.72 (*s*, OHC–C(2)). – MS.: 476 ($C_{31}H_{40}O_4^+$). – HR.-MS. for M^+: Found 476.2926; Calc. 476.2926.

Synthesis of 3-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)furan-2-methanol (**10**). The crude **9** (1.41 g), dissolved in 11 ml of THF/CH_3OH 10:1, was reduced with 225 mg of $NaBH_4$ at RT. The mixture was worked up in the usual manner, and the product was purified by chromatography on a *silicagel G* column with acetone/hexane 1:4 giving pure, oily **10** (1.35 g; 95%). – IR. ($CHCl_3$): 3630, 3450 (OH). – ^{1}H-NMR. ($CDCl_3$): 0.85 (*s*, 3 H–C(18′)); 1.01 (*s*, 3 H–C(19′)); 3.75 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.37 (br. *t*, $J=7$, H–C(15′)); 4.50 (*s*, CH_2Ph); 4.55 (br. *s*, CH_2OH); 6.33 (*d*, $J=2$, H–C(4)); 7.34 (br. *s*, H–C(5) and 5 arom. H). – MS.: 478 ($C_{31}H_{42}O_4^+$). – HR.-MS. for M^+: Found 478.3086; Calc. 478.3083.

*Synthesis of 4-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)-6-hydroxy-3,6-dihydro-2*H*-pyran-3-one* (**12**). A mixture of **10** (1.35 g) and CH_3COONa (324 mg) in CH_2Cl_2 (45 ml) was oxidized with *m*-chloroperbenzoic acid (718 mg) in an ice-bath for 2 h. The precipitate was filtered off through *Celite*, and the filtrate was washed successively with $Na_2S_2O_3$- and $NaHCO_3$-solution, and H_2O. The CH_2Cl_2-phase was then dried over anh. $MgSO_4$, evaporated to dryness, and the product was purified by chromatography on a column of *silicagel G*. The epimeric mixture **12** (1.25 g; 90%) was eluted with CH_2Cl_2/ether 4:1, and it crystallized from acetone, m.p. 158–160°. – UV. (EtOH): 237 (3.85). – IR. ($CHCl_3$): 3600, 3360 (OH), 1690 (C=O), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6]: 0.77 and 0.87 (2 *s*, 3 H–C(18′)); 1.00 (*s*, 3 H–C(19′)); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.03, 4.57 and 4.12, 4.61 (2 *d*, two sets, $J=17$ each, 2 H–C(2)); 4.37 (br. *t*, $J=7$, H–C(15′)); 4.50 (*s*, CH_2Ph); 5.70 (*d*, $J=4$, H–C(6)); 6.74 (*d*, $J=4$, H–C(5)); 7.36 (br. *s*, 5 arom. H). – MS.: 494 ($C_{31}H_{42}O_5^+$). – HR.-MS. for M^+: Found 494.3028; Calc. 494.3032.

$C_{31}H_{42}O_5$ (494.64) Calc. C 75.27 H 8.56% Found C 74.14 H 8.66%

*Synthesis of 4-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)-3-oxo-3,6-dihydro-2*H*-pyran-6-yl acetate* (**13**). A mixture of **12** (9.5 g), CH_3COONa (1.89 g), $(CH_3CO)_2O$ (2.17 ml), and benzene (250 ml) was heated under reflux for 1 h. After cooling, the mixture was diluted with ether and washed with aq. solutions of $NaHCO_3$ and NaCl. The organic phase was dried over anh. $MgSO_4$, the solvent was evaporated and the crude product chromatographed on a *silicagel G* column. Acetone/hexane 1:3 eluted 8.67 g (90%) of **13**. – IR. ($CHCl_3$): 3610, 3460 (OH), 1750 (ester), 1690 (C=O), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6][7]: 0.78 and 0.82 (2 *s*, 3 H–C(18′)); 1.00 (*s*, 3 H–C(19′)); 2.13 (*s*, CH_3COO); 3.75 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.09, 4.57 and 4.12, 4.57 (2 *d*, two sets, $J=17$ each, 2 H–C(2)); 4.33 (br. *t*, $J=7$, H–C(15′)); 4.50 (*s*, CH_2Ph); 6.57 and 6.60 (2 *d*, $J=4$ each, H–C(6)); 6.72 (*d*, $J=4$, H–C(5)); 7.35 (br. *s*, 5 arom. H). – MS.: 536 ($C_{33}H_{44}O_6^+$). – HR.-MS. for $M^+ - CH_3COOH$: Found 476.2921; Calc. 476.2926 ($C_{31}H_{40}O_4$).

*Synthesis of 4-(3′β-benzyloxy-5′β-androst-14′-en-17′β-yl)-3-oxo-3,6-dihydro-2*H*-pyran-6-yl acetate* (**14**). Compound **13** (135 mg) in pyridine (1 ml) was cooled in an ice-bath and treated with $SOCl_2$ (38 mg) for 1 h. The mixture was worked up in the usual manner, and the product was purified by prep. TLC. on silicagel giving the pure epimers **14** (114 mg; 88%) as a foam. – IR. ($CHCl_3$): no OH, 1745 (C=O, ester), 1690 (C=O, ketone), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6][7]: 0.69 and 0.73 (2 *s*, 3 H–C(18′)); 0.97 (*s*, 3 H–C(19′)); 2.12 (*s*, CH_3COO); 3.72 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.14, 4.58 and 4.20, 4.58 (2 *d*, two sets, $J=17$ each, 2 H–C(2)): 5.23 (*m*, $W_{1/2}\approx 6$, H–C(15′)); 6.55 and 6.58 (2 *d*, $J=4$ each, H–C(6)); 6.73 (*d*, $J=4$, H–C(5)); 7.33 (br. *s*, 5 arom. H). – MS.: 518 ($C_{33}H_{42}O_5^+$). – HR.-MS. for $M^+ - CH_3COOH$: Found 458.2825; Calc. 458.2821 ($C_{31}H_{38}O_3$).

*Synthesis of 4-(3′β-benzyloxy-5′β-androst-14′-en-17′β-yl)-6-hydroxy-3,6-dihydro-2*H*-pyran-3-one* (**15**). Compound **14** (276 mg) was saponified at RT. in a solution of THF (10.9 ml), methanol (15.5 ml) and 1N KOH (0.82 ml) for 1 h. The solution was carefully neutralized with dil. HCl-solution, and extracted with ether. The ether phase was washed with aq. NaCl-solution, dried over anh. $MgSO_4$ and evaporated to dryness. The product was purified on a prep. TLC.-plate (*silicagel G*, acetone/hexane 1:5) giving 226 mg (90%) of foamy epimeric mixture **15**. – IR. ($CHCl_3$): 3590, 3350 (OH), 1690 (C=O), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6]: 0.69 and 0.74 (2 *s*, 3 H–C(18′)); 0.97 (*s*, 3 H–C(19′)); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.04, 4.58 and 4.11, 4.61 (2 *d*, two sets, $J=17$ each, 2 H–C(2)); 4.51 (*s*, CH_2Ph); 5.23 (*m*, $W_{1/2}\approx 6$, H–C(15′));

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[6]) It will be noted that some signals are doubled in view of the presence of the two epimers.

[7]) For the purpose of an easier NMR. comparison, the pyran ring of **13** and **14** is numbered as in **12**.

5.67 (*m*, $W_{1/2}\approx 9$, H–C(6)); 6.76 (*d*, $J=4$, H–C(5)); 7.37 (br. *s*, 5 arom. H). – MS.: 476 ($C_{31}H_{40}O_4^+$). – HR.-MS. for M^+: Found 476.2931; Calc. 476.2926.

*Synthesis of 4-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-one* (**16**). A solution of **15** (120 mg in 3 ml of CH_2Cl_2) was added to a stirred solution of the CrO_3/dipyridine complex (390 mg in 20 ml CH_2Cl_2) at RT. After 10 min, 20 ml of ether were added, and the precipitate was filtered off through *Celite*. The filtrate was reduced to 10 ml, and a large excess of $Zn(BH_4)_2$ in ether was added. After 1 h of stirring, a few drops of water were added, and the precipitate was filtered off through *Celite*. The filtrate was evaporated to dryness, and the epimers **16** were purified on a TLC.-plate (*silicagel G*, acetone/hexane 1:4). The mixture of epimers crystallized, and it was recrystallized from CH_2Cl_2/ether, m.p. 198–204°, yield 98 mg (80%). – IR. ($CHCl_3$): 3580, 3400 (OH), 1710 (C=O), 1630 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6]: 0.80 and 0.86 (2 *s*, 3 H–C(18')); 0.99 (*s*, 3 H–C(19')); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3')); 4.16 (*m*, $W_{1/2}\approx 10$, H–C(5)); 4.41 (*d*, $J=4$, 2 H–C(6)); 4.51 (*s*, CH_2Ph); 5.27 (*m*, $W_{1/2}\approx 6$, H–C(15')); 5.90 and 5.96 (2 *s*, H–C(3)); 7.36 (br. *s*, 5 arom. H). – MS.: 476 ($C_{31}H_{40}O_4^+$).

$C_{31}H_{40}O_4$ (476.63) Calc. C 78.11 H 8.46% Found C 77.79 H 8.62%

*Synthesis of 4-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-2-oxo-5,6-dihydro-2*H*-pyran-5-yl methanesulfonate* (**17**). Compound **16** (180 mg) in CH_2Cl_2 (4 ml) and triethylamine (2 ml) was cooled in an ice-bath and mesyl chloride (60 mg) was added to it. The mixture was stirred in the ice-bath for 30 min, and then it was diluted with CH_2Cl_2. The solution was washed with 5% citric acid- and $NaHCO_3$-solution, dried over anh. $MgSO_4$ and evaporated to dryness. The crude product was purified on *silicagel G* plates developed with $CHCl_3$/ether 5:95. Pure, relatively unstable **17** (180 mg; 80%) was obtained. – IR. ($CHCl_3$): no OH, 1725 (C=O), 1630 (C=C), 1635, 1165 (CH_3SO_2). – ^{1}H-NMR. ($CDCl_3$)[6][8]: 0.82 and 0.88 (2 *s*, 3 H–C(18')); 0.98 (*s*, 3 H–C(19')); 3.13 (*s*, CH_3SO_2); 3.72 (*m*, $W_{1/2}\approx 7$, H–C(3')); 4.27–4.82 (*m*, 2 H–C(6)); 4.50 (*s*, CH_2Ph); 5.21 (*m*, $W_{1/2}\approx 9$, H–C(15'); and H–C(5)); 6.12 and 6.19 (2 *s*, H–C(3)); 7.34 (br. *s*, 5 arom. H). – MS.: 554 ($C_{32}H_{42}O_6S^+$). – HR.-MS for $M^+ - CH_3SO_3H$: Found 458.2821; Calc. 458.2821 ($C_{31}H_{38}O_3$).

*Synthesis of 4-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-2*H*-pyran-2-one* (**18**). A mixture of **17** (180 mg) and DBN (121 mg) in benzene (8 ml) was heated under reflux for 1 h. The solution was washed with dilute HCl- and $NaHCO_3$-solution and water, and dried over anh. $MgSO_4$. After evaporation of the solvent, the product was purified on *silicagel G* plates developed with acetone/hexane 1:5 yielding 128 mg (86%) of **18**. The compound crystallized from ether/$CHCl_3$, m. p. 144–145° and 162°. – IR. ($CHCl_3$): 1720 (C=O), 1635 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.75 (*s*, 3 H–C(18')); 0.98 (*s*, 3 H–C(19')); 3.72 (*m*, $W_{1/2}\approx 7$, H–C(3')); 4.50 (*s*, CH_2Ph); 5.24 (*m*, $W_{1/2}\approx 6$, H–C(15')); 6.13 (*d*, $J=6$, H–C(5)); 6.18 (br. *s*, H–C(3)); 7.33 (br. *s*, 5 arom. H); 7.41 (*d*, $J=6$, H–C(6)). – MS.: 458 ($C_{31}H_{38}O_3^+$). – HR.-MS. for M^+: Found 458.2819; Calc. 458.2821.

$C_{31}H_{38}O_3$ (458.61) Calc. C 81.18 H 8.35% Found C 80.99 H 8.23%

*Synthesis of 4-(3'β-benzyloxy-14'-hydroxy-5'β,14'β-androstan-17'β-yl)-2*H*-pyran-2-one* (**19**). Compound **18** (138 mg) in 6 ml of acetone/H_2O 9:1 was treated with NBS (67 mg) and 3 drops of 1% $HClO_4$-solution at RT. for 30 min. The mixture was diluted with CH_2Cl_2 and washed with aq. $NaHSO_3$-solution and H_2O, dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in 12 ml of CH_3OH/CH_2Cl_2 1:1, and CH_3COONa (25 mg) and an excess of *Raney*-Ni were added. After 20 min of stirring, the *Raney*-Ni was filtered off and the solution evaporated to dryness. The product was purified on a silicagel plate developed by ether/CH_2Cl_2 5:95 and by crystallization from ether/$CHCl_3$ giving 102 mg (72%) of **19**, m.p. 215–217°. – IR. ($CHCl_3$): 3610, 3460 (OH), 1720 (C=O), 1635 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.78 (*s*, 3 H–C(18')); 0.96 (*s*, 3 H–C(19')); 3.75 (*m*, $W_{1/2}\approx 7$, H–C(3')); 4.53 (*s*, CH_2Ph); 6.15 (*d*, $J=2$, H–C(3)); 6.72 (*d* × *d*, $J=6$, and 2, H–C(5)); 7.38 (br. *s*, 5 arom. H); 7.42 (*d*, $J=6$, H–C(6)). – MS.: 476 ($C_{31}H_{40}O_4^+$). – HR.-MS. for M^+: Found 476.2928; Calc. 476.2926.

*Synthesis of 4-(3'β,14'-dihydroxy-5'β,14'β-androstan-17'β-yl)-2*H*-pyran-2-one* (= *α-isobufalin*; **1**). Compound **19** (90 mg) was dissolved in 18 ml of benzene/ethanol 1:2, and cyclohexane (350 mg) $Pd(OH)_2$/C (42 mg) were added. The mixture was heated under reflux for 2 h, filtered through *Celite* and evaporated to dryness *in vacuo*. The residue was purified by crystallization from ether/$CHCl_3$ giving 52.8 g (88%) of pure **1**, m.p. 128–129°, identical in all respects with the same material recently prepared in our laboratory from digitoxigenin[2]. – UV. (EtOH): 289 (3.73). – IR. ($CHCl_3$): 3610, 3450 (OH), 1715

[8]) For the purpose of an easier ^{1}H-NMR. comparison, the pyran ring of **17** is numbered as in **16**.

(C=O), 1635 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.77 (*s*, 3 H–C(18′)); 0.95 (*s*, 3 H–C(19′)); 4.13 (*m*, $W_{1/2}\approx 8$, H–C(3′)); 6.10 (*d*, *J*=2, H–C(3)); 6.65 (*d*×*d*, *J*=6 and 2, H–C(5)); 7.35 (*d*, *J*=6, H–C(6)). – MS.: 386 ($C_{24}H_{34}O_4^+$). – HR.-MS. for M^+: Found 386.2457; Calc. 386.2457.

$C_{24}H_{34}O_4$ (386.51) Calc. C 74.57 H 8.87% Found C 74.32 H 8.90%

*Synthesis of 4-(3′β-benzyloxy-14′,15′β-epoxy-5′β,14′β-androstan-17′β-yl)-2*H*-pyran-2-one* (**20**). Compound **18** (120 mg) was treated with NBS as described above and converted into the intermediate bromohydrin. This material was dissolved in CH_2Cl_2 (8 ml) and stirred with 0.5 g of basic alumina for 30 min at RT. The alumina was filtered off, and **20** was crystallized from ether/$CHCl_3$ giving 104 mg (85%), m. p. 197–198°. – IR. ($CDCl_3$): no OH, 1710 (C=O), 1630 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.85 (*s*, 3 H–C(18′)); 0.99 (*s*, 3 H–C(19′)); 3.53 (br. *s*, H–C(15′)); 3.73 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.49 (*s*, CH_2Ph); 6.05 (*d*, *J*=2, H–C(3)); 6.66 (*d*×*d*, *J*=6 and 2, H–C(5)); 7.34 (br. *s*, H–C(6) and 5 arom. H). – MS.: 474 ($C_{31}H_{38}O_4^+$).

*Synthesis of 4-(14′15′β-epoxy-3′β-hydroxy-5′β,14β-androstan-17′β-17′β-yl)-2*H*-pyran-2-one* (*α-isoresibufogenin;* **2**). Compound **20** (60 mg) was debenzylated by the *Hanessian* technique [6] as described above. The product was purified by crystallization from $CHCl_3$/hexane yielding 35 mg (84%) of **2**, m. p. 210–212°. IR. ($CDCl_3$): 3605, 3420 (OH), 1710 (C=O), 1630 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.85 (*s*, 3 H–C(18′)); 1.00 (*s*, 3 H–C(19′)); 3.53 (br. *s*, H–C(15′)); 4.13 (*m*, $W_{1/2}\approx 8$, H–C(3′)); 6.06 6*d*, *J*=2 H, H–C(3)); 6.63 (*d*×*d*, *J*=6 and 2, H–C(5)); 7.33 (*d*, *J*=6, H–C(6)). – MS.: 384 ($C_{24}H_{32}O_4^+$). – HR.-MS. for M^+: Found 384.2295, Calc. 384.2300.

Synthesis of 4-(3′β-benzyloxy-17′β-hydroxy-5′β-androst-15′-en-17′α-yl)furan-2-carbaldehyde ethylene acetal[9] (**22**). The bromoacetal **XXV** [5] (2 g) and **XXIII** (2.83 g) were converted to **22** exactly as described for the preparation of **5**. A small sample of crude **22** was purified on a silicagel plate developed by ether/hexane 1:1 to give pure, foamy **22** for spectroscopy. – IR. ($CHCl_3$): 3610 (OH). – ^{1}H-NMR. ($CDCl_3$)[9]: 0.98 (*s*, 3 H–C(19)); 1.02 (*s*, 3 H–C(18)); 3.70 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.05 (*m*, $W_{1/2}\approx 6$, OCH_2CH_2O); 4.47 (*s*, CH_2Ph); 5.68 (*d*×*d*, *J*=6 and 3, H–C(15)); 5.87 (*s*, H–C(24)); 6.05 (br. *d*, *J*=6, H–C(16)); 6.45 (br. *s*, H–C(22)); 7.15 (br. *s*, H–C(21)); 7.32 (br. *s*, 5 arom. H). – MS.: 518 ($C_{33}H_{42}O_5^+$). – HR.-MS. for M^+: Found 518.3038; Calc. 518.3032.

Synthesis of 4-(3′β-benzyloxy-15′β-hydroxy-5′β-androst-16′-en-17′-yl)furan-2-carbaldehyde ethylene acetal[9] (**23**). The crude compound **22** was acetylated and subjected to an allylic rearrangement as described above (*cf.* **5**→**7**). The product was purified by chromatography on silicagel with hexane/acetone 6:1 and by crystallization from hexane/CH_2Cl_2 giving 2.09 g (54% from **XXIII**) of **23** m. p. 172°. – IR. ($CHCl_3$): 3605 (OH). – ^{1}H-NMR. ($CDCl_3$)[9]: 1.06 (*s*, 3 H–C(19)); 1.16 (*s*, 3 H–C(18)); 3.71 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.05 (*m*, $W_{1/2}\approx 3$, OCH_2CH_2O); 4.40–4.65 (*m*, H–C(15)); 4.48 (*s*, CH_2Ph); 5.80 (*s*, H–C(24)); 5.92 (*d*, *J*=3.5, H–C(16)); 6.53 (br. *s*, H–C(22)); 7.32 (br. *s*, 5 arom. H); 7.49 (br. *s*, H–C(21)). – MS.: 518 ($C_{33}H_{42}O_5^+$).

$C_{33}H_{42}O_5$ (518.67) Calc. C 76.41 H 8.16% Found C 76.33 H 8.31%

Synthesis of 4-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)furan-2-carbaldehyde ethylene acetal[9] (**24**). The oily **24** was obtained in quantitative yield by hydrogenation of **23** as described above (*cf.* **7**→**8**). – IR. ($CHCl_3$): 3610 (OH). – ^{1}H-NMR. ($CDCl_3$/CCl_4 1:1)[9]: 0.75 (*s*, 3 H–C(18)); 1.01 (*s*, 3 H–C(19)); 3.68 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.00 (*m*, $W_{1/2}\approx 5$, OCH_2CH_2O); 4.17–4.52 (*m*, H–C(15)); 4.48 (*s*, CH_2Ph); 5.80 (*s*, H–C(24)); 6.28 (br. *s*, H–C(22)); 7.14 (br. *s*, H–C(21)); 7.27 (br. *s*, 5 arom. H). – MS.: 520 ($C_{33}H_{44}O_5^+$). – HR.-MS. for M^+: Found 520.3192; Calc. 520.3188.

Synthesis of 4-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)furan-2-methanol[9] (**25**). Deprotection and reduction of the aldehyde group in **24** was performed as described above (*cf.* **8**→**9**→**10**) and yielded 94% of **25** which was purified on silica gel plates developed by hexane/EtOAc 1:1. The TLC.-pure **25** remained oily. – IR. ($CHCl_3$): 3605 (OH). – ^{1}H-NMR. ($CDCl_3$)[9]: 0.76 (*s*, 3 H–C(18)); 1.02 (*s*, 3 H–C(19)); 3.72 (*m*, $W_{1/2}\approx 7$, H–C(3′)); 4.45 (br. *t*, *J*=7, H–C(15)); 4.48 (*s*, CH_2Ph); 4.53 (br. *s*, 2 H–C(24)); 6.18 (br. *s*, H–C(22)); 7.15 (br. *s*, H–C(21)); 7.32 (br. *s*, 5 arom. H). – MS.: 478 ($C_{31}H_{42}O_4^+$). – HR.-MS. for M^+: Found 478.3084; Calc. 478.3083.

*Synthesis of 3-(3′β-benzyloxy-15′β-hydroxy-5′β-androstan-17′β-yl)-2-hydroxy-2,5-dihydro-2*H*-pyran-5-one*[9] (**26**). Diol **25** (832 mg) was oxidized with *m*-chloroperbenzoic acid as described above (*cf.* **10**→**12**). Chromatography on silicagel with hexane/EtOAc 2:1 and 1:1 yielded 731 mg (85%) of the TLC.-pure epimers **26** which remained oily. However, spectral data left no doubt as to the analogous structures of this material and **12**. – UV. (EtOH): 243 (4.32). – IR. ($CHCl_3$): 3615, 3580 (OH), 1675 (C=O), 1627 (C=C). – ^{1}H-NMR. ($CDCl_3$)[6)9]: 0.90 and 0.96 (2 *s*, 3 H–C(18)); 1.02 (*s*, H–C(19)); 3.74

(*m*, $W_{1/2} \approx 7$, H–C(3)); 4.07, 4.53 and 4.07, 4.60 (2 *d*, two sets, $J = 17$ each, 2 H–C(24)); 4.33 (br. *t*, $J = 7$, H–C(15)); 4.51 (*s*, CH_2Ph); 5.47 and 5.53 (2 *m*, $W_{1/2} \approx 4$ each H–C(21)); 5.98 and 6.09 (2 br. *s*, H–C(22)); 7.35 (br. *s*, 5 arom. H). – MS.: 494 ($C_{31}H_{42}O_5^+$). – HR.-MS. for $M^+ - H_2O$: Found 476.2913; Calc. 476.2926 ($C_{31}H_{40}O_4$).

Synthesis of 3-(3'β-benzyloxy-15'β-hydroxy-5'β-androstan-17'β-yl)-5-oxo-2,5-dihydro-2H-pyran-2-yl acetate[9]) (**27**). The mixture **26** (850 mg) was acetylated as described above (*cf.* **12** → **13**). The products were chromatographed on silica gel with hexane/EtOAc 5:2 and 1:1. The yield was 674 mg (73%) of **27** and 139 mg (14%) of the diacetyl derivative which was saponified to starting material. Compound **27** was practically derived from one epimer (9:1). Nevertheless it remained oily. – UV. (EtOH): 240 (4.03). – IR. ($CHCl_3$): 3605 (OH), 1747 (ester), 1680 (C=O), 1646 (C=C). – ^{1}H-NMR. ($CDCl_3$[9]): 0.93 (*s*, 3 H–C(18)); 1.00 (*s*, 3 H–C(19)); 2.13 (*s*, CH_3COO); 4.10 and 4.45 (2 *d*, $J = 17$ each, 2 H–C(24)); 4.52 (*s*, CH_2Ph); 4.33 (br. *t*, $J = 7$, H–C(15)); 6.18 (*m*, $W_{1/2} \approx 2$, H–C(21)); 6.47 (br. *s*, H–C(22)); 7.32 (br. *s*, 5 arom. H). – MS.: 536 ($C_{33}H_{44}O_6^+$).

Synthesis of 3-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-5-oxo-2,5-dihydro-2H-pyran-2-yl acetate[9]) (**28**). The dehydration of **27** (240 mg) was performed as described above (*cf.* **13** → **14**), and the virtually pure olefin **28** was obtained in a yield of 90% without use of chromatography. One epimer predominated in a ratio 9:1, and the spectral data refer to this major compound. – IR. (CCl_4): no OH, 1754 (ester), 1690 (C=O), 1633 (C=C). – ^{1}H-NMR. (CCl_4[9]): 0.90 (*s*, 3 H–C(18)); 1.01 (*s*, 3 H–C(19)); 2.13 (*s*, CH_3COO); 3.66 (*m*, $W_{1/2} \approx 7$, H–C(3)); 4.08 and 4.32 (2 *d*, $J = 17$ each, 2 H–C(24)); 4.47 (*s*, CH_2Ph); 5.18 (*m*, $W_{1/2} \approx 6$, H–C(15)); 6.10 (*m*, $W_{1/2} \approx 3$, H–C(21)); 6.43 (br. *s*, H–C(22)); 7.27 (br. *s*, 5 arom. H).

Synthesis of the two 5-epimers of 3-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-5-hydroxy-5,6-dihydro-2H-pyran-2-one[9]) (**29**). All crude material obtained in the previous experiment was saponified, oxidized with CrO_3/dipyridine complex and reduced with $Zn(BH_4)_2$ as described above (*cf.* **14** → **15** → **16**). Chromatography on silica gel plates developed with CH_2Cl_2/ether/CH_3OH 19:1:0.1 yielded 122 mg (57% from **27**) of the epimers **29**. Repeated chromatography with the same system separated the two epimers and one of them crystallized from hexane/CH_2Cl_2.

Data of epimer **29-A**: m. p. 163.5°. – IR. (CCl_4): 3620, 3590 (OH), 1735, 1714 (C=O), 1642 (C=C). – ^{1}H-NMR. ($CDCl_3$[9]): 0.75 (*s*, 3 H–C(18)); 0.95 (*s*, 3 H–C(19)); 3.70 (*m*, $W_{1/2} \approx 7$, H–C(3)); 3.80–4.70 (*m*, 2 H–C(24) and H–C(23)); 4.46 (*s*, CH_2, CH_2Ph); 5.18 (*m*, $W_{1/2} \approx 6$, H–C(15)); 6.66 (*m*, $W_{1/2} \approx 6$, H–C(22)); 7.32 (br. *s*, 5 arom. H). – MS.: 476 (M^+).

$C_{31}H_{40}O_4$ (476.63) Calc. C 78.11 H 8.46% Found C 77.69 H 8.61%

Data of epimer **29-B**: IR. (CCl_4): 3590 (OH), 1732, 1708 (C=O), 1640 (C=C). – ^{1}H-NMR. ($CDCl_3$): 0.69 (*s*, H–C(18)); 1.00 (*s*, H–C(19)); 3.70 (*m*, $W_{1/2} \approx 7$, H–C(3)); 4.20–4.60 (*m*, 2 H–C(24) and H–C(23)); 4.50 (*s*, CH_2Ph); 5.20 (*m*, $W_{1/2} \approx 6$, H–C(15)); 6.73 (*m*, $W_{1/2} \approx 12$, H–C(22)); 7.33 (br. *s*, 5 arom. H.) – MS.: 476 ($C_{31}H_{40}O_4^+$). – HR.-MS. for M^+: Found 476.2931; Calc. 476.2926.

Synthesis of 3-(3'β-benzyloxy-5'β-androst-14'-en-17'β-yl)-2H-pyran-2-one[9]) (**30**). Compound **29** (mixture of epimers **A** and **B**, 120 mg) was mesylated as described above (*cf.* **16** → **17**), and the unstable mesyl derivative was immediately treated with 5 g of 5% K_2CO_3-solution on silica gel in 10 ml of benzene. After 2½ h, the slurry was eluted with CH_2Cl_2/CH_3OH 9:1, and the product was chromatographed on silicagel plates with hexane/ether 1:1. The yield was 78.4 mg (68%) of **30** and 10.5 mg (8.5%) of starting material. Compound **30** unlike the isomeric **18** remained as a semisolid and could not be crystallized. – UV. ($CHCl_3$): 294 (3.74). – IR. (CCl_4): no OH, 1731 (C=O), 1639 (C=C). – ^{1}H-NMR. ($CDCl_3$[9]): 0.73 (*s*, 3 H–C(18)); 0.98 (*s*, H–C(19)); 3.72 (*m*, $W_{1/2} \approx 7$, H–C(3)); 4.48 (*s*, CH_2Ph); 5.32 (*m*, $W_{1/2} \approx 6$, H–C(15)); 6.15 (*d* × *d*, $J = 7$ and 5, H–C(23)); 7.02–7.60 (*m*, H–C(22), H–C(24) and 5 arom. H). – MS.: 458 ($C_{31}H_{38}O_3^+$). – HR.-MS for M^+: Found 458.2827; Calc. 458.2821.

Synthesis of 3-(3'β-benzyloxy-14',15'β-epoxy-5'β,14'β-androstan-17'β-yl)-2H-pyran-2-one[9]) (**31**). Compound **30** (80 mg) was treated first with NBS and then with 1.2 g of basic alumina as described above (*cf.* **18** → **20**). Chromatography on a silica gel plate with CH_2Cl_2/hexane/ether 16:4:1 yielded 54 mg (65%) of **31** which was crystallized from hexane/CH_2Cl_2, m. p. 199–200°. – UV. ($CHCl_3$): 294 (3.74). – IR. (CCl_4): no OH, 1721 (C=O), 1638 (C=C). – ^{1}H-NMR. ($CDCl_3$[9]): 0.86 (*s*, 3 H–C(18)); 0.99

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[9]) Compound **22–32** and **3** can also be named systematically as 5β-cholane derivatives. *e. g.* 3β-benzyloxy-17β-hydroxy-5β,17α-chola-15,20,22-trien-24-al ethylene acetal (**22**), 3β-benzyloxy-21,24-epoxy-15β,21ξ-dihydroxy-5β-chol-20(22)-en-23-one (**26**), and 14β,15β-epoxy-3β-hydroxy-5β-chola-20(22),23-dieno-21,24-lactone (**3**). In the ^{1}H-NMR. spectra, this numeration is used.

(*s*, 3 H–C(19)); 3.50 (br. *s*, H–C(15)); 3.71 (*m*, $W_{1/2} \approx 7$, H–C(3)); 4.48 (*s*, CH_2Ph); 6.16 (*d* × *d*, *J* = 7 and 5, H–C(23)); 7.12–7.40 (*m*, H–C(24) and 5 arom. H); 7.50 (*d* × *d*, *J* = 7 and 2, H–C(22)). – MS.: 474 ($C_{31}H_{38}O_4^+$).

$C_{31}H_{38}O_4$ (474.61) Calc. C 78.45 H 8.07% Found C 78.18 H 8.17%

Synthesis of 3-(14'β,15'β-epoxy-3'β-hydroxy-5'β,14'β-androstan-17'β-yl)-2H-pyran-2-one[9] (= *β-isoresibufogenin* **3**) *and 3-(14'β,15'β-epoxy-3'β-hydroxy-5'β,14'β-androstan-17'β-yl)-5,6-dihydro-2H-py-ran-2-one*[9] (**32**). A solution of **31** (50 mg) in 6 ml of ethanol was hydrogenated over 20 mg of 10% Pd/C. Chromatography on a silicagel plate with 3% methanol in ether/hexane 3:2 gave 19 mg (47%) of **3** and 15 mg (37%) of **32**, besides 4 mg of starting material. Both products were recrystallized from hexane/CH_2Cl_2.

The *β*-isoresibufogenin (**3**) was identical in all respects with the material of the same structure which we have recently prepared from digitoxigenin[5]), m. p. 229–231°. – UV. ($CHCl_3$): 294 (3.74). – IR. ($CHCl_3$): 3605, 3350 (OH), 1703 (C=O), 1630 (C=O). – ^{1}H-NMR. ($CDCl_3$)[9]): 0.85 (*s*, H–C(18)); 1.00 (*s*, 3 H–C(19)); 3.58 (br. *s*, H–C(15)); 4.13 (*m*, $W_{1/2} \approx 8$, H–C(3)); 6.20 (*d* × *d*, *J* = 7 and 5, H–C(23)); 7.33 (*d* × *d*, *J* = 5, and 2, H–C(24)); 7.53 (*d* × *d*, *J* = 7 and 2, H–C(22)). – MS.: 384 ($C_{24}H_{32}O_4^+$).

$C_{24}H_{32}O_4$ (384.50) Calc. C 74.97 H 8.39% Found C 74.68 H 8.61%

Data of compound **32.** M. p. 234–236°. – UV. (EtOH): 226 (3.31). – IR. ($CHCl_3$): 3615 (OH), 1709 (C=O). – ^{1}H-NMR. ($CDCl_3$): 0.89 (*s*, 3 H–C(18)); 0.99 (*s*, 3 H–C(19)); 3.48 (br. *s*, H–C(15)); 3.93–4.55 (*m*, 2 H–C(24) and H–C(3)); 6.95 (br. *t*, *J* = 5, H–C(22)). – MS.: 386 ($C_{24}H_{34}O_4^+$). – HR.–MS. for M^+: Found 386.2454; Calc. 386.2457.

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