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# ON CARDIOACTIVE STEROIDS. XVII. THE SYNTHESIS OF γ-ISOBUFALIN[1]

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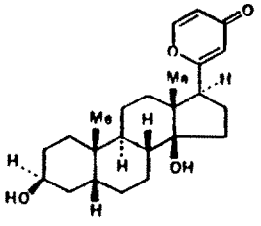
Abstract - γ-Isobufalin[1] 1 was synthesized from testosterone. A novel use of α-furans as masking groups of a carboxylic acid is also reported.

A large number of bufadienolides of general formula 2 (a-i) (Figure 1) was prepared by K. Wiesner and coworkers.[2] The corresponding β-glucosides of these cardiac steroids have been tested at Professor Mendez's Institute[3] for their pharmacological activity in the hope of discovering derivatives more potent and with a wider margin of safety than the natural glycosides of digitalis. Among these derivatives, those that are connected to the steroid moiety by the β-carbon of the enone system of the six membered ring showed both a potency and a margin of safety superior to those of natural cardioactive steroid glycosides. These considerations brought us to the synthesis of a compound such as γ-isobufalin 1 where the γ-pyrone ring still retains the right setup for the enone system, but possesses electronic and chemical properties (i.e., dipole moment, $pK_a$) quite different from those of the isomeric α-pyrones.[4]




1

γ-Pyrones are widely distributed in nature[4] and, as a consequence, have become accessible in the laboratory by a variety of synthetic methods.[5] Essentially, all of them employ strong acid conditions for the cyclization step[6,7] and they often proceed only in moderate yields. Only recently, new methods for the preparation of γ-pyrones[8,9] and 5,6-dihydro-γ-pyrones[10] have been reported via in situ cyclocondensation of 4-methoxy-3-buten-2-one enolates with acid derivatives[8,9] and of sililoxydienes with aldehydes.[10]

The problem of setting up a carbonyl or a carboxylic function at C(17) without having to deal with easy epimerizations at C(17) or acetal or lactone formation with the C(14) hydroxyl group[11] was easily solved by using the "furan methodology"[12] which enabled K. Wiesner and

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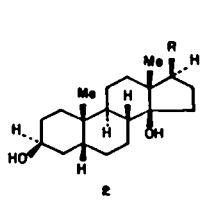
*Deceased November 28, 1986.



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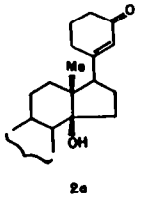

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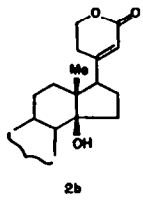

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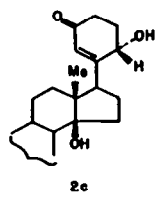

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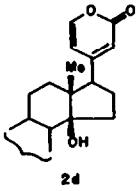
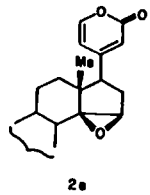


2d

Active and with a good margin of safety.



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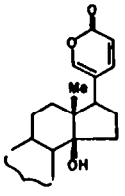

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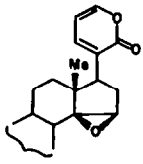

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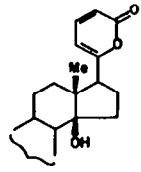
Inactive or toxic



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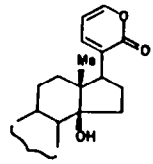

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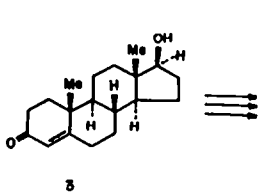
Figure 1



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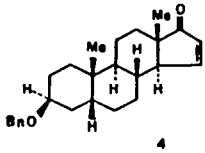

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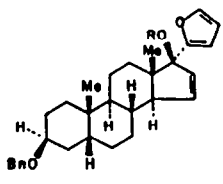
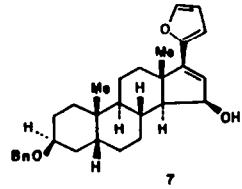


5 R = H
6 R = Ac



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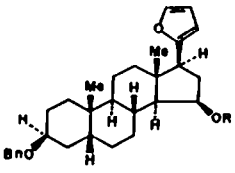
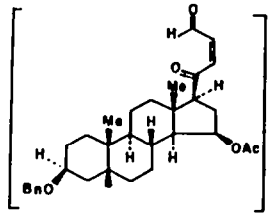


8 R = H
9 R = Ac



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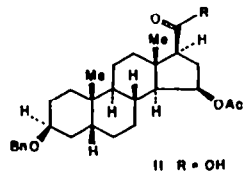
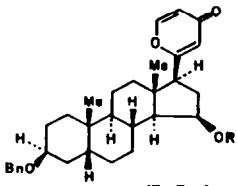
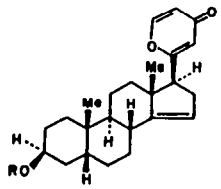


11 R = OH
12 R = Imidazole



13 R = Ac
14 R = H



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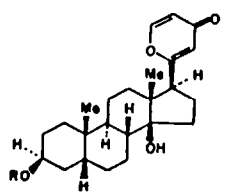

16 R = Bn
1 R = H

Scheme 1

coworkers to prepare over 50 natural and synthetic cardenolides and bufadienolides.[2] In this case, the inexpensive furan, after having been exploited for its electron releasing properties in assisting the "allylic rearrangement",[13] served perfectly the purpose of a masking group of a carboxylic acid. In fact, upon treatment with NBS followed by a $KMnO_4/NaIO_4$ oxidation, the α-substituted furan ring[14] led, in one pot, to the carboxylic acid 11. The synthesis of the target compound 1 was achieved without any difficulty as described in Scheme 1.

## Discussion

Testosterone 3 was converted, according to a well-established procedure,[15] to the α,β-unsaturated ketone 4 which was alkylated in dry ether at 0°C with a preformed solution of α-furyl lithium (furan and n-butyl lithium in dry ether at -78°C). The crude tertiary alcohol was acetylated with acetic anhydride in pyridine to compound 6 which was subjected to allylic rearrangement in refluxing aqueous acetone in the presence of calcium carbonate to yield the allylic alcohol 7. The crude product 7 was hydrogenated with $Pd/CaCO_3$ in ethanol to yield, in agreement with previous experiences,[15,16] the 15β-hydroxy compound 8 in a yield of 71% over four steps. Now that the correct β-configuration at C(17) had been established, the 15β-hydroxy group, needed as a "handle" for the functionalization and inversion of configuration at C(14),[2,15] was acetylated with acetic anhydride in pyridine to yield compound 9 in a quantitative yield. It was now time to convert the α-furan ring into a carboxylic group. Treatment of compound 9 with NBS in dioxane/water followed by $KMnO_4/NaIO_4$ oxidation in the same solvent mixture in the presence of potassium carbonate yielded 81% of the carboxylic acid 11, very likely via the keto-aldehyde 10.[16a] The carboxylic acid 11, upon treatment with 1,1'-carbonyldiimidazole in dry chloroform at 50°C, yielded quantitatively the carbonyl imizadole derivate 12 which was immediately reacted with a preformed solution of 4-methoxy-3-buten-2-one potassium enolate in dry THF at -78°C. Quenching at -78°C yielded the expected γ-pyrone[9] 13 in a 68% yield. The uv, ir, and $^1$H-nmr spectra confirmed the presence of the γ-pyrone ring [uv (EtOH): 247 nm (log ε = 3.85); ir ($CHCl_3$): 1655, 1610 $cm^{-1}$; $^1$H-nmr ($CDCl_3$): δ 6.18 (d, J = 2 Hz, H-C(3)); 56.31 (dd, J = 2, J = 6 Hz, H-C(5)); 7.73 (d, J = 6 Hz, H-C(6))].

With the obtention of compound 13, the synthetic problem was practically solved since now the functionality and configuration of this material is perfectly suited for an uneventful conversion to the target compound 1. Hydrolysis of the acetyl group of compound 13 with aqueous HCl in refluxing methanol yielded 83% of the secondary alcohol 14 which was regioselectively dehydrated with thionyl chloride in pyridine at -15°C to yield the unsaturated compound 15 in a 74.2% yield. Finally, the introduction of the 14β-hydroxy group was achieved by the modified method[15] of Engel and Bach.[17] Treatment of the unsaturated compound 15 with NBS in the presence of aqueous $HClO_4$ in acetone/water followed immediately by debromination with a large excess of Raney-Ni in the presence of acetic acid in dichloromethane/water at room temperature yielded the 3-benzyl-γ-isobufalin 16 in 55.1% yield. Debenzylation of compound 16 in refluxing ethanol/benzene with cyclohexene over $Pd(OH)_2/C$[18] yielded γ-isobufalin 1 in 67.9% yield.

## Experimental Part

The infrared spectra were recorded on a Perkin-Elmer spectrophotometer model 237B using chloroform as solvent. The ultraviolet spectra were taken on a Beckman Model 25 spectrophotometer in ethanol. The $^1$H-NMR spectra were recorded on a Varian XL-200 spectrometer in deuteriochloroform using TMS as internal standard. Chemical shifts are expressed in δ and the coupling constants, J, are measured in Hz. The high resolution mass spectra were recorded on an AEI MS-50 spectrometer at the Mass Spectrometry Lab, University of Alberta, and the elemental analyses were performed by Mikroanalytisches Labor Pascher, Bonn, Germany. All the melting points were determined on a Kofler hot stage apparatus and are uncorrected.

2-(3'β-Benzyloxy-17'β-hydroxy-5'β-androst-15'-en-17'α-yl)furan 5[16b]

n-Butyl lithium (1.6 M in hexane, 45.0 ml) was added to a stirred soln. of furan (7.1 ml) in dry ether (70 ml) at -78°C under $N_2$. The temperature was raised to 0°C and stirring was continued for 3 more h. To this soln. compd. 4[15] (11.34 g), dissolved in benzene/ether 1:4 (200 ml), was added dropwise and stirring was continued for a further 40 min at 0°C under $N_2$. The excess of reagent was quenched with water and the reaction mixture was diluted with ether, washed with citric acid (5%) and $NaHCO_3$ (5%), dried ($MgSO_4$) and the solvent evaporated in vacuo to yield 14.08 g of crude 5 which was used in the next step without purification.

Ir: no C=O; 3600, 3430 $cm^{-1}$ (OH); $^1$H-nmr: 0.97 (s, 3H-C(18')); 1.04 (s, 3H-C(19')); 3.65 (br. s, H-C(3')); 4.47 (s, $CH_2Ph$); 5.70 (dd, J = 3, J = 6, H-C(15')); 6.12 (m, H-C(16'), H-C(3)); 6.33 (dd, J = 2, J = 3, H-C(4)); 7.33 (s, 5 aromatic H); 7.43 (br. s, H-C(5)).

2-(3'β-Benzyloxy-15'β-hydroxy-5'β-androst-16'-en-17'-yl)furan 7[16b]

Crude compd. 5 (14.08 g) was acetylated with acetic anhydride (18.8 ml) in pyridine (97.5 ml) in the presence of DMAP (363 mg) at rt for 36 h. Pyridine was distilled off at reduced pressure at 40°C and the residue, redissolved in ether, was washed with citric acid (5%) and $NaHCO_3$ (5%). The solvent was evaporated in vacuo and the residue was dissolved in acetone/water 3:1 (600 ml) and heated to reflux in the presence of $CaCO_3$ (7.48 g) for 42 hr. The cooled soln. was filtered and most of the acetone was evaporated in vacuo. The residue was extracted with ether and the combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to dryness to yield 14 g of crude 7 which was used in the next step without purification.

Ir: no OC=O; 3620, 3450 $cm^{-1}$ (OH); $^1$H-nmr: 1.07 (s, 3H-C(19')); 1.33 (s, 3H-C(18')); 3.74 (br. s, H-C(3')); 4.50 (s, $CH_2Ph$); 4.58 (br. s, H-C(15')); 6.18 (d, J = 3, H-C(3)); 6.39 (m, H-C(4), H-C(16')); 7.33 (br. s, H-C(5), 5 aromatic H).

2-(3'β-Benzyloxy-15'β-hydroxy-5'β-androstan-17'β-yl)furan 8[16b]

Crude 7 (14 g) was hydrogenated in ethanol (300 ml) in the presence of aq. NaOAc (5%, 9 ml) and Pd/$CaCO_3$ (10%, 1.36 g) for 2 hr. The catalyst was filtered off through Celite and the filtrate was evaporated to dryness in vacuo to yield, after chromatography on silica gel from hexane/acetone 9:1, 9.54 g (71.0% after 4 steps) of 8 which crystallized from ether/hexane, mp 106-107°C, identical to that reported.[16b]

Ir: 3620, 3470 $cm^{-1}$ (OH); $^1$H-nmr: 0.75 (s, 3H-C(18')); 1.00 (s, 3H-C(19')); 3.74 (br. s, H-C(3')); 4.35 (m, H-C(15')); 4.50 (s, $CH_2Ph$); 6.05 (d, J = 3, H-C(3)); 6.30 (dd, J = 3, J = 6, H-C(4)); 7.34 (br. s, H-C(5), 5 aromatic H).

2-(3'β-Benzyloxy-15'β-acetoxy-5'β-androstan-17'β-yl)furan 9

Compd. 8 (21.26 g) was acetylated with acetic anhydride/pyridine 1:2 (72 ml) in the presence of DMAP (54 mg) at rt for 24 h. The reaction was worked up as usual and chromatography on silica gel from hexane/acetone 9.5:0.5 yielded 23.02 g (99.0%) of 9 which crystallized from ether/hexane, mp 115-116°C.

Ir: no OH; 1725 $cm^{-1}$ (OC=O); $^1$H-nmr: 0.70 (s, 3H-C(18')); 1.00 (s, 3H-C(19')); 2.05 (s, $OCOCH_3$); 2.74 (m, 2H-C(16')); 3.75 (br. s, H-C(3')); 4.50 (s, $CH_2Ph$); 5.19 (m, H-C(15')); 6.01 (d, J = 3, H-C(3)); 6.30 (dd, J = 2, J = 3, H-C(4)); 7.34 (m, H-C(5), 5 aromatic H); MS(HR): 490.3087 ($M^+$ calc. 490.3083).

3β-Benzyloxy-15β-acetoxy-5β-androstan-17β-carboxylic acid 11

NBS (1.96 g) was added portionwise to a well-stirred soln. of compd. 9 (4.92 g) in dioxane/water 4:1 (230 ml) in the presence of NaOAc (1.02 g) at rt. When the colour no longer discharged, more dioxane (2000 ml) and 18-crown-6 (30 mg) were added. To this new soln., a soln. of $NaIO_4$ (26.68 g), $KMnO_4$ (320 mg), and $K_2CO_3$ (6.21 g) in water[19] (4000 ml) was slowly added under vigorous stirring. The reaction was practically instantaneous. The reaction mixture was acidified with 2N HCl, saturated with NaCl and two phases separated. The aqueous phase was extracted several times with ether and all the organic phases were combined together, washed with $Na_2CO_3$ (5%) and brine, dried ($MgSO_4$) and evaporated to dryness in vacuo to yield, after chromatography on silica gel, 3.8 g (80.9%) of 11 as a white foam.

Ir: 3500, 3020, 1710 $cm^{-1}$ (COOH); 1725 $cm^{-1}$ (OC=O); $^1$H-nmr: 0.96 (br. s, 3H-C(18)); 1.02 (s, 3H-C(19)); 2.05 (s, $OCOCH_3$); 3.73 (br. s, H-C(3)); 4.52 (s, $CH_2Ph$); 5.15 (m, H-C(15)); 7.36 (m, 5 aromatic H); MS(HR): 377.2323 ($M^+$ - $CH_2Ph$, calc. 377.2328).

Compd. 11 was esterified with $CH_2N_2$.

Ir: no COOH, 1725 $cm^{-1}$ ($COOCH_3$); $^1$H-nmr: 0.89 (s, 3H-C(18)); 1.01 (s, 3H-C(19)); 2.05 (s, $OCOCH_3$), 3.71 (s, $COOCH_3$); 3.74 (br. s, H-C(3)); 4.52 (s, $CH_2Ph$); 5.15 (m, H-C(15)); 7.36 (m, 5 aromatic H); MS(HR): 451.2846 ($M^+$ - $OCH_3$, calc. 451.2848).

**3β-Benzyloxy-15β-acetoxy-5β-androstan-17β-carbonyl Imidazole 12**

1,1'-Carbonyldiimidazole[20] (201 mg) was added under $N_2$ to a soln. of compd. 11 (589 mg) in dry $CHCl_3$ (19 ml). The soln. was stirred at 40-50°C until $CO_2$ no longer evolved and then was evaporated to dryness, redissolved in ether, washed rapidly with citric acid (5%) and $NaHCO_3$ (5%), dried ($MgSO_4$) and evaporated to dryness, yielding 634.5 mg (98.8%) of 12 as a white unstable foamy compd.

Ir: no (COOH); 1725 $cm^{-1}$ ($OCOCH_3$) (O=C-$C_3H_3N_2$); $^1$H-nmr: 0.96 (s, 3H-C(18)); 1.01 (s, 3H-C(19)); 2.10 (s, $OCOCH_3$); 2.35-2.69 (m, 2H-C(16)); 3.03 (t, J = 9, H-C(17)); 3.74 (br. s, H-C(3)); 4.51 (s, $CH_2Ph$); 5.24 (m, H-C(15)); 7.13 (br. s, H-C(4')); 7.36 (m, 5 aromatic H); 7.55 (br. s, H-C(5')); 8.20 (br. s, H-C(2')).

**2-(3'β-Benzyloxy-15'β-acetoxy-5'β-androstan-17'β-yl)-4H-pyran-4-one 13**

4-Methoxy-3-buten-2-one (1.196 g) was slowly added to a stirred soln. of potassium tert-butoxide (1.340 g) in dry THF (50 ml) at -78°C under $N_2$. After a few min, an intense orange colour developed and compd. 12 (1.549 g) in dry THF (26 ml) was added. The reaction was followed by TLC and when the disappearance of 12 was observed, the reaction was quenched with water at -78°C. The temperature was allowed to rise to rt and the mixture was stirred for 1 h, saturated with NaCl and extracted several times with ether. The organic layers were combined, washed with citric acid (5%), dried ($MgSO_4$) and evaporated to dryness. The crude product was chromatographed on silica gel G with hexane/acetone 7:3 yielding 950 mg (68% based on recovered 11) of compd. 13 which was crystallized from acetone/hexane, mp 163.5-165°C.

Uv: 247 nm (log ε = 3.85); 208 nm (log ε = 3.87); ir: 1725 $cm^{-1}$ ($OCOCH_3$); 1655 $cm^{-1}$ (C=O); 1610 $cm^{-1}$ (C=C); $^1$H-nmr: 0.82 (s, 3H-C(18')); 1.01 (s, 3H-C(19')); 2.08 (s, $OCOCH_3$); 2.36-2.69 (m, 2H-C(16')); 3.74 (br. s, H-C(3')); 4.51 (s, $CH_2Ph$); 5.20 (m, H-C(15')); 6.18 (d, J = 2, H-C(3)); 6.31 (dd, J = 2, J = 6, H-C(5)); 7.36 (m, 5 aromatic H); 7.73 (d, J = 6, H-C(6)); MS(HR); 518.3038 ($M^+$, calc. 518.3032).

Anal. $C_{33}H_{42}O_5$ (518.69): Found C 76.09%, H 8.15%; calc. C 76.41%, H 8.16%.

**2-(3'β-Benzyloxy-15'β-hydroxy-5'β-androstan-17'β-yl)-4H-pyran-4-one 14**

Compd. 13 (697 mg) was refluxed for 10 days in methanol (90 ml) in the presence of aq HCl (1N, 20 ml). The soln. was neutralized with $NaHCO_3$ (5%) and methanol was removed under vacuum. The mixture was extracted several times with ether and the organic layers were combined, dried ($MgSO_4$) and evaporated to dryness in vacuo. The crude product was chromatographed on silica gel G with hexane/acetone 7:3 yielding 531.6 mg (83.0%) of 14 and 27.2 mg (4.4%) of 15. Compd. 14 was crystallized from acetone/hexane, mp 151.5-152.5°C.

Uv: 247 nm (log ε = 3.89); 205 nm (log ε = 4.01); ir: 3600, 3420 $cm^{-1}$ (OH); 1655 $cm^{-1}$ (C=O); 1610 $cm^{-1}$ (C=C); $^1$H-nmr: 0.88 (s, 3H-C(18')); 1.01 (s, 3H-C(19')); 3.46 (m, 2H-C(16')); 3.75 (br. s, H-C(3')); 4.41 (br. s, H-C(15')); 4.51 (d, J = 1, $CH_2Ph$); 6.23 (d, J = 2, H-C(3)); 6.31 (dd, J = 2, J = 6, H-C(5)); 7.37 (m, 5 aromatic H); 7.74 (d, J = 6, H-C(6)); MS(HR): 476.2926 ($M^+$, calc. 476.2926).

Anal. $C_{31}H_{40}O_4$ (476.65): Found C 77.80%, H 8.44%; calc. C 78.11%, H 8.46%.

**2-(3'β-Benzyloxy-5'β-androst-14'-en-17'β-yl)-4H-pyran-4-one 15**

Thionyl chloride (0.964 ml) was added to a soln. of compd. 14 (332 mg) in $CH_2Cl_2$/pyridine 2:1 (24 ml) cooled at -15°C. The reaction was stirred for 30 min at -15°C, neutralized with HCl (1N) and extracted several times with ether. The organic layers were combined, dried ($MgSO_4$) and evaporated to dryness in vacuo. The crude product was chromatographed on silica gel with hexane/acetone 8:2 yielding 237 mg (74.2%) of 15 which was crystallized from acetone/hexane, mp 161-163°C.

Uv: 246 nm (log ε = 3.83), 205 nm (log ε = 3.94); ir: no (OH); 1655 $cm^{-1}$ (C=O); 1610 $cm^{-1}$ (C=C); $^1$H-nmr: 0.81 (s, 3H-C(18')); 1.00 (s, 3H-C(19')); 2.26-2.73 (m, 2H-C(16')); 2.99 (t, J = 9, H-C(17')); 3.74 (br. s, H-C(3')); 4.52 (s, $CH_2Ph$); 5.24 (br. s, H-C(15')); 6.28 (d, J = 2, H-C(3)); 6.32 (dd, J = 2, J = 6, H-C(5)); 7.37 (m, 5 aromatic H); 7.76 (d, J = 6, H-C(6)); MS(HR): 458.2829 ($M^+$, calc. 458.2821).

Anal. $C_{31}H_{38}O_3$ (458.64): Found C 81.02%, H 8.31%; calc. C 81.18%, H 8.35%.

**2-(3'β-Benzyloxy-14'-hydroxy-5'β,14'β-androstan-17'β-yl)-4H-pyran-4-one 16**

Compd. 15 (126.1 mg) in acetone/water 9:1 (13.8 ml) was treated with 5 drops of aq $HClO_4$ (0.5%) and NBS (58.8 mg) at rt for 30 min. The mixture was diluted with $CH_2Cl_2$, washed with $NaHSO_3$ (5%) and water, dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue was dissolved in $CH_2Cl_2$/MeOH 1:1 (62 ml) containing AcOH (26.5 mg) and treated with a large excess of Raney-Ni. After 20 min of stirring, the catalyst was filtered off and the solution was concentrated in vacuo, diluted with $CHCl_3$, washed with aqueous $NaHCO_3$ (5%), dried ($MgSO_4$) and evaporated to dryness. The crude product was chromatographed on silica gel G with hexane/$CHCl_3$/acetone 5.5:2:2.5 yielding 72.2 mg (55.1%) of 16 which was crystallized from

$CHCl_3$/hexane, mp 225-228°C.
Uv: 250 nm (log ε = 3.90), 210 nm (log ε = 3.90); ir: 3600, 3410 $cm^{-1}$ (OH); 1655 $cm^{-1}$ (C=O); 1610 $cm^{-1}$ (C=C); $^1$H-nmr: 0.87 (s, 3H-C(18')); 0.96 (s, 3H-C(19')); 2.71 (m, H-C(17')); 3.76 (br. s, H-C(3')); 4.53 (s, $CH_2Ph$); 6.31 (dd, J = 2, J = 6, H-C(5)); 6.35 (d, J = 2, H-C(3)); 7.38 (m, 5 aromatic H); 7.74 (d, J = 6, H-C(6)); MS(HR): 476.2929 ($M^+$, calc. 476.2926).

Anal. $C_{31}H_{40}O_4$ (476.65): Found H 77.82%, H 8.45%; calc. C 78.11%, H 8.46%.

2-(3'β,14'-Dihydroxy-5'β,14'β-androstan-17'β-yl)-4H-pyran-4-one 1

Compd. 16 (85.6 mg) was refluxed for 4.5 h in ethanol/benzene 2:1 (18 ml) in the presence of cyclohexene (326 mg) and $Pd(OH)_2$[18] (39.9 mg). The catalyst was filtered off and the soln. was evaporated to dryness. The crude product was chromatographed on silica gel G plates with hexane/acetone 6:4 yielding 47.15 mg (67.9%) of 1 which was crystallized from $CHCl_3$/hexane, double mp: 228°C (crystal transformation), 265-268°C (with decomposition).
Uv: 250 nm (log ε = 4.12); 211 nm (log ε = 3.85); ir: 3600, 3400 $cm^{-1}$ (OH); 1655 $cm^{-1}$ (C=O); 1610 $cm^{-1}$ (C=C); $^1$H-nmr: 0.86 (s, 3H-C(18')); 0.97 (s, 3H-C(19')); 2.71 (m, H-C(17')); 4.16 (br. s, H-C(3')); 6.30 (dd, J = 2, J = 6, H-C(5)); 6.33 (d, J = 2, H-C(3)); 7.73 (d, J = 6, H-C(6)); MS(HR): 386.2456 ($M^+$, calc. 386.2457).

Anal. $C_{24}H_{34}O_4$ (386.53): Found C 74.27%, H 8.85%; Calc. C 74.57%, H 8.87%.

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**References and Notes**

1. Systematic names of all compounds are given in the Experimental Part.

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14. β-Substituted furans also led to a carboxylic acid upon mCPBA, $KMnO_4/NaIO_4$ oxidation, but in a lower yield.

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